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Arthritis Care & Research

Aims and Scope

Arthritis Care & Research is an official journal of the American College of Rheumatology and the Association of Rheumatology Professionals, a division of the College. *Arthritis Care & Research* is a peer-reviewed journal that publishes both original research and review articles that promote excellence in the clinical practice of rheumatology. Relevant to the care of individuals with arthritis and related disorders, major topics are evidence-based practice studies, clinical problems, practice guide-lines, health care economics, health care policy, educational, social, and public health issues, and future trends in rheumatology practice.

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Special Articles

Rheumatoid Arthritis

Osteoarthritis

COVID-19

Cover image: The image on the cover (from Aslam et al, page 1106) shows neutrophilic epitheliotropism on skin biopsy. Neutrophils extended into the epithelium of eccrine sweat glands (hematoxylin and eosin stained; original magnification x 600).

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American College of Rheumatology
Empowering Rheumatology Professionals

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Polyarteritis Nodosa

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Objective. To provide evidence-based recommendations and expert guidance for the management of systemic polyarteritis nodosa (PAN).

Methods. Twenty-one clinical questions regarding diagnostic testing, treatment, and management were developed in the population, intervention, comparator, and outcome (PICO) format for systemic, non–hepatitis B–related PAN. Systematic literature reviews were conducted for each PICO question. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to assess the quality of evidence and formulate recommendations. Each recommendation required ≥70% consensus among the Voting Panel.

Results. We present 16 recommendations and 1 ungraded position statement for PAN. Most recommendations were graded as conditional due to the paucity of evidence. These recommendations support early treatment of severe PAN with cyclophosphamide and glucocorticoids, limiting toxicity through minimizing long-term exposure to both treatments, and the use of imaging and tissue biopsy for disease diagnosis. These recommendations endorse minimizing risk to the patient by using established therapy at disease onset and identify new areas where adjunctive therapy may be warranted.

Conclusion. These recommendations provide guidance regarding diagnostic strategies, use of pharmacologic agents, and imaging for patients with PAN.

The article is published simultaneously in *Arthritis & Rheumatology*.
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INTRODUCTION

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that primarily affects medium-sized vessels (1). Patients frequently present with systemic symptoms such as fever and weight loss. The most common clinical presentations include neurologic manifestations such as mononeuritis multiplex and peripheral neuropathy, cutaneous manifestations such as nodules and livedo reticularis, renal manifestations such as hypertension, and gastrointestinal manifestations such as abdominal pain (2). Diagnosis is generally confirmed by tissue biopsy of an affected organ or angiography if tissue biopsy cannot be obtained. Typical histologic findings include mixed-cell inflammatory infiltrates in the vessel wall and fibrinoid necrosis, with an absence of granulomas and giant cells (3). Findings on angiography include saccular or fusiform aneurysms and stenotic lesions in the mesenteric, hepatic, and renal arteries and their subsequent branches. Although PAN is becoming increasingly rare due to the prevention of hepatitis B viral (HBV) infection, it remains a potentially devastating diagnosis, with severe PAN having a mortality rate of 40% at 5 years (3).

Given the increasing options available to treat systemic vasculitis, the American College of Rheumatology (ACR) and the Vasculitis Foundation (VF) supported the development of guidelines for the management of large, medium, and small vessel vasculitis. This guideline presents evidence-based recommendations for the diagnostic testing, treatment, and management of PAN as an exemplar of medium vessel vasculitis. Of note, this guideline focuses on systemic PAN. Since HBV-associated PAN as well as cutaneous PAN are generally managed differently from systemic idiopathic PAN, they were excluded from this guideline.

Although this guideline may inform an international audience, these recommendations were developed considering the experience with and availability of treatment and diagnostic options in the US.

METHODS

This guideline followed the ACR guideline development process (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence and develop recommendations (4,5). ACR policy guided the management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Vasculitis). Supplementary Appendix 1 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24633/abstract) presents a detailed description of the methods. Briefly, the Literature Review team undertook systematic literature reviews for predetermined questions specifying the clinical population, intervention, comparator, and outcomes (PICO). An in-person Patient Panel of 11 individuals with different types of vasculitis (1 patient with PAN) was moderated by a member of the Literature Review team (ABD). This Patient Panel reviewed the evidence report (along with a summary and interpretation by the moderator) and provided patient perspectives and preferences. An Expert Panel provided expert knowledge to inform discussion of the PICO questions and findings of the literature review. The Voting Panel comprised 9 adult rheumatologists, 5 pediatric rheumatologists, and 2 patients; they reviewed the Literature Review team's evidence summaries and, bearing in mind the Patient Panel's deliberations, formulated and voted on recommendations. A recommendation required ≥70% consensus among the Voting Panel.

How to interpret the recommendations

A *strong* recommendation is typically supported by moderate- to high-quality evidence (e.g., multiple randomized controlled

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Dr. Langford has received consulting fees, speaking fees, and/or honoraria from Bristol Myers Squibb (less than $10,000) and research grants from Bristol Myers Squibb, GlaxoSmithKline, and Genentech. Dr. Grayson has submitted a patent application for the diagnosis and treatment of vacuoles, E1 enzyme, x-linked, autoinflammatory, somatic (VEXAS) syndrome. Dr. Merkel has received consulting fees, speaking fees, and/or honoraria from AbbVie, Biogen, Bristol Myers Squibb, CSL Behring, Genentech/Roche, Genzyme/GlaxoSmithKline, Insmed, Janssen, Kiniksa, Kyverna, Pfizer, Sparrow, and Takeda (less than $10,000 each) and from AstraZeneca, InflaRx, and ChemoCentryx (more than $10,000 each), research support from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, ChemoCentryx, Forbius, Genetech/Roche, Sanofi-Genzyme, GlaxoSmithKline, and InflaRx, and royalties from *UpToDate*. Dr. Stone has received consulting fees, speaking fees, and/or honoraria from Roche and Genentech (less than $10,000 each). Dr. Sule holds a patent related to the development of the Glucocorticoid Toxicity Index. Dr. Sundel has received royalties from *UpToDate*. Dr. Dua has received consulting fees, speaking fees, and/or honoraria from ChemoCentryx and AbbVie (less than $10,000 each). No other disclosures relevant to this article were reported.

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trials). For a strong recommendation, the recommended course of action would apply to all or almost all patients. Only a small proportion of clinicians/patients would not want to follow the recommendation. In rare instances, a strong recommendation may be based on very low– to low-certainty evidence. For example, an intervention may be strongly recommended if it is considered low-cost, without harms, and the consequence of not performing the intervention may be catastrophic. An intervention may be strongly recommended against if there is high certainty that the intervention leads to more harm than the comparison with very low or low certainty about its benefit (6).

A *conditional* recommendation is generally supported by lower-quality evidence or a close balance between desirable and undesirable outcomes. For a conditional recommendation, the recommended course of action would apply to the majority of the patients, but the alternative is a reasonable consideration. Conditional recommendations always warrant a shared decision-making approach. We specify conditions under which the alternative may be considered.

In some instances, the committee found that the evidence for a particular PICO question did not support a graded recommendation or did not favor one intervention over the other. However, the Voting Panel believed that the PICO question addressed a commonly encountered clinical question and thus felt that providing guidance for this question was warranted. For these situations, we present "ungraded position statements," which reflect general views of the Voting Panel.

In this evidence-based guideline, we explicitly used the best evidence available and present that in a transparent manner for the clinician reader/user (7). In some instances, this includes randomized trials in which the interventions under consideration are directly compared. The GRADE system rates evidence that comes exclusively from the collective experience of the Voting Panel and Patient Panel members as "very low quality" evidence (5).

For each recommendation, details regarding the PICO questions and the GRADE evidence tables can be found in Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24633/abstract).

RESULTS

For the evidence report, the Literature Review team summarized 127 articles to address 21 PICO questions for PAN.

The following recommendations and ungraded position statements are for systemic PAN and do not apply to isolated cutaneous or HBV-related PAN. Table 1 presents definitions of selected terms used in the recommendations, including the definition of severe and nonsevere disease, as well as dosing ranges for glucocorticoids. Table 2 presents the recommendations with their supporting PICO questions and levels of evidence. Figure 1 provides key recommendations for the treatment for PAN. All but 1 of the recommendations are conditional, primarily due to lack of high-quality evidence (e.g., randomized controlled trials) supporting the recommendation.

Vascular imaging, tissue biopsy, and diagnostic testing

Recommendation: For patients with suspected PAN, we conditionally recommend using abdominal vascular imaging to aid in establishing a diagnosis and determining the extent of disease.

Evidence for the use of routine diagnostic imaging is limited, with no comparative trials available. In single-arm studies that were performed when diagnostic criteria for PAN were not well defined,

Table 1. Definitions of selected terms used in the recommendations for PAN*

Term	Definition
Disease states	
Suspected disease	Clinical signs and/or symptoms suggestive of PAN and not explained by other conditions
Active disease	New, persistent, or worsening clinical signs and/or symptoms attributed to PAN and not related to prior damage
Severe disease	Vasculitis with life- or organ-threatening manifestations (e.g., renal disease, mononeuritis multiplex, muscle disease, mesenteric ischemia, coronary involvement, limb/digit ischemia)
Nonsevere disease	Vasculitis without life- or organ-threatening manifestations (e.g., mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis)
Remission	Absence of clinical signs or symptoms attributed to PAN, on or off immunosuppressive therapy
Refractory disease	Persistent active disease despite an appropriate course of immunosuppressive therapy
Relapse	Recurrence of active disease following a period of remission
Treatments	
IV pulse GCs	IV methylprednisolone 500–1,000 mg/day (adults) or 30 mg/kg/day (children; maximum 1,000 mg/day) or equivalent for 3–5 days
High-dose oral GCs	Prednisone 1 mg/kg/day (adults; generally up to 80 mg/day) or 1–2 mg/kg/day (children; generally up to 60 mg/day) or equivalent
Moderate-dose oral GCs	Prednisone 0.25–0.5 mg/kg/day (adults; generally 10–40 mg/day) or ~0.5 mg/kg/day (children; generally 10–30 mg/day) or equivalent
Low-dose oral GCs	Prednisone ≤10 mg/day (adults) or ≤0.2 mg/kg/day (children; maximum 10 mg/day) or equivalent
Non-GC immunosuppressive therapy	Azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil

* PAN = polyarteritis nodosa; IV = intravenous; GCs = glucocorticoids.

Table 2. Recommendations/statements for the management of PAN*

Recommendation/statement	PICO question informing recommendation and discussion	Level of evidence
Vascular imaging, tissue biopsy, and diagnostic testing		
Recommendation: For patients with suspected PAN, we conditionally recommend using abdominal vascular imaging to aid in establishing a diagnosis and determining the extent of disease.	1	Very low
Recommendation: For patients with a history of severe PAN with abdominal involvement who become clinically asymptomatic, we conditionally recommend follow-up abdominal vascular imaging.	19, 20	Very low
Recommendation: For patients with suspected PAN involving the skin, we conditionally recommend obtaining a deep-skin biopsy specimen (i.e., a biopsy reaching the medium-sized vessels of the dermis) over a superficial skin punch biopsy to aid in establishing a diagnosis.	2	Very low
Recommendation: For patients with suspected PAN and peripheral neuropathy (motor and/or sensory), we conditionally recommend obtaining a combined nerve and muscle biopsy over a nerve biopsy alone to aid in establishing a diagnosis.	3	Very low
Recommendation: For patients with a history of peripheral motor neuropathy secondary to PAN, we conditionally recommend serial neurologic examinations instead of repeated electromyography/nerve conduction studies (e.g., every 6 months) to monitor disease activity.	21	Very low
Treatment of active disease		
Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with IV pulse GCs over high-dose oral GCs.	4	Very low
Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with cyclophosphamide and high-dose GCs over high-dose GCs alone.	5, 6, 10	Very low to low
Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with cyclophosphamide and GCs over rituximab and GCs.	5, 6, 10	Very low to low
Recommendation: For patients with newly diagnosed active, severe PAN who are unable to tolerate cyclophosphamide, we conditionally recommend treating with other non-GC immunosuppressive agents and GCs over GCs alone.	8	Very low
Recommendation: For patients with newly diagnosed active, nonsevere PAN, we conditionally recommend treating with non-GC immunosuppressive agents and GCs over GCs alone.	12	Very low
Recommendation: In patients with newly diagnosed active, severe PAN, we conditionally recommend *against* using plasmapheresis combined with cyclophosphamide and GCs over cyclophosphamide and GCs alone.	7, 16	Low
Recommendation: For patients with PAN in remission who are receiving non-GC immunosuppressive therapy, we conditionally recommend discontinuation of non-GC immunosuppressive agents after 18 months over continued (indefinite) treatment.	13	Very low
Ungraded position statement: The optimal duration of GC therapy for PAN (e.g., tapering off by 6 months or longer than 6 months) is not well established, and thus, the duration of therapy should be guided by the patient's clinical condition, values, and preferences.	11	Very low
Treatment of refractory disease		
Recommendation: For patients with severe PAN that is refractory to treatment with GCs and non-GC immunosuppressive agents other than cyclophosphamide, we conditionally recommend switching the non-GC immunosuppressive agent to cyclophosphamide, over increasing GCs alone.	17	Very low
Remission maintenance		
Recommendation: For patients with newly diagnosed PAN who have achieved disease remission with cyclophosphamide, we conditionally recommend transitioning to another non-GC immunosuppressive agent over continuing cyclophosphamide.	9	Very low
Other considerations		
Recommendation: For patients with PAN with nerve and/or muscle involvement, we conditionally recommend physical therapy.	14	Very low
Recommendation: For patients with clinical manifestations of DADA2, we strongly recommend treatment with tumor necrosis inhibitors over GCs alone.	18	Low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for polyarteritis nodosa (PAN), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24633/abstract). IV = intravenous; GCs = glucocorticoids; DADA2 = deficiency of adenosine deaminase 2.

vascular imaging, in tandem with clinical signs and pathology, helped validate the diagnosis (8) and determine disease severity (9). This in turn can influence treatment decisions. Moreover, obtaining vascular imaging at disease onset facilitates identification of new vascular involvement during disease relapse. Vascular imaging may not be warranted if patients present with isolated findings such as mononeuritis multiplex or myopathy, or if there are no clinical features suggestive of abdominal arterial involvement (such as absence of gastrointestinal or genitourinary symptoms, including renovascular hypertension). For children, clinicians should be mindful of minimizing repeated radiation exposure.

Clinicians currently use both conventional catheter-based dye angiography and noninvasive methods such as computed tomography (CT) or magnetic resonance (MR) angiography to diagnose PAN (10–12). Conventional angiography is the current gold standard due to its ability to provide better resolution, but it can be

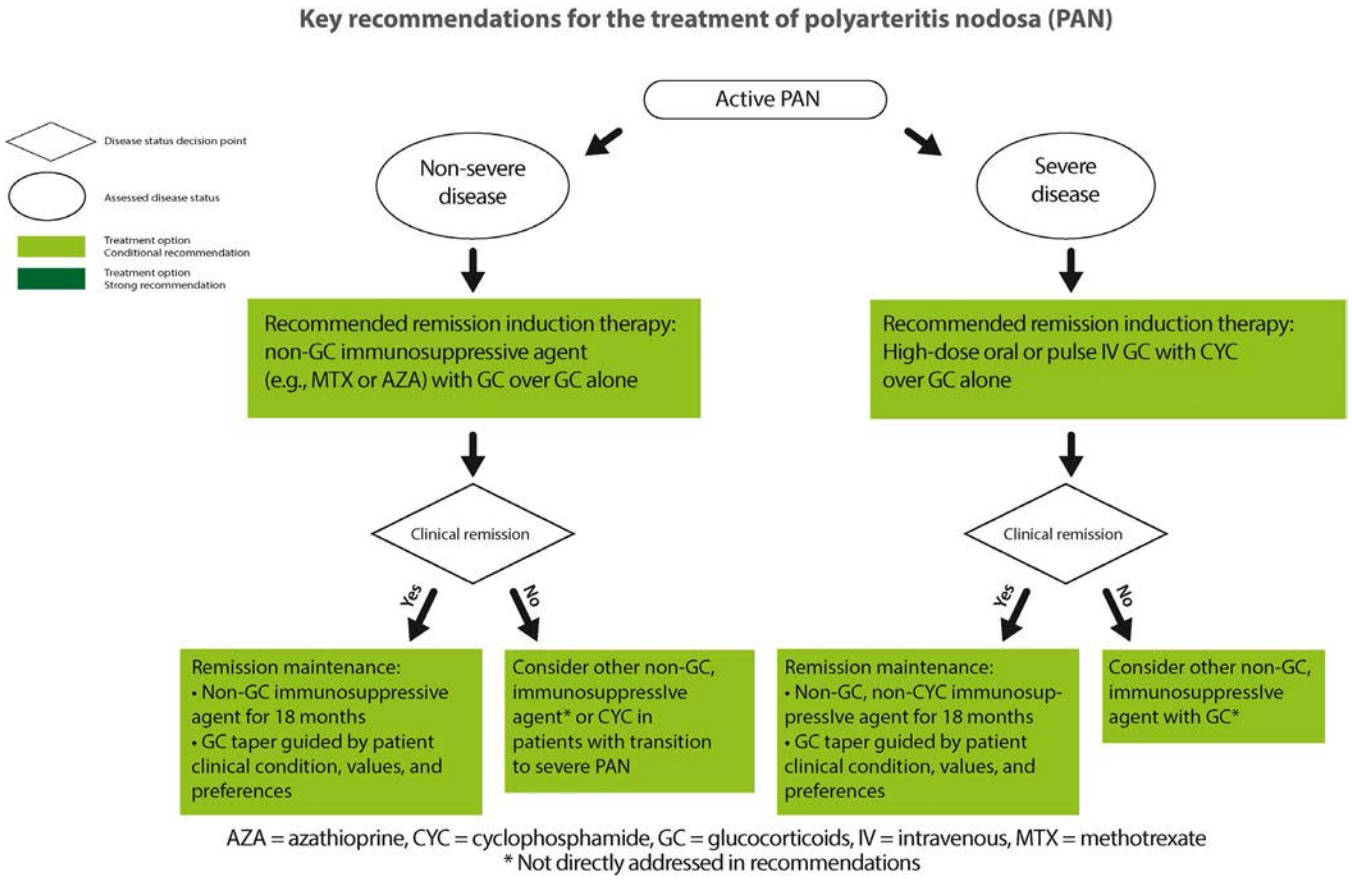

Figure 1. Key recommendations for the treatment of polyarteritis nodosa.

associated with complications, albeit at a very low rate (13,14). However, the resolution for noninvasive modalities is improving, and CT or MR angiography may provide additional information regarding the vessel wall that conventional angiography does not. Specifically, CT angiography may enable visualization of more of the distal branches of the mesenteric arteries than MR angiography, but MR angiography may be preferred in certain clinical situations (e.g., need to avoid iodinated contrast). In patients with a negative CT or MR angiogram result with a high degree of suspicion for abdominal involvement, it is reasonable to consider conventional angiography.

Recommendation: For patients with a history of severe PAN with abdominal involvement who become clinically asymptomatic, we conditionally recommend follow-up abdominal vascular imaging.

Follow-up imaging permits assessment of disease control and treatment response. In the view of the Voting Panel, follow-up imaging is particularly important when baseline imaging demonstrates aneurysmal disease. The timing of follow-up imaging is dependent, in part, on clinical factors, such as the extent and severity of vascular abnormalities, overall disease course, and response to therapy. However, indefinite routine vascular imaging should be avoided if the abdominal vascular disease is shown to be quiescent.

Recommendation: For patients with suspected PAN involving the skin, we conditionally recommend obtaining a deep-skin biopsy specimen (i.e., a biopsy reaching the medium-sized vessels of the dermis) over a superficial skin punch biopsy to aid in establishing a diagnosis.

Indirect evidence (found in nonrandomized studies or studies in which findings were not primary aims) suggests that evaluation of deeper tissue is more effective at establishing a diagnosis of PAN (15,16), since a deeper-tissue sample is more likely to capture a medium-sized vessel. A deep-skin biopsy can be performed by a dermatologist as a deep (or "double") punch biopsy and does not necessarily require invasive resection. This recommendation had strong support from the Voting Panel but remains conditional due to limited evidence.

Recommendation: For patients with suspected PAN and peripheral neuropathy (motor and/or sensory), we conditionally recommend obtaining a combined nerve and muscle biopsy over a nerve biopsy alone to aid in establishing a diagnosis.

Several studies suggest an increased yield with nerve and concurrent muscle biopsy as opposed to nerve biopsy alone (15–19). However, the biopsy should sample involved tissue and not be performed "blind" (i.e., sampling tissue that does not appear

to be clinically affected). Of note, biopsy of an affected purely sensory nerve (e.g., sural nerve) is favored to avoid motor deficits.

Recommendation: For patients with a history of peripheral motor neuropathy secondary to PAN, we conditionally recommend serial neurologic examinations instead of repeated electromyography/nerve conduction studies (e.g., every 6 months) to monitor disease activity.

This recommendation is based on the opinion of the Voting Panel due to a lack of published evidence addressing the issue. Repeated electromyography in a patient with stable symptoms is *not* recommended due to the invasive nature of this study. However, repeated electromyography/nerve conduction study would be warranted if there were uncertainty as to whether a new (or worsening) process was developing.

Treatment of active disease

Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with intravenous (IV) pulse glucocorticoids over high-dose oral glucocorticoids.

In several single-arm and comparative studies, evaluations of medical therapy were confounded by the use of other medications and did not control for IV pulse or high-dose oral glucocorticoid use (20–22). However, for active and severe disease specifically, patients may benefit from the additional mechanism of action of high-dose pulse glucocorticoids. That is, glucocorticoids may rapidly alter cell membrane and receptor function to promote suppression of inflammation once the glucocorticoid receptor is saturated (23). The Voting Panel noted that this recommendation was focused on patients with active, severe disease. For many patients with disease that is not associated with life-threatening manifestations (such as immediate risk of visceral infarct), oral glucocorticoids would be preferred due to lower overall glucocorticoid burden. For pediatric patients, pulse glucocorticoid therapy in other systemic immune disorders appears to have a favorable side-effect profile and is not more strongly associated with infections or other morbidities compared to oral glucocorticoids (24).

Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with cyclophosphamide and high-dose glucocorticoids over high-dose glucocorticoids alone.

In newly diagnosed severe PAN, a single observational study and indirect evidence suggest that the use of cyclophosphamide has more benefits than glucocorticoid therapy alone, with no differences seen between oral and IV cyclophosphamide (25,26). Moreover, the use of additional cyclophosphamide cycles may provide a medium-term protection (3 years) against disease relapse, although this benefit wanes by 10 years (21). Use of cyclophosphamide may mitigate glucocorticoid toxicity by decreasing the cumulative steroid dose (27).

Recommendation: For patients with newly diagnosed active, severe PAN, we conditionally recommend initiating treatment with cyclophosphamide and glucocorticoids over rituximab and glucocorticoids.

While case reports have recently raised the question about the efficacy of rituximab use in PAN (28–30), its efficacy in PAN remains uncertain due to the lack of comparative or large single-arm studies in this disease.

Recommendation: For patients with newly diagnosed active, severe PAN who are unable to tolerate cyclophosphamide, we conditionally recommend treating with other nonglucocorticoid immunosuppressive agents and glucocorticoids over glucocorticoids alone.

Indirect evidence (i.e., data obtained from secondary outcomes in prior trials [25,31]) suggests that the combination of nonglucocorticoid immunosuppressive agents, such as azathioprine or methotrexate, with glucocorticoids is superior to glucocorticoids alone. Mycophenolate mofetil has not been well studied in PAN. No direct trials comparing glucocorticoid monotherapy with nonglucocorticoid combination therapy are available. In general, patients with severe PAN should be treated with cyclophosphamide over other immunosuppressive agents (26), but in patients unable to tolerate cyclophosphamide, another agent, such as azathioprine or methotrexate, is recommended over glucocorticoid monotherapy. Use of nonglucocorticoid immunosuppressive therapy may provide a glucocorticoid-sparing effect and minimize glucocorticoid toxicity, which is particularly significant in pediatric populations.

Recommendation: For patients with newly diagnosed active, nonsevere PAN, we conditionally recommend treating with nonglucocorticoid immunosuppressive agents and glucocorticoids over glucocorticoids alone.

In cases of nonsevere disease, a patient's age, clinical condition, and their values and preferences are important factors in assessing treatment. Although some patients achieve disease remission while receiving glucocorticoids alone, a substantial number of patients ultimately require additional nonglucocorticoid therapy, usually azathioprine or methotrexate (20). This recommendation contradicts management recommendations based on the Five-Factor Score (32), in which patients without factors of severe disease can be treated with glucocorticoids alone. We favor the use of nonglucocorticoid therapy in nonsevere disease, since the addition of nonglucocorticoid therapy may minimize glucocorticoid use and subsequent toxicity.

Recommendation: In patients with newly diagnosed active, severe PAN, we conditionally recommend *against* using plasmapheresis combined with cyclophosphamide and glucocorticoids over cyclophosphamide and glucocorticoids alone.

In a single trial conducted in 1995, the use of plasmapheresis in PAN was evaluated, but a distinction between PAN and HBV-associated PAN was not made (33). Confidence intervals in this study were very wide. Thus, evidence supporting the use of plasmapheresis in non–HBV-associated PAN is unavailable and the benefit unclear. Plasmapheresis may be considered in catastrophic cases unresponsive to the recommended aggressive immunosuppressive therapies and may have a role in the management of HBV-related PAN.

Recommendation: For patients with PAN in remission who are receiving nonglucocorticoid immunosuppressive therapy, we conditionally recommend discontinuation of nonglucocorticoid immunosuppressive agents after 18 months over continued (indefinite) treatment.

Evidence for this recommendation is based on a single study that was performed in 1979 (31). Although a significant number of patients with PAN have disease relapse, the majority experience monophasic disease (20). Indefinite treatment may therefore not be needed. Disease needs to be in sustained remission (Table 1) before discontinuing therapy.

Ungraded position statement: The optimal duration of glucocorticoid therapy for PAN (e.g., tapering off by 6 months or longer than 6 months) is not well established, and thus, the duration of therapy should be guided by the patient's clinical condition, values, and preferences.

In PAN, studies to determine the optimal length of time for glucocorticoid use have not been performed. In studies of other types of vasculitis (34), faster tapers led to more flares, which were often not organ-threatening and may have been mild. The Patient Panel preferred a longer taper, as a primary concern was disease control rather than glucocorticoid toxicity. Thus, duration of glucocorticoid use should be influenced by the patient's clinical condition, values, and preferences.

Treatment of refractory disease

Recommendation: For patients with severe PAN that is refractory to treatment with glucocorticoids and nonglucocorticoid immunosuppressive agents other than cyclophosphamide, we conditionally recommend switching the nonglucocorticoid immunosuppressive agent to cyclophosphamide over increasing glucocorticoids alone.

Based on the effectiveness of cyclophosphamide in new-onset severe PAN (26), indirect evidence suggests that cyclophosphamide should be used in patients with PAN that has evolved from a nonsevere presentation to one that is severe and does not adequately respond to other immunosuppressive agents.

Remission maintenance

Recommendation: For patients with newly diagnosed PAN who have achieved disease remission with cyclophosphamide, we conditionally recommend transitioning to another nonglucocorticoid immunosuppressive agent over continuing cyclophosphamide.

Due to its toxicity, cyclophosphamide therapy should not continue indefinitely and should generally be limited to 3–6 months per course (21). Based on the experience in antineutrophil cytoplasmic antibody–associated vasculitis, transitioning to another less toxic agent such as methotrexate or azathioprine is recommended once disease remission has been attained. Given the lack of clinical trials investigating remission maintenance in PAN, this recommendation was based on expert experience.

Other considerations

Recommendation: For patients with PAN with nerve and/or muscle involvement, we conditionally recommend physical therapy.

Indirect evidence for PAN is available for this recommendation from studies in inflammatory myositis. Based on this, we conditionally recommend this intervention due to its potential benefit and minimal risk. Physical therapy may be more beneficial for those with more substantial motor involvement. Patients on the Voting Panel expressed a high degree of enthusiasm for physical therapy as a modality for recovery and rehabilitation, in that they felt they had personally experienced benefit from physical therapy.

Recommendation: For patients with clinical manifestations of deficiency of adenosine deaminase 2 (DADA2), we strongly recommend treatment with tumor necrosis factor inhibitors over glucocorticoids alone.

DADA2 was first described in a series of patients with an early-onset (often childhood) PAN-like vasculitis (35). DADA2 is characterized by recurrent strokes and skin changes and diagnosed using *ADA2* sequencing or ADA2 functional assays, and ADA2 mutations have been identified in patients diagnosed as having systemic PAN (36). Although only 1 case series has been published, the strong signal of benefit of tumor necrosis inhibitors provides evidence that treatment with tumor necrosis inhibitors, instead of conventional immunosuppressive agents such as cyclophosphamide, prevents strokes (35,37). Thus, physicians should consider DADA2 in the setting of a PAN-like syndrome with

strokes, and if confirmed, we strongly recommend use of tumor necrosis factor inhibitors. The Voting Panel voted for a strong recommendation despite the small number of cases, stressing the prevention of severe adverse events.

DISCUSSION

This is the first guideline issued by the ACR, in conjunction with the VF, for the management of systemic PAN. These recommendations constitute a guide to help physicians treat patients with this disease. Because many recommendations are conditional, a patient's clinical condition, values, and preferences should influence the management decisions that are made. These recommendations should not be used by any agency to restrict access to therapy or require that certain therapies be utilized prior to other therapies.

Classic systemic PAN, although rare, remains a disease with a high mortality rate (22). Therefore, recommendations in this guideline indicate that patients with severe disease should be treated with cyclophosphamide and glucocorticoids. However, when patients present with nonsevere disease (i.e., without life- or organ-threatening manifestations such as renal insufficiency and tissue ischemia), use of alternative immunosuppressive agents and a glucocorticoid-sparing regimen is reasonable for remission induction. Use of diagnostic procedures such as angiography, electromyography/nerve conduction studies, and nerve and muscle biopsy is recommended to aid in diagnosis. However, the use of routinely repeated procedures during periods of disease quiescence is discouraged.

PAN has become increasingly rare, and no large clinical trials that focused solely on idiopathic (non–HBV-associated) PAN have been published. In addition, studies of PAN conducted prior to the recognition of microscopic polyangiitis may have included such patients and should be interpreted with caution. Many recommendations were based on expert experience of the Voting Panel and/or trials that were performed several years and, in some cases, decades ago. Strong recommendations will require larger interventional studies but will be challenging to conduct due to the rarity of this disease.

The process of developing these guidelines has brought to our attention other gaps in our understanding of the optimal treatment for PAN. These gaps include the role of longitudinal vascular imaging studies, the comparative effectiveness of nonglucocorticoid immunosuppressive agents, and the lack of biomarkers to inform disease activity or treatment response. Therefore, we encourage continued research in this disease. Future study and specific areas to investigate include the following: 1) determining how informative longitudinal vascular imaging is for assessing disease activity and determining disease prognosis; 2) conducting randomized clinical trials (including comparative efficacy trials) to assess the efficacy of nonglucocorticoid immunosuppressive agents, as well as identifying the optimal dosing, duration, and population that would benefit from these agents; 3) developing novel, targeted, and/or glucocorticoid-sparing therapies with minimal toxicity; and 4) identifying biomarkers to inform assessment of disease activity and prognosis.

In summary, the ACR and the VF present these recommendations to assist physicians in managing PAN, and this guideline can serve as a touchstone for basic principles of management. We hope this guideline will evolve as new research is conducted and new diagnostic and treatment strategies for PAN are identified.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Chung and Gorelik had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions, and drug formularies or other third-party analyses that cite ACR guidelines should state this. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

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Objective. To provide evidence-based recommendations and expert guidance for the management of giant cell arteritis (GCA) and Takayasu arteritis (TAK) as exemplars of large vessel vasculitis.

Methods. Clinical questions regarding diagnostic testing, treatment, and management were developed in the population, intervention, comparator, and outcome (PICO) format for GCA and TAK (27 for GCA, 27 for TAK). Systematic literature reviews were conducted for each PICO question. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to rate the quality of the evidence. Recommendations were developed by the Voting Panel, comprising adult and pediatric rheumatologists and patients. Each recommendation required ≥70% consensus among the Voting Panel.

Results. We present 22 recommendations and 2 ungraded position statements for GCA, and 20 recommendations and 1 ungraded position statement for TAK. These recommendations and statements address clinical questions relating to the use of diagnostic testing, including imaging, treatments, and surgical interventions in GCA and TAK. Recommendations for GCA include support for the use of glucocorticoid-sparing immunosuppressive agents and the use of imaging to identify large vessel involvement. Recommendations for TAK include the use of nonglucocorticoid immunosuppressive agents with glucocorticoids as initial therapy. There were only 2 strong recommendations; the remaining recommendations were conditional due to the low quality of evidence available for most PICO questions.

Conclusion. These recommendations provide guidance regarding the evaluation and management of patients with GCA and TAK, including diagnostic strategies, use of pharmacologic agents, and surgical interventions.

INTRODUCTION

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are systemic vasculitides that primarily affect large- and medium-sized vessels (1). GCA can present with both cranial and extracranial manifestations. Cranial manifestations include headaches, scalp tenderness, vision loss, and jaw claudication. Large vessel ("extracranial") involvement results in arterial stenosis and aneurysms, causing absent pulses and limb claudication (2). GCA is more common in individuals of Northern European descent who are older than 50 years of age. Diagnosis is based on clinical presentation, pathologic abnormalities on temporal artery biopsy, and/or evidence of large vessel involvement on vascular imaging (1–6). Glucocorticoids are the mainstay treatment for GCA, but tocilizumab has been approved by the US Food and Drug Administration for the treatment of GCA (7,8).

TAK causes granulomatous inflammation of the aorta and its branches. It is more common in younger women (9,10). Clinical manifestations include constitutional symptoms, elevated levels of inflammation markers, and arterial stenosis and/or aneurysms resulting in limb claudication and absent pulses (11). Treatment options include glucocorticoids, nonglucocorticoid immunosuppressive agents, and surgical management of vascular abnormalities (12).

As GCA and TAK share clinical manifestations, similar questions arise regarding their treatment and management. Recent studies have broadened treatment options for GCA, and vascular imaging is increasingly used for diagnosis and management. This guideline was developed to provide evidence-based recommendations for the evaluation and management of GCA and TAK.

METHODS

This guideline followed the American College of Rheumatology (ACR) guideline development process (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence and develop recommendations (13–15). ACR policy guided the management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Vasculitis). Supplementary Appendix 1 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24632/abstract) presents a detailed description of the methods. Briefly, the Literature Review team undertook systematic literature reviews for predetermined questions specifying the clinical population, intervention, comparator, and outcomes (PICO). An in-person Patient Panel of 11 individuals with different types of vasculitis (3 patients with GCA or TAK) was moderated by a member of the Literature Review team (ABD). This Patient Panel reviewed the evidence report (along with a summary and interpretation by the moderator) and provided patient perspectives and preferences about their personal experiences regarding clinical and treatment aspects of their disease. The Voting Panel comprised 9 adult rheumatologists, 5 pediatric rheumatologists, and 2 patients; they reviewed the Literature Review team's evidence summaries and, bearing in mind the Patient Panel's deliberations, formulated and voted on recommendations. A recommendation required ≥70% consensus among the Voting Panel.

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How to interpret the recommendations

A *strong* recommendation is typically supported by moderate- to high-quality evidence (e.g., multiple randomized controlled trials). For a strong recommendation, the recommended course of action would apply to all or almost all patients. Only a small proportion of clinicians/patients would not want to follow the recommendation. In rare instances, a strong recommendation may be based on very low– to low-certainty evidence. For example, an intervention may be strongly recommended if it is considered low-cost, without harms, and the consequence of not performing the intervention may be catastrophic. An intervention may be strongly recommended against if there is high certainty that the intervention will lead to more harm than the comparison with very low or low certainty about its benefit (16).

A *conditional* recommendation is generally supported by lower-quality evidence or a close balance between desirable and undesirable outcomes. For a conditional recommendation, the recommended course of action would apply to the majority of the patients, but the alternative is a reasonable consideration. Conditional recommendations always warrant a shared decision-making approach. We specify conditions under which the alternative may be considered.

In some instances, the committee found that the evidence for a particular PICO question did not support a graded recommendation or did not favor one intervention over another. However, the Voting Panel believed that the PICO question addressed a commonly encountered clinical question which has not been fully clarified and requires further investigation, and thus felt that providing guidance for this question was warranted. For these situations, we present "ungraded position statements," which reflect general views of the Voting Panel.

In this evidence-based guideline, we explicitly used the best evidence available and present that in a transparent manner for the clinician reader/user (10). In some instances, this includes randomized trials in which the interventions under consideration are directly compared. The GRADE system rates evidence that comes exclusively from the collective experience of the Voting Panel and Patient Panel members as "very low–quality" evidence (15).

For each recommendation, details regarding the PICO questions and the GRADE evidence tables can be found in Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24632/abstract).

RESULTS

For the GCA evidence report, 399 articles were reviewed to address 27 PICO questions. For the TAK evidence report, 347 articles were reviewed to address 27 PICO questions.

Table 1. Definitions of selected terms used in the recommendations and ungraded position statements for GCA and TAK*

Term	Definition
Disease states	
Suspected disease	Clinical signs and/or symptoms suggestive of GCA/TAK and not explained by other conditions
Active disease	New, persistent, or worsening clinical signs and/or symptoms attributed to GCA/TAK and not related to prior damage
Severe disease	Vasculitis with life- or organ-threatening manifestations (e.g., vision loss, cerebrovascular ischemia, cardiac ischemia, limb ischemia)
Nonsevere disease	Vasculitis without life- or organ-threatening manifestations (e.g., constitutional symptoms, headache, jaw claudication, symptoms of polymyalgia rheumatica)
Remission	Absence of clinical signs or symptoms attributed to active GCA/TAK, on or off immunosuppressive therapy
Refractory disease	Persistent active disease despite an appropriate course of immunosuppressive therapy
Relapse	Recurrence of active disease following a period of remission
Cranial ischemia	Visual and neurologic involvement including amaurosis fugax, vision loss, and stroke
Treatments	
IV pulse GCs	IV methylprednisolone 500–1,000 mg/day (adults) or 30 mg/kg/day (children; maximum 1,000 mg/day) or equivalent for 3–5 days
High-dose oral GCs	Prednisone 1 mg/kg/day up to 80 mg or equivalent
Moderate-dose oral GCs	Prednisone 0.5 mg/kg/day (generally 10–40 mg/day in adults) or equivalent
Low-dose oral GCs	Prednisone ≤10 mg/day or equivalent
Non-GC nonbiologic immunosuppressive therapy	Azathioprine, leflunomide, methotrexate, mycophenolate mofetil, cyclophosphamide
Biologics	Abatacept, tumor necrosis factor inhibitor, tocilizumab
Surgical intervention	Angioplasty, stent placement, vascular bypass, vascular graft
Disease assessments	
Clinical monitoring	Assessing for clinical signs and symptoms of active disease, obtaining 4 extremity blood pressures, and obtaining clinical laboratory results, including inflammation marker levels
Inflammation markers	Erythrocyte sedimentation rate, C-reactive protein level
Noninvasive imaging	Computed tomography angiogram, magnetic resonance angiogram, positron emission tomography scan, vascular ultrasound, magnetic resonance imaging of temporal and scalp arteries
Invasive imaging	Conventional catheter-based angiogram

* GCA = giant cell arteritis; TAK = Takayasu arteritis; IV = intravenous; GCs = glucocorticoids.

Recommendations and ungraded position statements for the management of GCA

Table 1 presents definitions of selected terms used in the recommendations, including disease states such as severe disease, dosing ranges for glucocorticoids, categorization of medications, and disease assessments. Tables 2 and 3 present the recommendations with their supporting PICO questions and levels of evidence. We present 22 recommendations and 2 ungraded position statements for GCA. All but 1 of the recommendations are conditional due to very low– to low-quality evidence. Figure 1 presents key recommendations for the treatment of GCA.

Diagnostic testing

Recommendation: For patients with suspected GCA, we conditionally recommend an initial unilateral temporal artery biopsy over bilateral biopsies.

Initially, a unilateral biopsy is recommended. However, bilateral temporal artery biopsies may be appropriate if the symptoms are not clearly localized to 1 temporal artery. Proceeding with the contralateral biopsy is also appropriate if the unilateral biopsy result is negative and additional evidence for cranial GCA is sought (17).

Recommendation: For patients with suspected GCA, we conditionally recommend a long-segment temporal artery biopsy specimen (>1 cm) over a short-segment temporal artery biopsy specimen (<1 cm).

A longer segment of the temporal artery is preferred, since GCA is a focal and segmental disease, and the added morbidity of obtaining a larger segment is very low. A shorter segment obtained on biopsy can result in reduced diagnostic yield and a missed diagnosis. This recommendation is conditional due to a lack of high-quality evidence, but the Voting Panel emphasized obtaining longer biopsy specimens when possible (18,19).

Recommendation: For patients with suspected GCA, we conditionally recommend obtaining a temporal artery biopsy specimen within 2 weeks of starting oral glucocorticoids over waiting longer than 2 weeks for a biopsy.

Overall, biopsy specimens should be obtained as soon as possible to maximize the likelihood of detecting histopathologic changes. Studies suggest that histopathologic changes indicating GCA are more likely to be detected in a temporal artery biopsy if obtained within 2 weeks of starting glucocorticoids; however, histopathologic changes have been detected in biopsy specimens obtained much later than 2 weeks after the start of glucocorticoid treatment (20–28). A biopsy specimen obtained 2 weeks after starting glucocorticoids could be informative and may be considered at the discretion of the physician and patient.

Recommendation: For patients with suspected GCA, we conditionally recommend temporal artery biopsy over temporal artery ultrasound for establishing a diagnosis of GCA.

In general, rheumatologists and radiologists in the US are less experienced in using ultrasound to diagnose temporal artery involvement in GCA compared to their counterparts in Europe. Therefore, temporal artery biopsy remains the optimal approach to diagnosing GCA in the US, because ultrasound is operator-dependent and results are influenced by treatment (i.e., signs of inflammation quickly disappear with glucocorticoid treatment). In centers with appropriate training and expertise in using temporal artery ultrasound, ultrasound may be a useful and complementary tool for diagnosing GCA (29–33).

Table 2. Recommendations for diagnostic testing in GCA*

Recommendation	GCA PICO question informing recommendation and discussion	Level of evidence
Recommendation: For patients with suspected GCA, we conditionally recommend an initial unilateral temporal artery biopsy over bilateral biopsies.	1	Low
Recommendation: For patients with suspected GCA, we conditionally recommend a long-segment temporal artery biopsy specimen (>1 cm) over a short-segment temporal artery biopsy specimen (<1 cm).	2	Low
Recommendation: For patients with suspected GCA, we conditionally recommend obtaining a temporal artery biopsy specimen within 2 weeks of starting oral GCs over waiting longer than 2 weeks for a biopsy.	3	Low
Recommendation: For patients with suspected GCA, we conditionally recommend temporal artery biopsy over temporal artery ultrasound for establishing a diagnosis of GCA.	4	Low
Recommendation: For patients with suspected GCA, we conditionally recommend temporal artery biopsy over MRI of the cranial arteries for establishing a diagnosis of GCA.	5	Low
Recommendation: For patients with suspected GCA and a negative temporal artery biopsy result (or results), we conditionally recommend noninvasive vascular imaging of the large vessels with clinical assessment to aid in diagnosis over clinical assessment alone.	6, 7	Very low to low
Recommendation: For patients with newly diagnosed GCA, we conditionally recommend obtaining noninvasive vascular imaging to evaluate large vessel involvement.	9	Very low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for giant cell arteritis (GCA), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24632/abstract). GCs = glucocorticoids; MRI = magnetic resonance imaging.

Table 3. Recommendations/statements for treatment (medical management and surgical intervention) and clinical/laboratory monitoring in GCA*

Recommendation/statement	GCA PICO question informing recommendation and discussion	Level of evidence
Medical management		
Recommendation: For patients with newly diagnosed GCA without manifestations of cranial ischemia, we conditionally recommend initiating treatment with high-dose oral GCs over IV pulse GCs.	11	Very low to low
Recommendation: For patients with newly diagnosed GCA with threatened vision loss, we conditionally recommend initiating treatment with IV pulse GCs over high-dose oral GCs.	12	Very low
Recommendation: For patients with newly diagnosed GCA, we conditionally recommend dosing oral GCs daily over an alternate-day schedule.	18	Low
Recommendation: For patients with newly diagnosed GCA, we conditionally recommend initiating treatment with high-dose oral GCs over moderate-dose oral GCs.	14	Very low to low
Recommendation: For patients with newly diagnosed GCA, we conditionally recommend the use of oral GCs with tocilizumab over oral GCs alone.	15, 16, 17	Low to high
Recommendation: For patients with GCA with active extracranial large vessel involvement, we conditionally recommend treatment with oral GCs combined with a non-GC immunosuppressive agent over oral GCs alone.	21	Very low to low
Ungraded position statement: The optimal duration of therapy with GCs for GCA is not well established and should be guided by the patient's values and preferences.	20	Low to moderate
Recommendation: In patients with newly diagnosed GCA, we conditionally recommend *against* the use of an HMG-CoA reductase inhibitor ("statin") specifically for the treatment of GCA.	19	Very low
Recommendation: For patients with GCA who have critical or flow-limiting involvement of the vertebral or carotid arteries, we conditionally recommend adding aspirin.	13	Very low to moderate
Recommendation: For patients with GCA who experience disease relapse while receiving moderate-to-high–dose GCs, we conditionally recommend adding a non-GC immunosuppressive drug.	Relapse 2	†
Recommendation: For patients with GCA who experience disease relapse with symptoms of cranial ischemia, we conditionally recommend adding a non-GC immunosuppressive agent and increasing the dose of GCs over increasing the dose of GCs alone.	Relapse 1, 3	†
Recommendation: For patients with GCA who experience disease relapse with symptoms of cranial ischemia while receiving GCs, we conditionally recommend adding tocilizumab and increasing the dose of GCs over adding methotrexate and increasing the dose of GCs.	Relapse 4	†
Surgical intervention		
Ungraded position statement: For any patient requiring surgical vascular intervention for GCA, the type and timing of intervention should be a collaborative decision between the vascular surgeon and rheumatologist.	‡	‡
Recommendation: For patients with severe GCA and worsening signs of limb/organ ischemia who are receiving immunosuppressive therapy, we conditionally recommend escalating immunosuppressive therapy over surgical intervention with escalation of immunosuppressive therapy.	24	Very low to low
Recommendation: For patients with GCA undergoing vascular surgical intervention, we conditionally recommend the use of high-dose GCs during the periprocedural period, if the patient has active disease.	27	Very low
Clinical/laboratory monitoring		
Recommendation: For patients with GCA in apparent clinical remission, we strongly recommend long-term clinical monitoring over no clinical monitoring.	10	Very low to low
Recommendation: For patients with GCA who have an increase in levels of inflammation markers alone, we conditionally recommend clinical observation and monitoring without escalation of immunosuppressive therapy.	23	Very low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for giant cell arteritis (GCA), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24632/abstract). GCs = glucocorticoids; IV = intravenous; HMG-CoA = hydroxymethylglutaryl-coenzyme A.
† PICO question was developed after completion of literature review and evidence reports. Data from studies already included in evidence reports were reviewed, but no dedicated literature review was performed for these questions. Recommendation was formed from available evidence and expert opinion.
‡ Ungraded position statement was not based on a specific PICO question.

Recommendation: For patients with suspected GCA, we conditionally recommend temporal artery biopsy over magnetic resonance imaging (MRI) of the cranial arteries for establishing a diagnosis of GCA.

Protocols to image the cranial vessels using different modalities, including MRI, have been developed, which can be helpful to establish a diagnosis of GCA (30,31,34–37). However, lack of technical expertise with this modality in the US, as well as the lack of widespread validation of this approach, limits the applicability of MRI with contrast of the cranial vessels as a replacement for temporal artery biopsy at the current time.

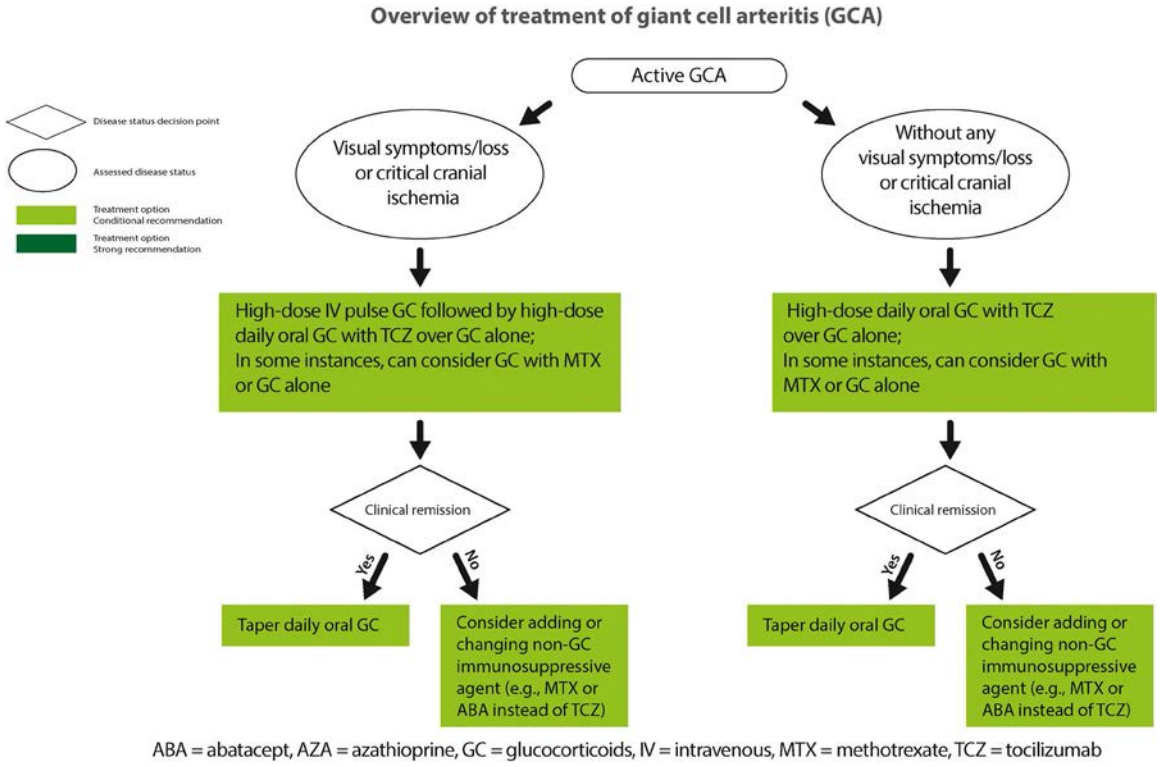

Figure 1. Overview of treatment of giant cell arteritis.

Recommendation: For patients with suspected GCA and a negative temporal artery biopsy result (or results), we conditionally recommend noninvasive vascular imaging of the large vessels with clinical assessment to aid in diagnosis over clinical assessment alone.

Imaging the large vessels may provide additional evidence of disease (e.g., extracranial GCA) when the diagnosis is uncertain following negative temporal artery biopsy results (28,34,38–44). Potential diagnostic imaging modalities include MR or computed tomography (CT) angiography of the neck/chest/abdomen/pelvis, ultrasonography, and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) (43,45).

Recommendation: For patients with newly diagnosed GCA, we conditionally recommend obtaining noninvasive vascular imaging to evaluate large vessel involvement.

Baseline noninvasive imaging with MR or CT angiography of the neck/chest/abdomen/pelvis in patients with newly diagnosed GCA can detect large vessel involvement and may be compared with subsequent routine monitoring if indicated (46). In a patient with large vessel involvement, routine noninvasive vascular imaging can identify early and long-term complications, such as aneurysms and stenoses, and assess stability of existing lesions. In patients without large vessel involvement, routine and repeated monitoring with vascular imaging may or may not be necessary.

Medical management

Recommendation: For patients with newly diagnosed GCA without manifestations of cranial ischemia, we conditionally recommend initiating treatment with high-dose oral glucocorticoids over intravenous (IV) pulse glucocorticoids.

Cranial ischemic manifestations include visual and neurologic involvement such as amaurosis fugax, vision loss, and stroke. Some studies have suggested that the use of IV pulse glucocorticoids in this patient group could decrease disease relapse and increase remission rates. However, routine use of IV pulse glucocorticoids can also be associated with increased risks, including infections, that may outweigh the benefits, especially in the elderly (47,48).

Recommendation: For patients with newly diagnosed GCA with threatened vision loss, we conditionally recommend initiating treatment with IV pulse glucocorticoids over high-dose oral glucocorticoids.

Studies investigating the effect of IV pulse glucocorticoids in patients with GCA and cranial ischemia have demonstrated conflicting results. However, this population is at high risk for vision loss as well as toxicity from glucocorticoid use. IV pulse glucocorticoids can be used in patients with the highest risk of vision loss, but this decision should be guided by the patient's clinical condition, values, and preferences (49,50).

Recommendation: For patients with newly diagnosed GCA, we conditionally recommend dosing oral glucocorticoids daily over an alternate-day schedule.

This recommendation is conditional solely due to the low level of evidence, which indicates higher remission rates in patients receiving daily dosing. The panel did not identify any situations in which alternate-day dosing of prednisone would be preferred (51).

Recommendation: For patients with newly diagnosed GCA, we conditionally recommend initiating treatment with high-dose oral glucocorticoids over moderate-dose oral glucocorticoids.

We recommend starting high-dose oral glucocorticoids to achieve rapid disease control followed by tapering the glucocorticoid dose (weeks to months) to avoid prolonged high-dose treatment and reduce toxicity. The dosing and duration of oral glucocorticoid therapy can be variable depending on a patient's manifestations and comorbidities and whether the use of a glucocorticoid-sparing agent was also initiated. Studies supporting the efficacy and lower toxicity of moderate-dose glucocorticoids are of low quality, which prevents the Voting Panel from recommending moderate-dose glucocorticoids as initial therapy. Moderate-dose glucocorticoids may be used in patients with significant risk of severe glucocorticoid toxicity and in patients with low risk of vision loss or other life- or organ-threatening complications (48–53).

Recommendation: For patients with newly diagnosed GCA, we conditionally recommend the use of oral glucocorticoids with tocilizumab over oral glucocorticoids alone.

A trial published in 2017 (8) demonstrated that tocilizumab has a significant glucocorticoid-sparing effect in GCA, and thus, tocilizumab should be considered for initial treatment. However, methotrexate with glucocorticoids, as well as glucocorticoids alone, can also be considered as initial treatment for newly diagnosed GCA. The decision to treat with tocilizumab and glucocorticoids, methotrexate and glucocorticoids, or glucocorticoid monotherapy for initial therapy should be made based on the physician's experience and the patient's clinical condition, values, and preferences. Lack of long-term follow-up data on tocilizumab and cost may limit its use (8,54). Abatacept with glucocorticoids can also be considered if these other agents are not effective (55).

Recommendation: For patients with GCA with active extracranial large vessel involvement, we conditionally recommend treatment with oral glucocorticoids combined with a nonglucocorticoid immunosuppressive agent over oral glucocorticoids alone.

Management of GCA in patients with new, persistent, or worsening extracranial symptoms (e.g., limb claudication) or signs (e.g., imaging findings) attributed to GCA can include the addition of nonglucocorticoid immunosuppressive agents. These agents include biologic agents (e.g., tocilizumab) as well as oral therapies (e.g., methotrexate) (56,57). However, the Voting Panel recognizes that there are few high-quality studies evaluating the efficacy of these agents for this patient group. While there is stronger clinical evidence supporting the use of tocilizumab compared to methotrexate for the treatment of GCA, methotrexate can be considered for patients unable to use tocilizumab due to factors such as recurrent infections, history of gastrointestinal perforations or diverticulitis, and cost.

Ungraded position statement: The optimal duration of therapy with glucocorticoids for GCA is not well established and should be guided by the patient's values and preferences.

Factors that may influence the duration of therapy include the patient's clinical manifestations, toxicity related to glucocorticoid use, number of flares, the physician's experience, and the patient's preferences (8). Overall, the Patient Panel emphasized minimizing the use of glucocorticoids as much as possible but recognized that longer-term use may be needed in some patients to avoid flares.

Recommendation: In patients with newly diagnosed GCA, we conditionally recommend *against* the use of a hydroxymethylglutaryl-coenzyme A reductase inhibitor ("statin") specifically for the treatment of GCA.

The use of statins is not known to provide a clinically significant immunosuppressive effect for GCA. Whether statins are warranted to decrease the patient's risk of cardiovascular events is a separate clinical question and depends on the patient's risk factors for cardiovascular disease (58–60).

Recommendation: For patients with GCA who have critical or flow-limiting involvement of the vertebral or carotid arteries, we conditionally recommend adding aspirin.

There are few data regarding this clinical question, but the antiplatelet activity of aspirin may be beneficial in preventing ischemic events in patients with vascular narrowing causing decreased cerebral blood flow (61–64). The efficacy of aspirin to prevent ischemic events in patients without vertebral or carotid narrowing remains unclear at this time.

Recommendation: For patients with GCA who experience disease relapse while receiving moderate-to-high–dose glucocorticoids, we conditionally recommend adding a nonglucocorticoid immunosuppressive drug.

Relapses of any type while receiving moderate-to-high–dose glucocorticoids indicate that it is unlikely that it will be possible for glucocorticoids to be tapered to a low dose. Therefore, glucocorticoid-sparing therapy should be considered.

Recommendation: For patients with GCA who experience disease relapse with symptoms of cranial ischemia, we conditionally recommend adding a nonglucocorticoid immunosuppressive agent and increasing the dose of glucocorticoids over increasing the dose of glucocorticoids alone.

Nonglucocorticoid immunosuppressive agents considered in this situation include tocilizumab and methotrexate (8,65,66). Relapses with symptoms of polymyalgia rheumatica may be controlled by increasing the dose of glucocorticoids alone.

Recommendation: For patients with GCA who experience disease relapse with cranial symptoms while receiving glucocorticoids, we conditionally recommend adding tocilizumab and increasing the dose of glucocorticoids over adding methotrexate and increasing the dose of glucocorticoids.

Tocilizumab is an effective glucocorticoid-sparing agent for GCA (8,54). While there are no comparative studies, the glucocorticoid-sparing effect seen with methotrexate is smaller than the effect seen with tocilizumab (8,55,65–67). While the glucocorticoid-sparing effect of tocilizumab is best quantified using the subcutaneous formulation (8), IV tocilizumab has also been shown to be glucocorticoid-sparing (54). Again, methotrexate can be considered for patients who are unable to tolerate or have limited access to tocilizumab.

Surgical intervention

Ungraded position statement: For any patient requiring surgical vascular intervention for GCA, the type and timing of intervention should be a collaborative decision between the vascular surgeon and rheumatologist.

Recommendation: For patients with severe GCA and worsening signs of limb/organ ischemia who are receiving immunosuppressive therapy, we conditionally recommend escalating immunosuppressive therapy over surgical intervention with escalation of immunosuppressive therapy.

Because patients can develop collateral blood vessels to improve distal blood flow, immunosuppressive therapy is recommended as initial therapy in patients with GCA and worsening limb/organ ischemia. However, clinical situations that would warrant consideration of immediate surgical intervention include aortic aneurysms at high risk for rupture and impending/progressive tissue or organ infarction or damage (68–70).

Recommendation: For patients with GCA undergoing vascular surgical intervention, we conditionally recommend the use of high-dose glucocorticoids during the periprocedural period, if the patient has active disease.

This recommendation pertains to patients with GCA who are undergoing a vascular surgical intervention due to a complication of GCA (e.g., aneurysm or stenosis). There are limited data regarding the use of high-dose glucocorticoids during the periprocedural period in GCA, and thus, support for this recommendation is based in part on their use in TAK. As in TAK, high doses of oral glucocorticoids in the perioperative setting are recommended if the disease is active or if the clinician is concerned that the patient may have active disease.

Clinical/laboratory monitoring

Recommendation: For patients with GCA in apparent clinical remission, we strongly recommend long-term clinical monitoring over no clinical monitoring.

The optimal frequency and length of monitoring are not well established and depend on factors including the duration of remission, site of involvement, risk of disease progression, whether the patient is receiving immunosuppressive therapy, and reliability of the patient to report new signs or symptoms (48,69). Clinical monitoring may include history taking, examinations, and laboratory and imaging studies. This is a strong recommendation given the minimal risks and potential catastrophic outcomes if monitoring is not performed.

Recommendation: For patients with GCA who have an increase in levels of inflammation markers alone, we conditionally recommend clinical observation and monitoring without escalation of immunosuppressive therapy.

Increases in levels of inflammation markers such as erythrocyte sedimentation rate and C-reactive protein can be nonspecific (69). Therefore, increasing immunosuppressive therapy is not warranted in the setting of increased levels of inflammation markers in the absence of other signs of disease activity. However, these increased levels may warrant more frequent clinical and/or radiographic assessments for active disease.

Recommendations and ungraded position statement for the management of TAK

Table 1 presents definitions of selected terms used in the recommendations, and Tables 4 and 5 present the recommendations with their supporting PICO questions and levels of evidence. We present 20 recommendations and 1 ungraded position statement for TAK. All recommendations except for 1 are conditional due to the availability of only very low– to low-quality evidence. Figure 2 presents key recommendations for the treatment of TAK.

Medical management

Recommendation: For patients with active, severe TAK who are not receiving immunosuppressive therapy, we conditionally recommend initiating treatment with high-dose oral glucocorticoids over IV pulse glucocorticoids followed by high-dose oral glucocorticoids.

There is no evidence that IV pulse glucocorticoids are more effective than high-dose oral glucocorticoids in this setting.

IV pulse glucocorticoids may be considered for patients with life- or organ-threatening disease. In children, alternate steroid dosing regimens (e.g., IV pulse glucocorticoids with low daily oral dosing) may be preferred to improve compliance and potentially reduce adverse consequences such as impacting growth (71).

Recommendation: For patients with newly active, severe TAK, we conditionally recommend initiating treatment with high-dose glucocorticoids over low-dose glucocorticoids.

A higher dose of glucocorticoids is recommended due to the potential for organ damage or life-threatening events. However, lower doses of glucocorticoids may be considered for patients with newly active, nonsevere disease (e.g., patients with constitutional symptoms and without limb ischemia) (72).

Recommendation: For patients with TAK who achieved remission while receiving glucocorticoids for ≥6–12 months, we conditionally recommend tapering off glucocorticoids over long-term treatment with low-dose glucocorticoids for remission maintenance.

The optimal duration of glucocorticoid use in TAK is unknown. Glucocorticoid exposure should be limited if possible in order to minimize toxicity. Glucocorticoids may be continued for a longer duration if disease is not adequately controlled or if the patient experiences frequent disease relapse.

Table 4. Recommendations/statement for treatment (medical management and surgical intervention) in TAK*

Recommendation/statement	TAK PICO question informing recommendation and discussion	Level of evidence
Medical management		
Recommendation: For patients with active, severe TAK who are not receiving immunosuppressive therapy, we conditionally recommend initiating treatment with high-dose oral GCs over IV pulse GCs followed by high-dose oral GCs.	6	Very low
Recommendation: For patients with newly active, severe TAK, we conditionally recommend initiating treatment with high-dose GCs over low-dose GCs.	5	Very low to low
Recommendation: For patients with TAK who achieved remission while receiving GCs for ≥6–12 months, we conditionally recommend tapering off GCs over long-term treatment with low-dose GCs for remission maintenance.	15	Very low
Recommendation: For patients with active TAK, we conditionally recommend the use of a non-GC immunosuppressive agent plus GCs over GCs alone.	7, 8, 9	Low
Recommendation: For patients with active TAK, we conditionally recommend the use of other non-GC immunosuppressive therapy over tocilizumab as initial therapy.	8, 10, 11, 12	Very low to low
Recommendation: For patients with TAK that is refractory to treatment with GCs alone, we conditionally recommend adding a tumor necrosis factor inhibitor over adding tocilizumab.	14	Very low
Recommendation: For patients with TAK and asymptomatic progression of a previously identified vascular lesion seen on imaging, without evidence of inflammation, we conditionally recommend continuing current therapy over escalating/changing immunosuppressive therapy.	16	Very low
Recommendation: For patients with active TAK and critical cranial or vertebrobasilar involvement, we conditionally recommend adding aspirin or another antiplatelet therapy.	13	Low
Surgical intervention		
Ungraded position statement: For any patient requiring surgical vascular intervention, the type and timing of intervention should be a collaborative decision between the vascular surgeon and rheumatologist.	†	†
Recommendation: In patients with known TAK and persistent limb claudication without evidence of ongoing active disease, we conditionally recommend *against* surgical intervention.	20	Very low to low
Recommendation: For patients with known TAK with worsening signs of limb/organ ischemia while receiving immunosuppressive therapy, we conditionally recommend escalating immunosuppressive therapy over surgical intervention with escalation of immunosuppressive therapy.	21, 24	Very low
Recommendation: For patients with TAK with renovascular hypertension and renal artery stenosis, we conditionally recommend medical management over surgical intervention.	26	Very low to low
Recommendation: For patients with TAK and stenosis of a cranial/cervical vessel without clinical symptoms, we conditionally recommend medical management over surgical intervention.	22	Very low to low
Recommendation: For patients with TAK with worsening signs of limb/organ ischemia, we conditionally recommend delaying surgical intervention until the disease is quiescent over performing surgical intervention while the patient has active disease.	23	Very low to low
Recommendation: For patients with TAK who are undergoing surgical intervention, we conditionally recommend the use of high-dose GCs in the periprocedure period if the patient has active disease.	25	Very low to low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for Takayasu arteritis (TAK), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24632/abstract). GCs = glucocorticoids; IV = intravenous.
† Ungraded position statement was not based on a specific PICO question.

Table 5. Recommendations for clinical/laboratory monitoring and vascular imaging in TAK*

Recommendation	TAK PICO question informing recommendation and discussion	Level of evidence
Clinical/laboratory monitoring		
Recommendation: For patients with TAK, we conditionally recommend adding inflammation markers to clinical monitoring as a disease activity assessment tool.	2	Very low to low
Recommendation: For patients with TAK in apparent clinical remission, we strongly recommend long-term clinical monitoring over no clinical monitoring.	4	Very low
Recommendation: For patients with TAK in apparent clinical remission but with an increase in levels of inflammation markers, we conditionally recommend clinical observation without escalation of immunosuppressive therapy.	19	Very low
Vascular imaging		
Recommendation: For patients with TAK, we conditionally recommend the use of noninvasive imaging over catheter-based dye angiography as a disease activity assessment tool.	1	Low
Recommendation: For patients with known TAK, we conditionally recommend regularly scheduled noninvasive imaging in addition to routine clinical assessment.	3	Very low to low
Recommendation: For patients with TAK in apparent clinical remission but with signs of inflammation in new vascular territories (e.g., new stenosis or vessel wall thickening) on vascular imaging, we conditionally recommend treatment with immunosuppressive therapy.	17, 18	Very low to low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for Takayasu arteritis (TAK), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24632/abstract).

Recommendation: For patients with active TAK, we conditionally recommend the use of a nonglucocorticoid immunosuppressive agent plus glucocorticoids over glucocorticoids alone.

Nonglucocorticoid immunosuppressive agents are recommended over monotherapy with glucocorticoids to minimize glucocorticoid-related toxicity. Methotrexate is often used as the initial nonglucocorticoid immunosuppressive agent, but other therapies such as tumor necrosis factor inhibitors and azathioprine can be considered as well (70–73). Methotrexate is often preferred for use in children since it is usually well tolerated. Glucocorticoid monotherapy can be considered for mild disease or if the diagnosis is uncertain.

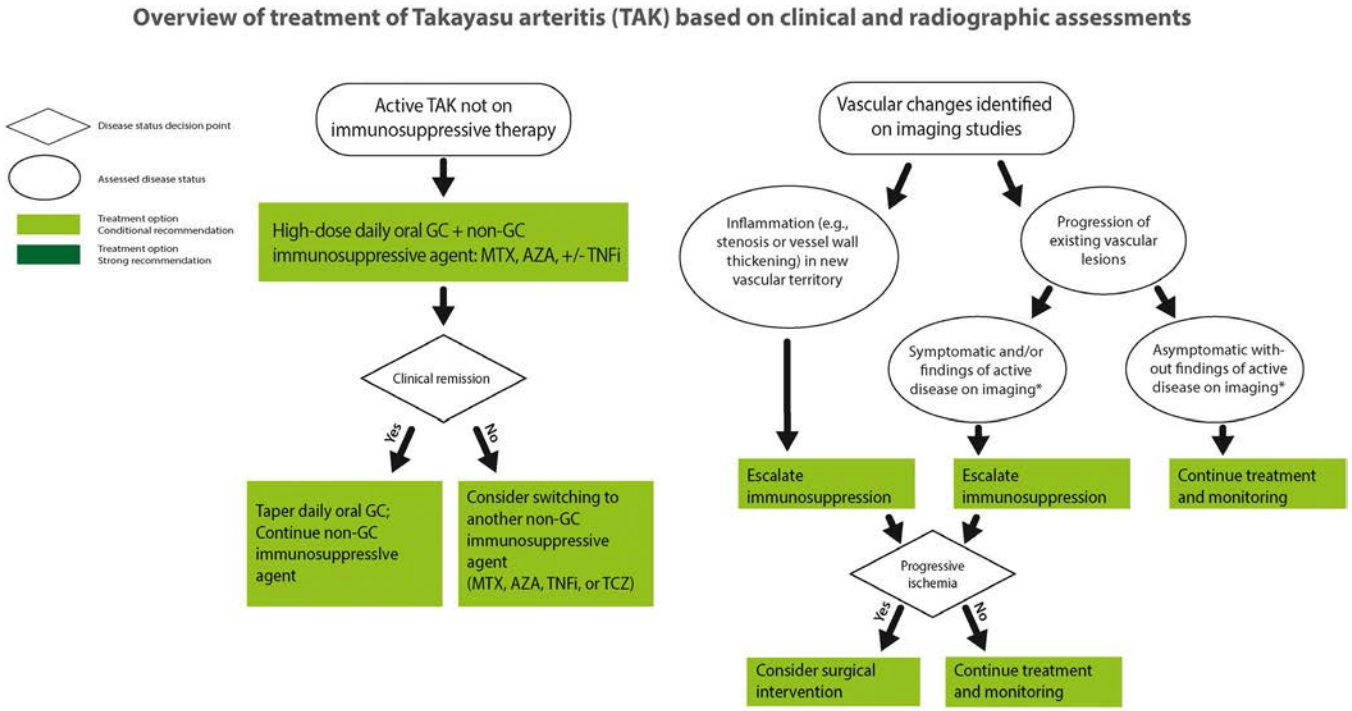

Figure 2. Overview of treatment of Takayasu arteritis based on clinical and radiographic assessments.

Patient-specific factors such as alcohol use, plans for childbearing, medication compliance, and medical comorbidities may influence the choice of immunosuppressant (73,74).

Recommendation: For patients with active TAK, we conditionally recommend the use of other nonglucocorticoid immunosuppressive therapy over tocilizumab as initial therapy.

As discussed above, nonglucocorticoid immunosuppressive agents such as methorexate, tumor necrosis factor inhibitors, and azathioprine can be used as initial therapy in TAK. We recommend these agents over tocilizumab for initial therapy, because the efficacy of tocilizumab in TAK is not established at this time. While tocilizumab has been shown to be efficacious for GCA, the primary efficacy end point was not achieved in the only randomized trial of tocilizumab in TAK conducted thus far (74,75). Tocilizumab may be considered for patients with inadequate response to other immunosuppressive therapies. Abatacept is not recommended, since it has been shown in a small randomized controlled trial to not be efficacious in TAK (74,76).

Recommendation: For patients with TAK that is refractory to treatment with glucocorticoids alone, we conditionally recommend adding a tumor necrosis factor inhibitor over adding tocilizumab.

We recognize that among biologic therapies, some practitioners favor TNF inhibition, while others favor interleukin-6 inhibition (tocilizumab) in this situation. Overall, the Voting Panel favored tumor necrosis factor inhibitors over tocilizumab, since there is more clinical experience with and data on tumor necrosis factor inhibitors in TAK compared to tocilizumab. In observational studies, tumor necrosis factor inhibitors have been shown to induce remission and decrease relapses (77–79). Clinical experience with tocilizumab in TAK has been demonstrated in a randomized controlled trial and small case series. In the randomized trial, a trend toward a longer time to relapse was seen in the tocilizumab arm, but the difference was not statistically significant. However, that study was felt to be underpowered (36 participants). Of note, tocilizumab use also affects acute-phase reactants, which may impact ability to gauge disease activity. Therefore, while the panel favors tumor necrosis factor inhibitor use, we recognize that tocilizumab may also be considered, especially when tumor necrosis factor inhibitors are contraindicated (75).

Recommendation: For patients with TAK and asymptomatic progression of a previously identified vascular lesion seen on imaging, without evidence of inflammation, we conditionally recommend continuing current therapy over escalating/changing immunosuppressive therapy.

Vascular lesions can progress due to a number of factors that may not be related to active disease, such as "healing fibrosis" in response to effective treatment. Intervention is not always needed, since collateral circulation frequently develops over time. However, the location and the extent of the lesion of the affected vessel should be considered. Escalating immunosuppressive therapy may be warranted if significant progression has developed rapidly (e.g., weeks to months) after a period of stable disease (80,81).

Recommendation: For patients with active TAK and critical cranial or vertebrobasilar involvement, we conditionally recommend adding aspirin or another antiplatelet therapy.

Small observational studies suggest a decreased risk of ischemic events with antiplatelet therapy but an increased risk of bleeding (82). Therefore, antiplatelet therapy is usually used for patients at higher risk of ischemic events (e.g., patients with flow-limiting vertebrobasilar disease or stents). Antiplatelet therapy should be used with caution after surgical procedures or if there is an increased risk of bleeding (81).

Clinical/laboratory monitoring

Recommendation: For patients with TAK, we conditionally recommend adding inflammation markers to clinical monitoring as a disease activity assessment tool.

While inflammation markers are an imperfect indicator of disease activity, they may be helpful for clinical monitoring (80,83).

Recommendation: For patients with TAK in apparent clinical remission, we strongly recommend long-term clinical monitoring over no clinical monitoring.

The frequency of monitoring depends on factors including the duration of remission, sites of involvement, risk of disease progression, the patient's immunosuppressive regimen, and the ability and likelihood of the patient reliably reporting new signs or symptoms of TAK. This is a strong recommendation given the minimal risks and potential catastrophic outcomes without monitoring (80,83).

Recommendation: For patients with TAK in apparent clinical remission but with an increase in levels of inflammation markers, we conditionally recommend clinical observation without escalation of immunosuppressive therapy.

As discussed above in the GCA recommendations, increases in levels of inflammation markers can be nonspecific, and intensifying immunosuppressive therapy in the setting of increased inflammation markers alone may not be warranted. More frequent clinical and/or radiographic assessments for active disease can be considered (77,80,83).

Vascular imaging

Recommendation: For patients with TAK, we conditionally recommend the use of noninvasive imaging over catheter-based dye angiography as a disease activity assessment tool.

Noninvasive imaging such as CT angiography, MR angiography, or FDG-PET are recommended because these imaging modalities provide information regarding vascular wall inflammation, while catheter-based angiography primarily provides information regarding the vascular lumen. Catheter-based angiography can be used to accurately determine central blood pressures, as part of surgical planning, or if noninvasive modalities do not provide adequate information. Identifying active disease based on noninvasive imaging at this time can be challenging, since the hallmarks of active disease have not been definitively established (43,45,84).

Recommendation: For patients with known TAK, we conditionally recommend regularly scheduled noninvasive imaging in addition to routine clinical assessment.

Routine imaging is recommended since vascular changes in TAK can occur when the disease is considered clinically quiescent. The optimal interval between imaging studies is not well established, and ranges vary (e.g., every 3–6 months or longer). The interval may be shorter early in the disease course and longer with established, quiescent disease. Since sedation may be required for imaging studies in children and can be associated with potential risks and complications, routine imaging of inactive disease in children is at the discretion of the treating clinician, while considering risks and benefits (85,86).

Recommendation: For patients with TAK in apparent clinical remission but with signs of inflammation in new vascular territories (e.g., new stenosis or vessel wall thickening) on vascular imaging, we conditionally recommend treatment with immunosuppressive therapy.

A new arterial stenosis is concerning as it can indicate recent active disease, and thus usually warrants immunosuppressive therapy. Other findings suggestive of active disease on MR angiography or CT angiography include vascular edema, contrast enhancement, and increased wall thickness, and may result in luminal damage over time. Findings of active disease by FDG-PET are defined by supraphysiologic FDG uptake in the arterial wall. However, abnormal findings in the vascular wall identified by imaging are not necessarily specific to vascular inflammation. The implication of finding vessel wall edema or enhancement on imaging remains an area of investigation, and the clinical importance of such findings on CT angiography, MR angiography, or FDG-PET is not certain (43,45,80,83–86). Therefore, all therapeutic decision-making in this context should occur after reviewing the imaging findings with a radiologist to help determine whether the observed imaging changes represent active disease.

Surgical intervention

Ungraded position statement: For any patient requiring surgical vascular intervention, the type and timing of intervention should be a collaborative decision between the vascular surgeon and rheumatologist.

Recommendation: In patients with known TAK and persistent limb claudication without evidence of ongoing active disease, we conditionally recommend *against* surgical intervention.

Patients with TAK can develop collateral circulation that bypasses the stenosis causing limb claudication, and thus, surgical intervention may not be needed (87). However, surgical intervention can be considered for patients whose activities are significantly impacted by limb claudication.

Recommendation: For patients with known TAK with worsening signs of limb/organ ischemia while receiving immunosuppressive therapy, we conditionally recommend escalating immunosuppressive therapy over surgical intervention with escalation of immunosuppressive therapy.

Immunosuppressive therapy is recommended to control vascular inflammation in order to improve or prevent worsening blood flow. However, clinical situations that could warrant immediate surgical intervention include coronary artery involvement and impending/progressive tissue or organ infarction (88–90).

Recommendation: For patients with TAK with renovascular hypertension and renal artery stenosis, we conditionally recommend medical management over surgical intervention.

Medical management includes antihypertensive drugs and immunosuppressive therapy if TAK is active. Surgical intervention (including catheter-based interventions) may be warranted for hypertension that is refractory to medical management in spite of optimized immunosuppressive therapy or in the setting of worsening renal function (12,91–94).

Recommendation: For patients with TAK and stenosis of a cranial/cervical vessel without clinical symptoms, we conditionally recommend medical management over surgical intervention.

Medical therapy is recommended if only a single vessel is involved, due to the substantial risks of surgery. Surgical interventions can be considered if multiple vessels are involved. This recommendation is based on indirect evidence obtained from neurologic experience and studies, because there is no direct evidence for TAK (90,95–98).

Recommendation: For patients with TAK with worsening signs of limb/organ ischemia, we conditionally recommend delaying surgical intervention until the disease is quiescent over performing surgical intervention while the patient has active disease.

Observational studies have suggested improved outcomes if surgical intervention is performed when disease is not active. However, surgical intervention during active disease may be necessary if the patient has life- or organ-threatening manifestations such as stroke, loss of viability of a limb, or myocardial ischemia (99–101). We recognize that determining the level of disease activity in TAK can be challenging.

Recommendation: For patients with TAK who are undergoing surgical intervention, we conditionally recommend the use of high-dose glucocorticoids in the periprocedure period if the patient has active disease.

This recommendation pertains to patients with TAK who are undergoing a vascular surgical intervention due to a complication of TAK. High doses of oral glucocorticoids in the perioperative setting are recommended if the disease is active or if the clinician is concerned that the patient may have active disease (90,96,102).

DISCUSSION

This guideline presents the ACR/Vasculitis Foundation recommendations for the use of diagnostic testing, treatment, clinical and laboratory monitoring, and surgical intervention for patients with GCA or TAK. Overarching themes of the recommendations include the preference, in the US, for temporal artery biopsy over cranial imaging studies for the diagnosis of GCA, the use of large vessel imaging for GCA and TAK for diagnosis and disease monitoring, and limiting glucocorticoid exposure in order to minimize toxicity. Almost all recommendations are conditional due to low-quality evidence, reflecting the paucity of randomized clinical trials in these diseases.

Our recommendations regarding the use of temporal artery imaging differ from those presented by the European Alliance of Associations for Rheumatology (EULAR). In its recommendations regarding the use of imaging in large vessel vasculitis, EULAR indicates that the diagnosis of GCA may be made with a positive imaging test (e.g., temporal artery ultrasound or MRI of the cranial vessels), without additional testing such as temporal artery biopsy (103). However, the imaging recommendations presented by EULAR assume adequate expertise with these modalities. In the US, there is limited experience with temporal artery ultrasound and MRI of the cranial vessels as a diagnostic replacement for temporal artery biopsy, and thus, we continue to recommend temporal artery biopsy as the diagnostic test of choice at this time. However, we hope and anticipate that as experience with imaging of the temporal arteries to detect GCA (e.g., temporal artery ultrasound, MRI, and/or FDG-PET) increases in the US, patients will be able to benefit from these diagnostic tests. Also, in contrast to EULAR, we favor initial treatment of GCA with glucocorticoids and a glucocorticoid-sparing agent, given the well-recognized toxicity of glucocorticoids (104,105).

When reviewing the data abstracted for the PICO questions, it was clear that many critical clinical questions remain unanswered for GCA and TAK, and the lack of sufficient clinical evidence for these questions is reflected in the ungraded position statements presented in this guideline. For example, the optimal duration of therapy for any treatment and how best to monitor disease status is unknown. Few glucocorticoid-sparing agents have been identified through high-quality data. Accurate and validated indicators of disease activity have not been established or widely used for GCA or TAK. Interpretation of imaging studies in GCA and TAK can be challenging, and the clinical significance of persistent vascular wall inflammation during clinically quiescent disease is unclear.

Given these critical gaps in knowledge, we encourage additional research into the management of GCA and TAK. Studies that may greatly benefit patient care include the following: 1) translational studies contributing to the understanding of disease pathogenesis to facilitate development of more targeted therapies; 2) randomized clinical trials identifying new therapeutic options for the management of GCA and TAK; 3) randomized clinical trials comparing the effectiveness of currently used immunosuppressive therapies; and 4) longitudinal studies with biospecimen collection and routine vascular imaging to identify biomarkers of disease activity, indicators of disease prognosis, and the clinical sequelae of abnormalities identified on vascular imaging. We are hopeful that additional investigations into GCA and TAK will enable a more tailored approach to disease management in order to improve outcomes and minimize treatment toxicities.

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AUTHOR CONTRIBUTIONS

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2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

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Objective. To provide evidence-based recommendations and expert guidance for the management of antineutrophil cytoplasmic antibody–associated vasculitis (AAV), including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).

Methods. Clinical questions regarding the treatment and management of AAV were developed in the population, intervention, comparator, and outcome (PICO) format (47 for GPA/MPA, 34 for EGPA). Systematic literature reviews were conducted for each PICO question. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to assess the quality of evidence and formulate recommendations. Each recommendation required ≥70% consensus among the Voting Panel.

Results. We present 26 recommendations and 5 ungraded position statements for GPA/MPA, and 15 recommendations and 5 ungraded position statements for EGPA. This guideline provides recommendations for remission induction and maintenance therapy as well as adjunctive treatment strategies in GPA, MPA, and EGPA. These recommendations include the use of rituximab for remission induction and maintenance in severe GPA and MPA and the use of mepolizumab in nonsevere EGPA. All recommendations are conditional due in part to the lack of multiple randomized controlled trials and/or low-quality evidence supporting the recommendations.

Conclusion. This guideline presents the first recommendations endorsed by the American College of Rheumatology and the Vasculitis Foundation for the management of AAV and provides guidance to health care professionals on how to treat these diseases.

INTRODUCTION

The antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV) comprise granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). These diseases affect small- and medium-sized vessels and are characterized by multisystem organ involvement.

GPA is characterized histologically by necrotizing granulomatous inflammation in addition to vasculitis. Common clinical manifestations include destructive sinonasal lesions, pulmonary nodules, and pauci-immune glomerulonephritis. GPA is most commonly associated with cytoplasmic ANCA and antibodies to proteinase 3 (PR3). Among European populations, prevalence ranges from 24 to 157 cases per million, with the highest prevalence reported in Sweden and the UK (1).

MPA is characterized histologically by vasculitis without granulomatous inflammation. Common clinical manifestations include rapidly progressive pauci-immune glomerulonephritis and alveolar hemorrhage. MPA is most commonly associated with perinuclear ANCA and antibodies to myeloperoxidase. The prevalence of MPA ranges from 0 to 66 cases per million among European countries and 86 cases per million in Japan (1,2).

EGPA is characterized histologically by eosinophilic tissue infiltration in addition to vasculitis. Common clinical manifestations include asthma, peripheral eosinophilia, and peripheral neuropathy. Only 40% of patients produce detectable ANCA. The overall prevalence of EGPA in European populations has been estimated to range from 2 to 38 cases per million (1,3).

Prior to the use of alkylating agents, survival with these diseases was quite poor (e.g., median survival of patients with GPA was ~5 months) (4). Current treatment regimens have reversed this poor prognosis, but treatments are still associated with toxicity. Recent clinical trials have investigated the efficacy and toxicity of both biologic and nonbiologic immunosuppressive agents for the treatment of AAV. Observational studies have provided additional insight regarding management strategies for these diseases. Therefore, this guideline was developed to provide evidence-based recommendations for the treatment and management of GPA, MPA, and EGPA. Although this guideline may inform an international audience, these recommendations were developed considering the experience with and availability of treatment and diagnostic options in the US.

METHODS

This guideline followed the American College of Rheumatology (ACR) guideline development process (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence and develop recommendations (5,6). ACR policy guided the management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Vasculitis). Supplementary Appendix 1 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract) presents a detailed description of the methods. Briefly, the Literature Review team undertook systematic literature reviews for predetermined questions addressing specific clinical populations, interventions,

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comparators, and outcomes (PICO). An in-person Patient Panel of 11 individuals with different types of vasculitis (4 patients with GPA, 1 patient with MPA, and 2 patients with EGPA) was moderated by a member of the Literature Review team (ABD). This Patient Panel reviewed the evidence report (along with a summary and interpretation by the moderator) and provided patient perspectives and preferences. The Voting Panel comprised 9 adult rheumatologists, 5 pediatric rheumatologists, and 2 patients; they reviewed the Literature Review team's evidence summaries and, bearing in mind the Patient Panel's deliberations, formulated and voted on recommendations.

The Voting Panel was assembled for the ACR and Vasculitis Foundation's broad effort to develop recommendations for 7 forms of systemic vasculitis: giant cell arteritis, Takayasu arteritis, polyarteritis nodosa, Kawasaki syndrome, and the 3 AAVs presented in this report. The physicians on this panel included rheumatologists who could provide insight on all of these diseases and did not include other subspecialists who would not have experience with many of the other vasculitides addressed in this effort (e.g., pulmonologists who would not have experience with large- or medium-sized vessel vasculitis). The Literature Review team chair was a nephrologist. The patients on the Voting Panel presented the views of the Patient Panel, which consisted of patients with different types of vasculitis. A recommendation required ≥70% consensus among the Voting Panel.

How to interpret the recommendations

A *strong* recommendation is usually supported by moderate- to high-quality evidence (e.g., multiple randomized controlled trials). For a strong recommendation, the recommended course of action would apply to all or almost all patients. Only a small proportion of clinicians/patients would not want to follow the recommendation. In rare instances, a strong recommendation may be based on very low– to low-certainty evidence. For example, an intervention may be strongly recommended if it is considered benign, low-cost, without harms, and the consequence of not performing the intervention may be catastrophic. An intervention may be strongly recommended against if there is high certainty that the intervention leads to more harm than the comparison with very low or low certainty about its benefit (7).

Table 1. Definitions of selected terms used in the recommendations and ungraded position statements for GPA, MPA, and EGPA*

Term	Definition
Disease states	
Active disease	New, persistent, or worsening clinical signs and/or symptoms attributed to GPA, MPA, or EGPA and not related to prior damage
Severe disease	Vasculitis with life- or organ-threatening manifestations (e.g., alveolar hemorrhage, glomerulonephritis, central nervous system vasculitis, mononeuritis multiplex, cardiac involvement, mesenteric ischemia, limb/digit ischemia)
Nonsevere disease	Vasculitis without life- or organ-threatening manifestations (e.g., rhinosinusitis, asthma, mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis)
Remission	Absence of clinical signs or symptoms attributed to GPA, MPA, or EGPA, on or off immunosuppressive therapy
Refractory disease	Persistent active disease despite an appropriate course of immunosuppressive therapy
Relapse	Recurrence of active disease following a period of remission
Treatments	
IV pulse GCs	IV methylprednisolone 500–1,000 mg/day (adults) or 30 mg/kg/day (children; maximum 1,000 mg/day) or equivalent for 3–5 days
High-dose oral GCs	Prednisone 1 mg/kg/day (adults; generally up to 80 mg/day) or 1–2 mg/kg/day (children; generally up to 60 mg/day) or equivalent
Remission induction therapy	
Methotrexate	Up to 25 mg/week (SC or oral)
Azathioprine	Up to 2 mg/kg/day
Mycophenolate mofetil	Up to 1,500 mg (oral) twice per day
Cyclophosphamide	Up to 2 mg/kg/day (oral) for 3–6 months; or intermittent 15 mg/kg (IV) every 2 weeks for 3 doses, followed by 15 mg/kg (IV) every 3 weeks for at least 3 doses (adults)
Rituximab	375 mg/m^2 (IV) weekly for 4 doses or 1,000 mg on days 1 and 15 (adults); or 375 mg/m^2 (IV) weekly for 4 doses or 575 mg/m^2 for patients with body surface area ≤1.5m^2 or 750 mg/m^2 for patients with body surface area >1.5m^2 with a typical maximum of 1 gm per infusion (both for 2 doses, days 1 and 15) (children)
Mepolizumab	300 mg (SC) every 4 weeks (adults)
Remission maintenance therapy	
Methotrexate, azathioprine, mycophenolate mofetil	Same dosing regimen as in remission induction therapy
Rituximab	500 mg (IV) every 6 months or 1 gm (IV) every 4 months (adults), 250 mg/m^2 (IV) every 6 months (children), or other doses
Mepolizumab	300 mg (SC) every 4 weeks
Omalizumab	300–600 mg (SC) every 2–4 weeks

* GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; EGPA = eosinophilic granulomatosis with polyangiitis; IV = intravenous; GCs = glucocorticoids; SC = subcutaneous.

A *conditional* recommendation is usually supported by lower-quality evidence or a close balance between desirable and undesirable outcomes. For a conditional recommendation, the recommended course of action would apply to the majority of the patients, but the alternative is a reasonable consideration. Conditional recommendations always warrant a shared decision-making approach. We specify some conditions under which the alternative may be considered.

In some instances, the committee found that the evidence for a particular PICO question did not support a graded recommendation or did not favor one intervention over the other. However, the Voting Panel believed that the PICO question addressed a commonly encountered clinical question and thus felt that providing guidance for this question was warranted. For these situations, we present "ungraded position statements," which reflect general views of the Voting Panel.

In this evidence-based guideline, we explicitly used the best evidence available and present it for the clinician and reader (8). In some instances, this includes randomized trials in which the interventions under consideration are directly compared. The GRADE system rates evidence that comes exclusively from the collective experience of the Voting Panel and Patient Panel members as "very low quality" evidence (6).

For each recommendation, details regarding the PICO questions and the GRADE evidence tables can be found in Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract).

RESULTS

For the evidence report for GPA and MPA, the Literature Review team reviewed 729 articles to address 47 PICO questions. For the evidence report for EGPA, 190 articles were reviewed to address 34 PICO questions.

Recommendations and ungraded position statements for GPA and MPA

GPA and MPA are recognized as different diseases for which disease-specific management approaches exist. However, many recommendations and ungraded position statements consider GPA and MPA together, because pivotal trials have enrolled both groups and presented results for these diseases together. Therefore, we present recommendations and ungraded position statements applicable to both GPA and MPA as well as recommendations and ungraded position statements only applicable to GPA. All recommendations for GPA/MPA are conditional, due in part to a lack of multiple randomized controlled trials supporting the recommendations. The complete list of studies reviewed to form the recommendations is provided in the evidence report (Supplementary Appendix 2, http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract). Given that these diseases affect multiple organ systems, collaboration between rheumatologists, nephrologists, pulmonologists, and otolaryngologists can enhance the care of patients with GPA and MPA.

Table 1 presents the definitions of selected terms used in the recommendations and ungraded position statements, including the definition of severe and nonsevere disease and the dosing regimens of medications used for remission induction and maintenance. Table 2 presents the recommendations and ungraded position statements with their supporting PICO questions and levels of evidence. Figure 1 presents key recommendations for the treatment of GPA and MPA.

Remission induction for active, severe disease

Recommendation: For patients with active, severe GPA/MPA, we conditionally recommend treatment with rituximab over cyclophosphamide for remission induction.

Both rituximab and cyclophosphamide, in combination with glucocorticoids, have been used for remission induction in GPA and MPA. Rituximab has been shown to provide similar benefits to cyclophosphamide for remission induction in a randomized controlled trial (9). Although the currently used cumulative doses of cyclophosphamide are lower than previous regimens and result in less toxicity per treatment course, rituximab is still preferred, since rituximab is considered less toxic than cyclophosphamide. A single course of cyclophosphamide can carry substantial risks such as neutropenia, bladder injury, and the small but present potential for infertility which can be devastating to a young patient. Risks of malignancy and infertility increase when repeated courses of cyclophosphamide are used. Rituximab was also preferred by the Patient Panel, as a generally better-tolerated treatment. Retrospective studies suggest that the 2 remission induction regimens for rituximab used in adults (375 mg/m^2 every week for 4 weeks [US Food and Drug Administration (FDA)–approved dosing schedule] and 1,000 mg on days 1 and 15) are equally efficacious. The choice between these regimens should be guided by the patient's preferences and values.

Cyclophosphamide (dosing provided in Table 1) may be used when rituximab needs to be avoided or when patients have active disease despite receiving rituximab treatment. It remains controversial whether cyclophosphamide should be preferred for certain types of severe disease, such as acute renal failure (e.g., serum creatinine >4.0 mg/dl). Either intravenous (IV) pulse or daily oral cyclophosphamide can be used (10,11). For adults, the decision between these 2 options should be based on patient and physician preferences. In children, IV cyclophosphamide may be preferred to facilitate compliance and limit toxicity. Data regarding the efficacy of combined cyclophosphamide and rituximab therapy for remission induction remain limited (12), and potential toxicity of this combination remains a concern. The combination of rituximab with cyclophosphamide is not widely used in the US, and its efficacy compared to rituximab

Table 2. Recommendations/statements for the management of GPA and MPA*

Recommendation/statement	PICO question informing recommendation and discussion	Level of evidence
Remission induction for active, severe disease		
Recommendation: For patients with active, severe GPA/MPA, we conditionally recommend treatment with rituximab over cyclophosphamide for remission induction.	4, 5, 6	Very low to moderate
Recommendation: In patients with GPA/MPA with active glomerulonephritis, we conditionally recommend *against* the routine addition of plasma exchange to remission induction therapy.	34	Low to high
Recommendation: In patients with active, severe GPA/MPA with alveolar hemorrhage, we conditionally recommend *against* adding plasma exchange to remission induction therapies.	35	Low to high
Ungraded position statement: For patients with active, severe GPA/MPA, either IV pulse GCs or high-dose oral GCs may be prescribed as part of initial therapy.	2	Very low to moderate
Recommendation: In patients with active, severe GPA/MPA, we conditionally recommend a reduced-dose GC regimen over a standard-dose GC regimen for remission induction.	3	Very low to moderate
Remission induction for active, nonsevere disease		
Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate over cyclophosphamide or rituximab.	12, 13	Very low to moderate
Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate and GCs over GCs alone.	14	Low
Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate and GCs over azathioprine and GCs or mycophenolate mofetil and GCs.	8, 9, 10	Low
Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate and GCs over trimethoprim/sulfamethoxazole and GCs.	11	Low
Remission maintenance		
Recommendation: For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with rituximab over methotrexate or azathioprine for remission maintenance.	15, 16, 17, 18	Very low to moderate
Recommendation: For patients with GPA/MPA who are receiving rituximab for remission maintenance, we conditionally recommend scheduled re-dosing over using ANCA titers or CD19+ B cell counts to guide re-dosing.	24, 25	Very low to low
Recommendation: For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with methotrexate or azathioprine over mycophenolate mofetil for remission maintenance.	19	Very low to moderate
Recommendation: For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with methotrexate or azathioprine over leflunomide for remission maintenance.	20	Very low to low
Recommendation: For patients with GPA whose disease has entered remission, we conditionally recommend treatment with methotrexate or azathioprine over trimethoprim/sulfamethoxazole for remission maintenance.	21, 22	Very low to low
Recommendation: In patients with GPA whose disease has entered remission, we conditionally recommend *against* adding trimethoprim/sulfamethoxazole to other therapies (e.g., rituximab, azathioprine, methotrexate, etc.) for the purpose of remission maintenance.	23	Low to moderate
Recommendation: For patients with GPA/MPA receiving remission maintenance therapy with rituximab who have hypogammaglobulinemia (e.g., IgG <3 gm/liter) and recurrent severe infections, we conditionally recommend immunoglobulin supplementation.	44	Very low
Ungraded position statement: The duration of non-GC remission maintenance therapy in GPA/MPA should be guided by the patient's clinical condition, preferences, and values.	26	Low to moderate
Ungraded position statement: The duration of GC therapy for GPA/MPA should be guided by the patient's clinical condition, preferences, and values.	27, 33	Low to moderate
Treatment of disease relapse		
Recommendation: For patients with GPA/MPA who have experienced relapse with severe disease manifestations and are not receiving rituximab for remission maintenance, we conditionally recommend treatment with rituximab over cyclophosphamide for remission re-induction.	28	Low
Recommendation: For patients with GPA/MPA who experienced relapse with severe disease manifestations while receiving rituximab for remission maintenance, we conditionally recommend switching from rituximab to cyclophosphamide over receiving additional rituximab for remission re-induction.	29	Very low
Treatment of refractory disease		
Recommendation: For patients with severe GPA/MPA that is refractory to treatment with rituximab or cyclophosphamide for remission induction, we conditionally recommend switching treatment to the other therapy over combining the 2 therapies.	30	Very low
Recommendation: For patients with GPA/MPA that is refractory to remission induction therapy, we conditionally recommend adding IVIG to current therapy.	31	Low to moderate

(Continued)

Table 2. *(Cont'd)*

Recommendation/statement	PICO question informing recommendation and discussion	Level of evidence
Treatment of sinonasal, airway, and mass lesions		
Ungraded position statement: For patients with sinonasal involvement in GPA, nasal rinses and topical nasal therapies (antibiotics, lubricants, and GCs) may be beneficial.	36, 37, 38, 39	Very low to low
Recommendation: For patients with GPA in remission who have nasal septal defects and/or nasal bridge collapse, we conditionally recommend reconstructive surgery, if desired by the patient.	45	Low
Recommendation: For patients with GPA and actively inflamed subglottic and/or endobronchial tissue with stenosis, we conditionally recommend treating with immunosuppressive therapy over surgical dilation with intralesional GC injection alone.	40	Low
Recommendation: For patients with GPA and mass lesions (e.g., orbital pseudotumor or masses of the parotid glands, brain, or lungs), we conditionally recommend treatment with immunosuppressive therapy over surgical removal of the mass lesion with immunosuppressive therapy.	41, 42	Very low to low
Other considerations		
Recommendation: In patients with GPA/MPA, we conditionally recommend *against* dosing immunosuppressive therapy based on ANCA titer results alone.	1	Very low
Recommendation: For patients with GPA who are receiving rituximab or cyclophosphamide, we conditionally recommend prophylaxis to prevent *Pneumocystis jirovecii* pneumonia.	43	Low
Recommendation: For patients with GPA/MPA in remission and stage 5 chronic kidney disease, we conditionally recommend evaluation for renal transplantation.	46	Low
Recommendation: For patients with active GPA/MPA who are unable to receive other immunomodulatory therapy, we conditionally recommend administering IVIG.	32	Low
Ungraded position statement: The optimal duration of anticoagulation is unknown for patients with GPA/MPA who experience venous thrombotic events.	47	Very low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract). IV = intravenous; GCs = glucocorticoids; ANCA = antineutrophil cytoplasmic antibody; IVIG = IV immunoglobulin.

or cyclophosphamide monotherapy is not established. This combination remains under study (ClinicalTrials.gov identifier: NCT03942887) at this time.

Recommendation: In patients with GPA/MPA with active glomerulonephritis, we conditionally recommend *against* the routine addition of plasma exchange to remission induction therapy.

Plasma exchange should not be initiated in all patients with active glomerulonephritis but can be considered for patients at higher risk of progression to end-stage renal disease (ESRD) who accept a potential increased risk of infection.

This recommendation is supported by data from the 2 largest trials of plasma exchange for the treatment of glomerulonephritis in AAV. The first trial, which required a serum creatinine level of ≥5.8 mg/dl for entry, showed that plasma exchange decreased the risk of ESRD but did not decrease mortality (13,14). In a more recent randomized trial of plasma exchange in AAV, the addition of plasma exchange to conventional remission induction therapy did not improve the composite outcome of ESRD or death; a decrease in the risk of ESRD was observed, but the result was not statistically significant (hazard ratio 0.81 [95% confidence interval (95% CI) 0.57–1.13]) (15).

However, combined data from these 2 trials show that there is probably a decreased risk of ESRD in patients with glomerulonephritis who received plasma exchange, compared to those who did not (hazard ratio 0.72 [95% CI 0.53–0.98]; moderate certainty) (Supplementary Appendix 2, http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract). The benefit was most pronounced in patients with the highest risk of ESRD (118 fewer cases of ESRD per 1,000 cases of active glomerulonephritis [95% CI between 217 and 7 fewer cases]), although no difference in mortality was demonstrated (risk ratio 1.15 [95% CI 0.78–1.70]; moderate certainty). In 4 trials of plasma exchange in AAV, a higher risk of severe infection was observed with plasma exchange (risk ratio 1.19 [95% CI 0.99–1.42]; moderate certainty).

These findings suggest that for patients with a low risk of progression to ESRD, the risk of plasma exchange may outweigh the benefit; however, in patients with a higher risk of progression to ESRD, the decrease in risk could outweigh the increased risk of serious infection with plasma exchange. Therefore, the Voting Panel does not recommend plasma exchange for all patients with active glomerulonephritis but favors consideration of the treatment for patients at a higher risk of progression to ESRD. Factors that could influence whether plasma exchange is initiated include the patient's kidney function upon presentation, rate of loss of kidney function, response to remission induction therapies, and the patient's ability to tolerate serious infections.

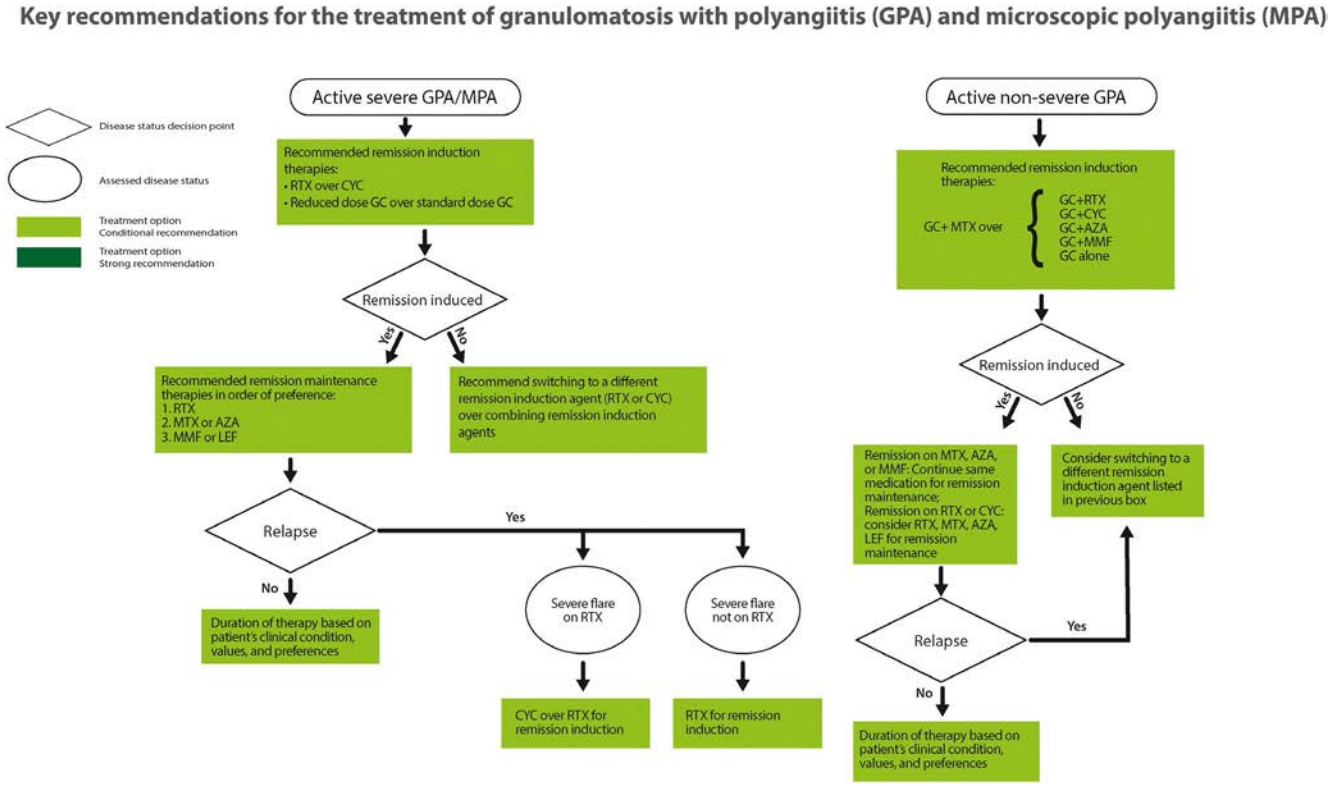

Figure 1. Key recommendations for the treatment of granulomatosis with polyangiitis and microscopic polyangiitis.

Plasma exchange remains advisable in patients with GPA or MPA who also have anti–glomerular basement membrane disease.

Recommendation: In patients with active, severe GPA/MPA with alveolar hemorrhage, we conditionally recommend *against* adding plasma exchange to remission induction therapies.

Two trials evaluated the use of plasma exchange in patients presenting with alveolar hemorrhage, and no differences in mortality or remission rates were observed. Thus, plasma exchange does not have an established benefit for patients with alveolar hemorrhage and is associated with an increased risk of serious infection (see above recommendation). Plasma exchange may be considered for certain patients with active glomerulonephritis or those who are critically ill and whose disease is not responding to recommended remission induction therapies (i.e., plasma exchange as "salvage" or "rescue" therapy).

Plasma exchange remains advisable in patients with GPA or MPA who also have anti–glomerular basement membrane disease.

Ungraded position statement: For patients with active, severe GPA/MPA, either IV pulse glucocorticoids or high-dose oral glucocorticoids may be prescribed as part of initial therapy.

There are no trials comparing the efficacy of IV pulse glucocorticoids to high-dose oral glucocorticoids. Higher doses of glucocorticoids (such as pulse glucocorticoids) are generally administered to patients with organ- or life-threatening disease manifestations but may be associated with an increased risk of infection (16).

Recommendation: For patients with active, severe GPA/MPA, we conditionally recommend a reduced-dose glucocorticoid regimen over a standard-dose glucocorticoid regimen for remission induction.

A recent study demonstrated that a reduced-dose glucocorticoid regimen provided a similar benefit compared to a standard-dose regimen for the composite outcome of ESRD or death, and was associated with a decreased risk of infection (15). Due to the known toxicities associated with long-term glucocorticoid use, minimizing glucocorticoid exposure is critical to improving outcomes. Glucocorticoid dosing may be individualized for each patient. Of note, the reduced-dose regimen started with pulse methylprednisolone (3 daily pulses for maximum total dose of 3 gm) and 1 week of high-dose oral glucocorticoids. The dosing regimens used in this study are described in Supplementary Appendix 3 (http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract).

Remission induction for active, nonsevere disease

Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate over cyclophosphamide or rituximab.

Nonsevere GPA is defined as GPA without life- or organ-threatening manifestations (Table 1). Methotrexate, rituximab, and cyclophosphamide are effective at inducing remission in this patient

group (11). However, like severe GPA, nonsevere GPA can be a chronic disease that requires multiple courses of therapy. Thus, the Voting Panel favored using therapies with potentially less toxicity before utilizing therapies with potentially more toxicity. Therefore, methotrexate is preferred due to the greater toxicity of cyclophosphamide. Methotrexate is currently recommended over rituximab because of the larger body of evidence and clinical experience with methotrexate treatment for this patient group; clinical trials are needed to compare their efficacy. Rituximab may be preferred in specific clinical situations, including for patients with hepatic or renal dysfunction, recurrent relapses while receiving methotrexate, or concerns regarding compliance.

Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate and glucocorticoids over glucocorticoids alone.

Methotrexate with glucocorticoids is recommended to minimize glucocorticoid exposure and toxicity. Overall, there are few clinical situations in which treatment with glucocorticoid monotherapy may be considered (e.g., arthralgias or inability to tolerate other remission maintenance therapies), and close monitoring is needed if this treatment strategy is used.

Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate and glucocorticoids over azathioprine and glucocorticoids or mycophenolate mofetil and glucocorticoids.

The use of methotrexate for remission induction in this patient group is supported by more available data than other treatments (11), but azathioprine and mycophenolate mofetil can be considered. Comparative effectiveness trials are needed to evaluate the efficacy of methotrexate, azathioprine, and mycophenolate mofetil for remission induction in active, nonsevere GPA. Clinical factors may influence the medication selected. For example, methotrexate should be used with caution or avoided in patients with moderate-to-severe renal insufficiency. Azathioprine is the preferred agent for pregnant patients or in patients who cannot tolerate methotrexate or mycophenolate mofetil, while methotrexate or mycophenolate mofetil is indicated in patients with total thiopurine S-methyltransferase deficiency or high-risk *TPMT* and/or *NUDT15* genotypes.

Recommendation: For patients with active, nonsevere GPA, we conditionally recommend initiating treatment with methotrexate and glucocorticoids over trimethoprim/sulfamethoxazole and glucocorticoids.

Methotrexate is considered more effective than trimethoprim/sulfamethoxazole for remission induction, based on previous findings (17). Low-dose trimethoprim/sulfamethoxazole may be administered concurrently with immunosuppressive agents to prevent *Pneumocystis jirovecii* pneumonia (see GPA/MPA recommendation on this topic).

Remission maintenance

Recommendation: For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with rituximab over methotrexate or azathioprine for remission maintenance.

Rituximab is associated with a lower relapse rate than azathioprine when used for remission maintenance after remission induction with cyclophosphamide (18). Methotrexate and azathioprine have comparable efficacy rates for remission maintenance (19). Therefore, rituximab is favored over methotrexate or azathioprine. However, more long-term safety data are available for methotrexate and azathioprine, and cost and other factors may limit rituximab use.

Different doses of rituximab have been used for remission maintenance, including IV 500 mg every 6 months (18) (FDA-approved), IV 1,000 mg every 4 months (20), and IV 1,000 mg every 6 months (21). No comparative trials have been conducted. Thus, the optimal dose of rituximab for remission maintenance remains uncertain.

If methotrexate or azathioprine treatment is being considered for remission maintenance, the patient's clinical situation, preferences, and values should guide selection between them, given their comparable efficacy.

Recommendation: For patients with GPA/MPA who are receiving rituximab for remission maintenance, we conditionally recommend scheduled re-dosing over using ANCA titers or CD19+ B cell counts to guide re-dosing.

In one randomized trial, patients who received rituximab for remission maintenance based on changes in CD19+ B cell counts and/or ANCA titers had similar rates of relapse as those receiving rituximab as a scheduled dose. However, this study was limited by the small sample size, and there were wide CIs for the effect size (22). This recommendation is based in part on the experience and expertise of the Voting Panel, which recognized that flares can occur when patients experience CD19+ B cell depletion and/or when test results for ANCA are negative. Thus, CD19+ B cell counts or ANCA titers may not accurately indicate the potential for a patient's disease to flare.

Recommendation: For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with methotrexate or azathioprine over mycophenolate mofetil for remission maintenance.

Methotrexate and azathioprine are equally efficacious for remission maintenance (19). Azathioprine is favored over mycophenolate mofetil because the relapse rate with mycophenolate mofetil was higher than with azathioprine when studied with remission maintenance (23). Mycophenolate mofetil may still be considered for those unable to tolerate or with contraindications to methotrexate, azathioprine, or rituximab.

Recommendation: For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with methotrexate or azathioprine over leflunomide for remission maintenance.

Methotrexate or azathioprine treatment is recommended over leflunomide due to the data supporting and clinical experience using methotrexate and azathioprine for remission maintenance. The data and clinical experience with leflunomide are more limited. In one clinical trial comparing leflunomide to methotrexate treatment, leflunomide treatment demonstrated a decreased rate of relapse but a higher rate of drug withdrawal (24). The trial used a leflunomide dose of 30 mg/day, which may have contributed to toxicity.

Recommendation: For patients with GPA whose disease has entered remission, we conditionally recommend treatment with methotrexate or azathioprine over trimethoprim/sulfamethoxazole for remission maintenance.

The Voting Panel strongly favored the use of methotrexate or azathioprine over trimethoprim/sulfamethoxazole, but this recommendation is conditional due to the lack of sufficient high-quality evidence comparing the 2 treatments.

Recommendation: In patients with GPA whose disease has entered remission, we conditionally recommend *against* adding trimethoprim/sulfamethoxazole to other therapies (e.g., rituximab, azathioprine, methotrexate, etc.) for the purpose of remission maintenance.

Trimethoprim/sulfamethoxazole may have benefit for patients with sinonasal involvement (25), but its use potentially increases toxicity (e.g., severe hypersensitivity reactions) and medication burden. Trimethoprim/sulfamethoxazole may still be indicated for prophylaxis against *P jirovecii* pneumonia (see GPA/MPA recommendation on this topic). There is a potential drug interaction between methotrexate and trimethoprim/sulfamethoxazole when trimethoprim/sulfamethoxazole is dosed at 800 mg/160 mg twice a day. The trimethoprim/sulfamethoxazole dose used for *Pneumocystis* prophylaxis is generally tolerated, but its use should be monitored when used in conjunction with methotrexate.

Recommendation: For patients with GPA/MPA receiving remission maintenance therapy with rituximab who have hypogammaglobulinemia (e.g., IgG <3 gm/liter) and recurrent severe infections, we conditionally recommend immunoglobulin supplementation.

Immunoglobulin supplementation at replacement doses (e.g., 400–800 mg/kg/month) should be considered if a patient has hypogammaglobulinemia and is experiencing recurrent infections. Immunoglobulin supplementation can also be considered for patients with hypogammaglobulinemia without recurrent infections but with impaired vaccine responses (26). These considerations should be made in collaboration with an allergist/immunologist.

Ungraded position statement: The duration of nonglucocorticoid remission maintenance therapy in GPA/MPA should be guided by the patient's clinical condition, preferences, and values.

The optimal duration of remission maintenance therapy is not well established. Although clinical trials have typically administered remission maintenance therapy for ≥18 months, patients may benefit from continuing remission maintenance therapy for a longer duration (27). The Patient Panel favored remission maintenance therapy for ≥18 months and potentially longer depending on patient-specific factors. Factors to be considered include previous relapse history, extent of organ involvement, and disease characteristics such as ANCA status (with PR3-ANCA–positive patients more likely to experience disease relapse [28]).

Ungraded position statement: The duration of glucocorticoid therapy for GPA/MPA should be guided by the patient's clinical condition, preferences, and values.

The optimal duration of glucocorticoid therapy for GPA/MPA is not well established. The immunosuppressive effects of glucocorticoids contributing to disease control should be balanced with the toxicities associated with its use. Overall, patients expressed a desire to minimize the glucocorticoid dose as much as possible but recognized that some patients may require low-dose glucocorticoids long-term to maintain disease quiescence. Screening for toxicities of glucocorticoid use (e.g., bone mineral density testing for osteoporosis) should be conducted.

Treatment of disease relapse

Recommendation: For patients with GPA/MPA who have experienced relapse with severe disease manifestations and are not receiving rituximab for remission maintenance, we conditionally recommend treatment with rituximab over cyclophosphamide for remission re-induction.

Rituximab is more effective than oral cyclophosphamide for re-induction of remission among patients who previously received cyclophosphamide and then experienced relapse, based on subgroup analysis of a randomized controlled trial (9). In addition, the cumulative toxicity of cyclophosphamide raises concerns over repeated use of this agent.

Recommendation: For patients with GPA/MPA who experienced relapse with severe disease manifestations while receiving rituximab for remission maintenance, we conditionally recommend switching from rituximab to cyclophosphamide over receiving additional rituximab for remission re-induction.

Multiple factors can influence whether rituximab or cyclophosphamide treatment (IV or oral) is used, such as time since last rituximab infusion and cumulative cyclophosphamide dose. Cyclophosphamide is recommended if the patient recently received rituximab, while a remission induction dose of rituximab may be

effective if an extended period has passed since the last rituximab infusion. As is standard for remission induction, these agents should be used in conjunction with glucocorticoids.

Treatment of refractory disease

Recommendation: For patients with severe GPA/MPA that is refractory to treatment with rituximab or cyclophosphamide for remission induction, we conditionally recommend switching treatment to the other therapy over combining the 2 therapies.

Disease refractory to remission induction therapy is rare, and there are limited data to guide treatment recommendations. Practitioners should evaluate whether other conditions such as infection could be mimicking vasculitis. However, if a patient's disease is refractory to one remission induction therapy, it is important to change the remission induction strategy. We recommend switching to the other remission induction agent prior to using combination therapy.

Recommendation: For patients with GPA/MPA that is refractory to remission induction therapy, we conditionally recommend adding IV immunoglobulin (IVIG) to current therapy.

IVIG should not be used routinely to treat GPA/MPA but can be considered at certain treatment doses (e.g., 2 gm/kg) as adjunctive therapy for short-term control, while waiting for remission induction therapy (i.e., rituximab or cyclophosphamide) to become effective (see above recommendation) (29).

Treatment of sinonasal, airway, and mass lesions

Ungraded position statement: For patients with sinonasal involvement in GPA, nasal rinses and topical nasal therapies (antibiotics, lubricants, and glucocorticoids) may be beneficial.

We suggest collaborating with an otolaryngologist with expertise in treating GPA to determine whether these interventions should be used.

Recommendation: For patients with GPA in remission who have nasal septal defects and/or nasal bridge collapse, we conditionally recommend reconstructive surgery, if desired by the patient.

To optimize surgical outcomes, reconstructive surgery should be performed, after a period of sustained remission, by an otolaryngologist with expertise in treating GPA (30,31).

Recommendation: For patients with GPA and actively inflamed subglottic and/or endobronchial tissue with stenosis, we conditionally recommend treating with immunosuppressive therapy over surgical dilation with intralesional glucocorticoid injection alone.

Subglottic or endobronchial stenoses should be managed by an otolaryngologist or pulmonologist, respectively, with expertise in management of these lesions. Immunosuppressive therapy is recommended for initial treatment of active inflammatory stenoses and usually comprises glucocorticoids and other agents (32); the degree of immunosuppressive therapy utilized may be based on the severity of other disease manifestations. Surgical dilation with intralesional glucocorticoid injection may be more appropriate for stenoses that are longstanding, fibrotic, or unresponsive to immunosuppression (32–34). Surgical dilation with intralesional glucocorticoid injection concurrent with medical treatment may also be considered as initial therapy for stenoses that require immediate intervention (e.g., critical narrowing).

Recommendation: For patients with GPA and mass lesions (e.g., orbital pseudotumor or masses of the parotid glands, brain, or lungs), we conditionally recommend treatment with immunosuppressive therapy over surgical removal of the mass lesion with immunosuppressive therapy.

Immunosuppressive therapy (with remission induction followed by remission maintenance) is almost always the initial treatment of choice for mass lesions (35,36). While these lesions tend to respond primarily to glucocorticoids, other agents are also usually used in hopes of having a glucocorticoid-sparing effect. Debulking surgery may be considered if there is an urgent need for decompression, such as acute visual loss due to optic nerve compression, or other life- or organ-threatening compression.

Other considerations

Recommendation: In patients with GPA/MPA, we conditionally recommend *against* dosing immunosuppressive therapy based on ANCA titer results alone.

Increases in ANCA titers/levels are only modestly informative as an indicator of disease activity (37) and are not reliable predictors of disease flares for individual patients. Increasing immunosuppressive therapy based on changes in ANCA titers/levels alone can result in unnecessary immunosuppression resulting in adverse events. Persistence of ANCA positivity does not necessarily indicate that continued immunosuppressive therapy is required. Instead, treatment decisions should be based on a patient's clinical symptoms in conjunction with diagnostic studies (e.g., laboratory, imaging, and biopsy findings).

Recommendation: For patients with GPA/MPA who are receiving rituximab or cyclophosphamide, we conditionally recommend prophylaxis to prevent *P jirovecii* pneumonia.

Prophylaxis to prevent *P jirovecii* pneumonia is routinely used with cyclophosphamide treatment (38). The prescribing information for rituximab recommends prophylaxis for *P jirovecii* pneumonia for ≥6 months after the last rituximab dose for patients with GPA or MPA. While many on the Voting Panel felt strongly that patients with GPA/MPA receiving cyclophosphamide or rituximab should receive prophylaxis against *P jirovecii* pneumonia, this recommendation is conditional given the lack of moderate-

Table 3. Recommendations/statements for the management of EGPA*

Recommendation/statement	PICO question informing recommendation and discussion	Level of evidence
Remission induction for active, severe disease		
Ungraded position statement: For patients with active, severe EGPA, either IV pulse GCs or high-dose oral GCs may be prescribed as initial therapy.	3	Very low
Ungraded position statement: For patients with active, severe EGPA, either cyclophosphamide or rituximab may be prescribed for remission induction.	4	Very low
Recommendation: For patients with active, severe EGPA, we conditionally recommend treatment with cyclophosphamide or rituximab over mepolizumab for remission induction.	6, 7	Low
Remission induction for active, nonsevere disease		
Recommendation: For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with mepolizumab and GCs over methotrexate, azathioprine, or mycophenolate mofetil and GCs.	8, 9, 10, 13	Very low to low
Recommendation: For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with methotrexate, azathioprine, or mycophenolate mofetil and GCs over GCs alone.	14	Low
Recommendation: For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with methotrexate, azathioprine, or mycophenolate mofetil and GCs over cyclophosphamide or rituximab and GCs.	11, 12	Very low to low
Remission maintenance		
Recommendation: For patients with severe EGPA whose disease has entered remission with cyclophosphamide therapy, we conditionally recommend treatment with methotrexate, azathioprine, or mycophenolate mofetil over rituximab for remission maintenance.	15, 16, 17,18	Very low
Recommendation: For patients with severe EGPA whose disease has entered remission, we conditionally recommend treatment with methotrexate, azathioprine, or mycophenolate mofetil over mepolizumab for remission maintenance.	20	Very low
Ungraded position statement: The duration of GC therapy in EGPA should be guided by the patient's clinical condition, values, and preferences.	21, 22, 23, 29, 30	Very low to low
Treatment of relapse		
Recommendation: For patients with EGPA who have experienced relapse with severe disease manifestations after prior successful remission induction with cyclophosphamide, we conditionally recommend treatment with rituximab over cyclophosphamide for remission re-induction.	25	Very low
Recommendation: For patients with EGPA who have experienced relapse with severe disease manifestations after prior successful remission induction with rituximab, we conditionally recommend treatment with rituximab over switching to cyclophosphamide for remission re-induction.	25	Very low
Recommendation: For patients with EGPA who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil, we conditionally recommend adding mepolizumab over switching to another agent.	26	Very low
Recommendation: For patients with EGPA who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving low-dose GCs and no other therapy, we conditionally recommend adding mepolizumab over adding methotrexate, azathioprine, or mycophenolate mofetil.	28	Very low
Recommendation: For patients with EGPA and high serum IgE levels who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil, we conditionally recommend adding mepolizumab over adding omalizumab.	27	Very low
Other considerations		
Recommendation: For patients with newly diagnosed EGPA receiving leukotriene inhibitors, we conditionally recommend continuing leukotriene inhibitors over discontinuing them.	33	Very low
Ungraded position statement: Use of leukotriene inhibitors is not contraindicated for patients with EGPA with active asthma and/or sinonasal disease.	34	Very low
Recommendation: For patients with EGPA, we conditionally recommend obtaining an echocardiogram at the time of diagnosis.	2	Very low
Recommendation: For patients with EGPA, we conditionally recommend using the Five-Factor Score to guide therapy.	1	Very low
Ungraded position statement: In patients with sinonasal involvement in EGPA, treatment with nasal rinses and topical therapies (e.g., antibiotics, lubricants, and GCs) may be considered.	31	Very low
Recommendation: For patients with EGPA who are receiving cyclophosphamide or rituximab, we conditionally recommend prescribing medications for prophylaxis to prevent *Pneumocystis jirovecii* pneumonia.	32	Low

* For the population, intervention, comparator, and outcome (PICO) questions used in the Grading of Recommendations Assessment, Development and Evaluation methodology, as developed for eosinophilic granulomatosis with polyangiitis (EGPA), please refer to Supplementary Appendix 2 (available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24634/abstract). IV = intravenous; GCs = glucocorticoids.

or high-quality evidence directly addressing this question and the potential toxicity of the medications used for prophylaxis. Prophylaxis against *P jirovecii* pneumonia should also be considered for patients receiving moderate-dose glucocorticoids (e.g., >20 mg/day) or higher in combination with methotrexate, azathioprine, or mycophenolate mofetil (38). Prophylaxis

is less commonly used in younger children receiving rituximab but should be considered.

Recommendation: For patients with GPA/MPA in remission and stage 5 chronic kidney disease, we conditionally recommend evaluation for renal transplantation.

Outcomes of kidney transplantation in patients with AAV are similar to those in patients receiving transplants for other reasons, with disease relapses in the transplanted kidney being rare (39,40). GPA and MPA in remission should not be considered a contraindication to kidney transplantation, but these patients should be monitored for disease relapse after transplantation.

Recommendation: For patients with active GPA/MPA who are unable to receive other immunomodulatory therapy, we conditionally recommend administering IVIG.

IVIG should not be used routinely to treat GPA/MPA (see above recommendation). However, in the rare instances in which patients with active disease may not be able to receive conventional immunosuppressive therapy (e.g., sepsis or pregnancy), IVIG can be used as a short-term intervention until conventional remission induction therapies can be used (29).

Ungraded position statement: The optimal duration of anticoagulation is unknown for patients with GPA/MPA who experience venous thrombotic events.

AAV is associated with an increased risk of venous thrombotic events, including both deep vein thromboses and pulmonary emboli (41,42). Venous thromboembolic events that occur in a patient with active disease and no other risk factors can be considered a provoked event with a transient risk factor (assuming subsequent disease control). Thus, short-term instead of lifelong anticoagulation may be considered.

Recommendations and ungraded position statements for EGPA

EGPA is characterized by diverse features, including asthma/allergic rhinitis, peripheral and tissue eosinophilia, and vasculitis. As these clinical features can potentially have differing responses to treatment, the management approach is typically based on a patient's disease features and severity. The recommendations presented here focus primarily on the use of immunosuppressive medications to treat the vasculitic manifestations of EGPA. However, asthma and allergic manifestations are a significant component of EGPA, and measures directed toward these, including inhaled therapies and allergen avoidance, play an important role in management. Collaboration between rheumatologists, asthma/allergy specialists, and specialists in other medical disciplines can enhance the care of patients with EGPA.

In contrast to GPA/MPA, there have been very few randomized controlled trials conducted to date in EGPA. These recommendations and ungraded position statements therefore reflect reliance on lower-quality (i.e., indirect) evidence, including expert opinion.

Table 1 presents the definitions of selected terms used in the recommendations and ungraded position statements, including the definition of severe and nonsevere disease and the dosing regimens of medications used for remission induction and maintenance. Table 3 presents the recommendations and ungraded position statements with their supporting PICO questions and levels of evidence. Figure 2 presents key recommendations for the treatment of EGPA.

Remission induction for active, severe disease

Ungraded position statement: For patients with active, severe EGPA, either IV pulse glucocorticoids or high-dose oral glucocorticoids may be prescribed as initial therapy.

There are no data to support favoring either IV pulse or high-dose oral glucocorticoids over the other option in active, severe EGPA. Choosing an approach should be influenced by individual patient factors. In either instance, glucocorticoids should be combined with a nonglucocorticoid immunosuppressive agent such as cyclophosphamide or rituximab (see ungraded position statement below).

Ungraded position statement: For patients with active, severe EGPA, either cyclophosphamide or rituximab may be prescribed for remission induction.

Cyclophosphamide has been more commonly used for remission induction in patients with active, severe EGPA, given the experience with cyclophosphamide in other forms of vasculitis (43). Increasing experience with rituximab in GPA/MPA has also led to more patients with EGPA being treated with rituximab, and case series suggest that rituximab may also have efficacy for active, severe disease (44). Given that the comparative effectiveness of cyclophosphamide and rituximab for EGPA is unknown, the Voting Panel felt that both cyclophosphamide and rituximab could be considered for remission induction in active, severe EGPA. Cyclophosphamide would be preferred for patients with active cardiac involvement given the increased experience with cyclophosphamide, as cardiomyopathy has been found to be the main independent predictor of death in EGPA (25,26). Cyclophosphamide can also be considered for patients who are ANCA-negative and have severe neurologic or gastrointestinal manifestations. Rituximab may be considered for patients with positive ANCA results, active glomerulonephritis, prior cyclophosphamide treatment, or those at risk of gonadal toxicity from cyclophosphamide.

Recommendation: For patients with active, severe EGPA, we conditionally recommend treatment with cyclophosphamide or rituximab over mepolizumab for remission induction.

The efficacy of mepolizumab in severe EGPA has not been established, as patients with active, severe disease were excluded

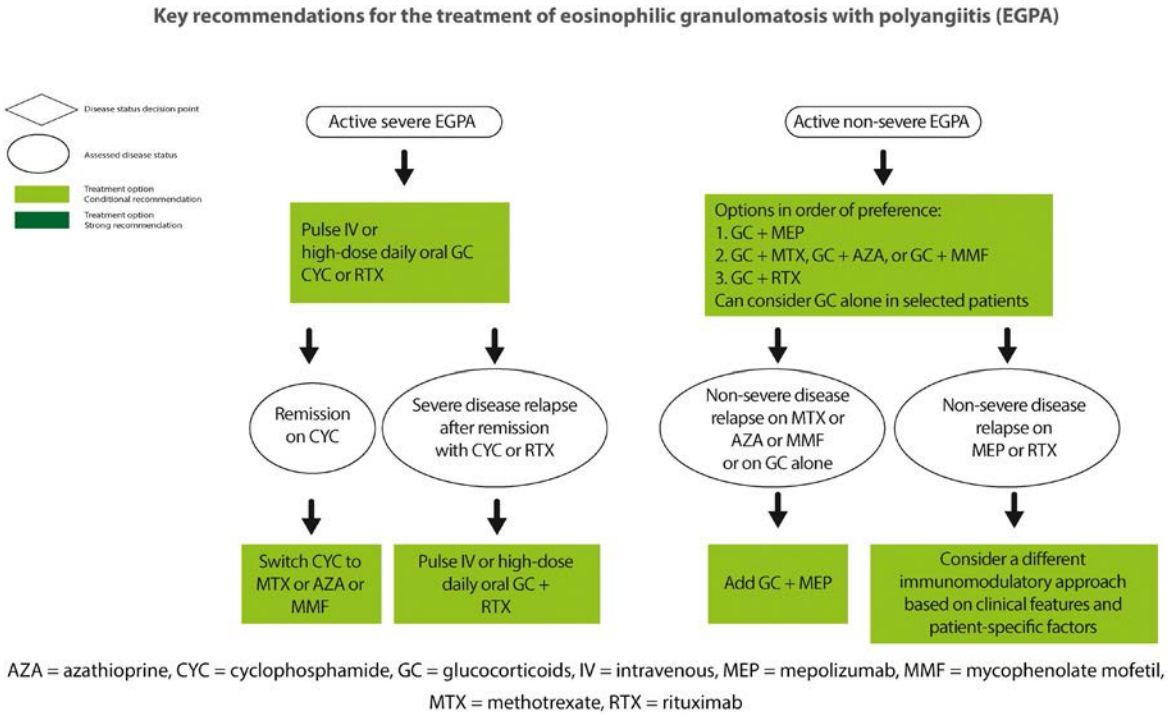

Figure 2. Key recommendations for the treatment of eosinophilic granulomatosis with polyangiitis.

from the randomized trial (45). Rituximab or cyclophosphamide is recommended over mepolizumab in this setting.

Remission induction for active, nonsevere disease

Recommendation: For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with mepolizumab and glucocorticoids over methotrexate, azathioprine, or mycophenolate mofetil and glucocorticoids.

A range of immunosuppressive agents may be considered in the treatment of active, nonsevere EGPA, all of which are used with glucocorticoids. The clinical profile of nonsevere EGPA includes predominantly asthma, sinus disease, and nonsevere vasculitis. While there is significant clinical experience with methotrexate, azathioprine, and mycophenolate mofetil, there are limited data regarding their efficacy, and these treatments have not been assessed in randomized clinical trials. The GRADE methodology used in the guideline development process weights clinical trials more heavily than observational studies. Thus, mepolizumab is recommended as the first choice, because it has been found to be efficacious for nonsevere EGPA in a randomized trial (45). All patients in this trial had relapsing or refractory disease, with 55% receiving an additional nonglucocorticoid immunosuppressive agent at the time of enrollment. A large proportion of patients in this trial had asthmatic and eosinophilic features, for which mepolizumab has also been found to be effective in non-EGPA disease settings. Although patients with nonsevere vasculitic manifestations were represented in this trial, questions remain about the effectiveness of mepolizumab for all aspects of nonsevere vasculitis. Individual factors, including disease manifestations, may impact the decision to use mepolizumab, in which case methotrexate, azathioprine, or mycophenolate mofetil may be used instead. There are insufficient data to favor one of these medications (methotrexate, azathioprine, or mycophenolate mofetil) over the others; therefore, the choice should be influenced by individual patient factors.

Recommendation: For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with methotrexate, azathioprine, or mycophenolate mofetil and glucocorticoids over glucocorticoids alone.

Patients should be treated with adjunctive methotrexate, azathioprine, or mycophenolate mofetil rather than glucocorticoids alone in order to minimize glucocorticoid toxicity. One randomized trial that combined patients with EGPA, MPA, and polyarteritis nodosa without poor prognosis factors showed that the addition of azathioprine did not provide benefit beyond glucocorticoids alone (46). Particularly for patients with asthma, this may impact the decision to use methotrexate, azathioprine, or mycophenolate mofetil concurrently with glucocorticoids and could lead to consideration of mepolizumab. Glucocorticoid monotherapy may be appropriate for mild asthma, allergic symptoms, use during pregnancy, or other individual patient situations.

Recommendation: For patients with active, nonsevere EGPA, we conditionally recommend initiating treatment with methotrexate, azathioprine, or mycophenolate mofetil and glucocorticoids over cyclophosphamide or rituximab and glucocorticoids.

While the comparative efficacy of methotrexate, azathioprine, mycophenolate mofetil, and rituximab is not well established, the use of methotrexate, azathioprine, or mycophenolate mofetil is favored, based on more experience with these agents in EGPA compared to rituximab. However, rituximab may be considered if other agents are not effective in controlling active, nonsevere disease, or if the patient has nonsevere vasculitis (which in some series included mononeuritis multiplex) and is positive for ANCA. Cyclophosphamide should be avoided when treating active, nonsevere disease due to its toxicity and is the least preferred option in this setting.

Remission maintenance

Recommendation: For patients with severe EGPA whose disease has entered remission with cyclophosphamide therapy, we conditionally recommend treatment with methotrexate, azathioprine, or mycophenolate mofetil over rituximab for remission maintenance.

Typically, a maintenance agent would be used after remission induction in severe EGPA to reduce toxicity and the risk of disease relapse (47), although monophasic disease can occur (48). Azathioprine has been commonly used in published EGPA series (46), but the lack of comparative evidence between methotrexate, azathioprine, and mycophenolate mofetil in EGPA precludes recommending one agent over another.

Use of methotrexate, azathioprine, or mycophenolate mofetil is recommended over rituximab, because there has been less experience with the use of rituximab for remission maintenance in EGPA. Rituximab could be considered if remission were induced with rituximab or if there are contraindications to other choices.

Recommendation: For patients with severe EGPA whose disease has entered remission, we conditionally recommend treatment with methotrexate, azathioprine, or mycophenolate mofetil over mepolizumab for remission maintenance.

While there are limited data informing the use of remission maintenance therapy in EGPA, remission induction therapies (e.g., cyclophosphamide) should not be indefinitely continued given the potential toxicity. Thus, methotrexate, azathioprine, or mycophenolate mofetil can be considered for remission maintenance based on experience in GPA/MPA, expert opinion, and results from small studies (49). The primary experience with mepolizumab is in refractory nonsevere disease, and thus it is difficult to extrapolate its efficacy as a remission maintenance agent for severe disease.

Ungraded position statement: The duration of glucocorticoid therapy in EGPA should be guided by the patient's clinical condition, values, and preferences.

There is insufficient published evidence to support a specific duration of glucocorticoid treatment, and thus, the length of glucocorticoid therapy should be determined based on each patient's clinical circumstances. Many patients with EGPA require some treatment with glucocorticoids, generally at a low dose, to maintain control of asthma and allergy symptoms. The minimum effective dose should be prescribed to minimize glucocorticoid toxicity.

Treatment of disease relapse

Recommendation: For patients with EGPA who have experienced relapse with severe disease manifestations after prior successful remission induction with cyclophosphamide, we conditionally recommend treatment with rituximab over cyclophosphamide for remission re-induction.

Rituximab is favored based on the general desire to avoid re-treatment with cyclophosphamide if possible and on the findings of an observational study of rituximab in relapsing or refractory EGPA (50). Cyclophosphamide may be considered in instances of recurrent cardiac involvement, since cardiac involvement is an independent predictor of death and is associated with ANCA-negative disease, as discussed in the ungraded position statement about remission induction in active, severe disease.

Recommendation: For patients with EGPA who have experienced relapse with severe disease manifestations after prior successful remission induction with rituximab, we conditionally recommend treatment with rituximab over switching to cyclophosphamide for remission re-induction.

Re-induction of remission with rituximab is favored over cyclophosphamide treatment to minimize toxicity. However, the duration of remission prior to the onset of relapse should be examined. Cyclophosphamide should be considered if a severe relapse occurred quickly after rituximab treatment, or if cardiac involvement is present (see ungraded position statement and recommendation on this topic).

Recommendation: For patients with EGPA who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil, we conditionally recommend adding mepolizumab over switching to another agent.

For patients with EGPA with active asthma, inhaled therapies should be maximized prior to increasing systemic immunosuppressive therapy. Although no direct comparative

data are available, mepolizumab was found to be efficacious in a randomized trial in patients specifically described in this recommendation: those with relapsing nonsevere EGPA who are receiving immunosuppressive therapy (45). It has also been independently proven to be effective in eosinophilic asthma (51). Based on this evidence, mepolizumab is recommended to treat nonsevere relapsing disease in patients receiving methotrexate, azathioprine, or mycophenolate mofetil rather than switching to an alternative agent of that group.

Recommendation: For patients with EGPA who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving low-dose glucocorticoids and no other therapy, we conditionally recommend adding mepolizumab over adding methotrexate, azathioprine, or mycophenolate mofetil.

Similar to the discussion about the above recommendation, use of inhaled agents should be optimized in patients experiencing disease relapse with asthma and/or sinonasal disease. For patients with nonsevere relapsing EGPA who are receiving glucocorticoid monotherapy, starting mepolizumab would be preferred over adding methotrexate, azathioprine, or mycophenolate mofetil, given the treatment's proven efficacy in this population in a randomized trial (45).

Recommendation: For patients with EGPA and high serum IgE levels who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil, we conditionally recommend adding mepolizumab over adding omalizumab.

The published evidence on omalizumab, an anti-IgE antibody, in EGPA has been limited. Therefore, even for a patient with high serum IgE levels, mepolizumab is the preferred choice based on evidence from the randomized controlled trial (45).

Other considerations

Recommendation: For patients with newly diagnosed EGPA receiving leukotriene inhibitors, we conditionally recommend continuing leukotriene inhibitors over discontinuing them.

Following the introduction of leukotriene inhibitors, concerns were raised about a link with the development of EGPA. In subsequent retrospective studies, it was not concluded that there is a causal relationship between leukotriene inhibitors and EGPA (52). Therefore, patients with newly diagnosed EGPA should have the option to continue a leukotriene inhibitor if it is beneficial in the management of their asthma or sinonasal disease.

Ungraded position statement: Use of leukotriene inhibitors is not contraindicated for patients with EGPA with active asthma and/or sinonasal disease.

Leukotriene inhibitors carry therapeutic indications for asthma and allergic rhinitis. As no clear causal association with EGPA has been demonstrated, a leukotriene inhibitor can be added to help manage asthma and sinonasal disease. However, leukotriene inhibitors are one of many options and are not the only choice in this setting. Leukotriene inhibitors should not be used to treat manifestations aside from asthma and sinonasal disease.

Recommendation: For patients with EGPA, we conditionally recommend obtaining an echocardiogram at the time of diagnosis.

Cardiac involvement is the major cause of disease-related mortality in EGPA (48). Echocardiography has minimal risk and can identify cardiac involvement, which, if present, can impact treatment decisions. Not identifying cardiac involvement could negatively impact patient outcomes. Thus, we recommend obtaining an echocardiogram for all patients with newly diagnosed EGPA, even in the absence of cardiac symptoms.

Recommendation: For patients with EGPA, we conditionally recommend using the Five-Factor Score to guide therapy.

The Five-Factor Score (FFS), first published in 1996 (53), was based on a cohort of 342 patients with either polyarteritis nodosa, as it was then defined, or EGPA. These 5 factors include proteinuria >1 gm/day, renal insufficiency with serum creatinine >1.58 mg/dl, gastrointestinal tract involvement, cardiomyopathy, and central nervous system involvement. The FFS is primarily a prognostic tool for which higher scores have been associated with a worse outcome (53). It has been used to guide treatment (43), but its applicability to newer therapies is unknown. The FFS was revisited in 2011 in a population of 1,108 patients with GPA, MPA, EGPA, or PAN (54). The 2011 version included ear, nose, and throat parameters and age >65 years. The 1996 FFS remains more commonly used and may be helpful in identifying organ-specific parameters associated with severe disease and in guiding treatment. Although the definitions of severe and nonsevere EGPA used in the present guideline were not based on the FFS, the tool was found to be useful to clinicians for making treatment decisions. The components of the FFS can serve as markers of severe disease that warrant more aggressive treatment.

Ungraded position statement: In patients with sinonasal involvement in EGPA, treatment with nasal rinses and topical therapies (e.g., antibiotics, lubricants, and glucocorticoids) may be considered.

Allergic rhinitis and sinonasal disease are frequent clinical features of EGPA. Although the efficacy of nasal rinses and topical

therapies in EGPA is not well established, some patients may benefit. Where possible, consultation with an otolaryngologist with expertise in treating AAV should be obtained to guide the use and choice of these agents. These interventions can continue to be beneficial even when symptoms have improved or resolved.

Recommendation: For patients with EGPA who are receiving cyclophosphamide or rituximab, we conditionally recommend prescribing medications for prophylaxis to prevent *P jirovecii* pneumonia.

Prophylaxis to prevent *P jirovecii* pneumonia is discussed above in the GPA/MPA recommendations. The same considerations regarding prophylaxis to prevent this condition in patients with GPA/MPA apply to those with EGPA.

DISCUSSION

In this guideline, we present the first ACR/Vasculitis Foundation recommendations for the management of GPA, MPA, and EGPA. Although these recommendations provide a general guide for disease management, the patient's clinical condition, preferences, and values should influence their treatment. Overall, these recommendations reflect the evolving management of these diseases, including the new roles for biologic therapies and aggressive strategies to minimize glucocorticoid toxicity. The recommendations for GPA and MPA are supported by a greater number of randomized trials than are currently available in EGPA. All of the recommendations made for these 3 diseases are conditional, which indicates that there are settings in which the evidence is not strong or an alternative is a reasonable consideration. These recommendations should not be used by any agency to restrict access to therapy or require that certain therapies be utilized prior to other therapies.

The physicians on the Voting Panel were primarily rheumatologists, because the recommendations were being developed for rheumatologists in the US. Since AAVs are multisystem diseases, patients with AAVs often receive care from other medical subspecialists (e.g., nephrologists, pulmonologists, and/or otolaryngologists). While the recommendations presented in this guideline are driven by the published data, other medical subspecialists may favor a different management strategy. We encourage rheumatologists to discuss treatment plans and coordinate care with other subspecialists as needed.

Recently, a clinical trial of avacopan in patients with GPA and MPA was published (55). This guideline development effort did not include consideration of avacopan, since the guidelines consider therapies that are approved by the FDA for use for any indication at the time of the last literature search. Therapies approved by the FDA after that date will be considered for inclusion in future updates to this guideline.

This guideline highlights gaps in our knowledge for the treatment of AAV. Most glaring is the lack of biomarker assessments or other noninvasive diagnostic testing with minimal toxicity that can accurately assess disease activity and predict outcomes. In addition, while we have evidence from randomized clinical trials to support recommendations regarding initial remission induction and maintenance therapy, critical questions remain unanswered, such as the optimal duration of therapy.

These gaps in knowledge reinforce the need for ongoing research in these diseases. Specific areas to investigate include the following: 1) biomarker studies to identify more specific, reliable indicators of disease activity that can guide treatment decisions; 2) trials to clarify how best to use the currently available medications (e.g., dosing, duration, effective combinations, and in which population to use which drugs); 3) trials to identify novel, targeted, and/or glucocorticoid-sparing agents with minimal toxicity; and 4) long-term studies to understand the course of disease and the safety of current therapies.

We hope significant progress will be made in these areas such that future recommendations provide a more tailored approach to disease management, minimize treatment toxicity, and prevent organ damage in these patients.

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CLINICOPATHOLOGIC CONFERENCE

A Man With Recurrent Fever, Episodic Rash, and Pain

Fawad Aslam, Julia E. Wiedmeier, and David J. DiCaudo

CASE PRESENTATION

Chief symptoms

A 61-year-old man presented with an intermittent rash of several years' duration, followed by the development of fever and bone and joint pain.

History of present illness

The patient presented to our clinic from outside the state in October 2018. Previously, in 2014, he underwent an elective, left total hip arthroplasty with a ceramic-on-polyethylene prosthesis for osteoarthritis. The surgery and recovery were uneventful. In November 2014, hives developed on his upper arms. Within weeks, the hives spread to his trunk and thighs but spared his face, palms, and soles. The symmetric, nonpruritic nonpainful rash was without angioedema. The hives initially persisted for 5 days, followed by resolution for several days. This rash eventually progressed to being present the majority of the time. Each individual lesion, however, remained for less than 24 hours. Alcohol intake exacerbated the rash, while temperature had no impact.

The patient first consulted his orthopedic surgeon to determine whether there was any association between the rash and the prosthesis. A small effusion of the left hip found on magnetic resonance imaging was aspirated and found sterile. Metal hypersensitivity testing was negative. The patient was then examined by an allergist. Results from skin-prick testing were positive for grasses, weeds, tree pollens, and molds. He was diagnosed with urticaria by a dermatologist. Treatment for the rash with antihistamines and histamine type 2 receptor antagonists was unsuccessful.

In February 2016, the patient developed night sweats, which had not resolved by presentation at our clinic. On occasion the night sweats were drenching, and the patient slept on towels. He experienced fever and chills, with documented temperatures up to 102ºF. Fevers were episodic and without a fixed pattern. He reported constant fatigue. A 5- to 10-kg weight loss occurred but stabilized.

In June 2017, the patient developed unprovoked severe bone pain in the left leg just above the knee. The pain was unresponsive to ibuprofen. At times, he rated his pain as an 8 on a scale of 1 to 10 (10 being the worst). He was examined by an orthopedic specialist. Magnetic resonance imaging of the knee showed an effusion, which was aspirated, and results were unremarkable. The patient then developed joint pain in his hips, back, and hands, without swelling or erythema. A rheumatology evaluation ensued. Results from a routine examination for inflammatory causes were negative. However, his C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) were moderately elevated. In addition, he had persistent leukocytosis. Prednisone, 60 mg daily, was initiated. The prednisone resolved the urticarial rash but did not improve the joint pain or systemic symptoms. When prednisone was reduced to 40 mg daily, the hives recurred. The patient reported irritability as a side effect from the prescribed prednisone, and subsequently the medication was terminated. Treatment with colchicine, hydroxychloroquine, and methotrexate was unsuccessful.

In March 2018, the patient was examined by an oncologist. An examination for an underlying malignancy was pursued due to leukocytosis, ESR elevation, and systemic symptoms. A serum monoclonal protein was identified. Kappa free light chain levels were elevated, but the kappa/lambda ratio was normal. Flow cytometry findings of peripheral blood testing were negative. Bone marrow testing showed a very small population (0.3%) of abnormal B cells. Fluorescence in situ hybridization, c-KIT mutation, immunohistochemical staining, and cytogenetic testing results were all negative. Computed tomography (CT) of the chest, abdomen, and pelvis showed diffuse, mildly enlarged lymph nodes without hepatosplenomegaly. Biopsy findings of the left axillary lymph node showed reactive changes. The patient's rheumatologist obtained a biopsy result of the urticarial rash, which was reported as consistent with urticaria.

Four years after symptom onset, the patient was frustrated with his undiagnosed, progressive condition and presented to our institution in October 2018. At presentation, he reported worsening

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hives, fatigue, and night sweats and persistent bone and joint pain most prominent in the left proximal tibia and distal femur.

Medical history

Additional medical history included osteoarthritis, seasonal allergies, Peyronie's disease, and a diverticulitis episode. He took ibuprofen for his musculoskeletal complaints.

Family and social history

The patient is of partial Irish descent. His father had osteoarthritis and may have had rheumatoid arthritis. His sister died of leukemia after a bone marrow transplant. There was no known inflammatory disease in the family. He did not smoke and consumed alcohol very rarely, although he had been a heavy drinker in the past. He denied unusual travel or animal exposures. He worked as a machinist.

Review of systems

Review of systems was positive for intermittent symptoms of allergic rhinitis and postnasal drip, intermittent tinnitus, a dry cough without dyspnea, poor libido, and erectile dysfunction. Ocular inflammatory symptoms, hearing loss, chronic sinusitis, voice change, hemoptysis, fragility fractures, episodic abdominal pain, gastroesophageal reflux, inflammatory back pain, and genitourinary tract symptoms were absent.

Physical examination

On examination, the patient was afebrile with stable vital signs. His body mass index was 25.3 kg/m^2. He had extensive, raised, erythematous, well-demarcated, and blanchable plaques and papules present on the extremities and trunk (Figure 1), but none on the face, palms, and soles. No other rash was noted. Bilateral axillary lymph nodes were palpable and mildly tender but not firm. Test results for dermatographism were negative. Synovitis and joint or bone tenderness on palpation were absent. Otolaryngologic, ophthalmic, cardiovascular, pulmonary, gastrointestinal, and neurologic examination results were unremarkable.

Laboratory evaluation

Laboratory results from our institution are shown in Table 1. Infectious testing results for hepatitis B and C, tuberculosis, Lyme disease, HIV, and *Brucella* were negative. Urinalysis test results were also negative.

Radiologic evaluation

Radiography of the hands, knees, and hips was reviewed by our radiology department and showed findings of mild-to-moderate osteoarthritis. A review of the previous CT of the chest and abdomen confirmed mild enlargement of the axillary and femoral lymph nodes.

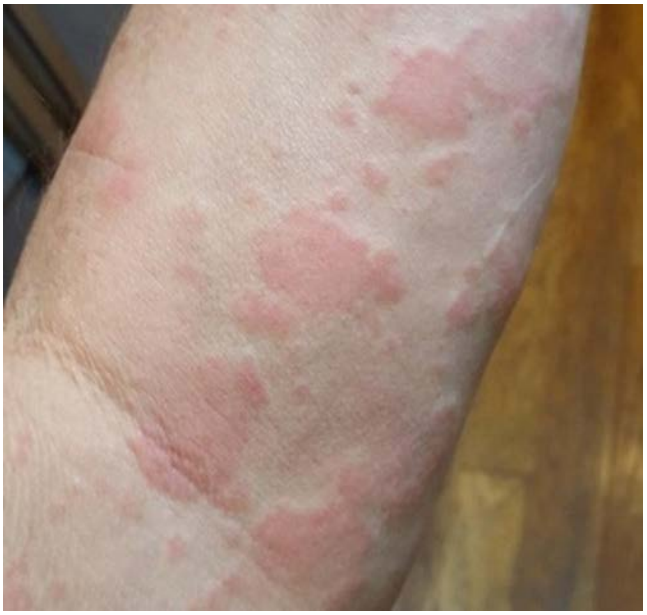

Figure 1. Raised, erythematous, well-demarcated plaques and papules present on the arm.

CASE SUMMARY

A 61-year-old man presented with an initial history of nonpruritic urticarial rash followed by the development of fever, night sweats, and bone and joint pain. Neutrophilia, elevated inflammatory markers, and a monoclonal protein were detected after testing. Test results for malignancies were negative except for reactive lymphadenopathy. Treatment with antihistamines, glucocorticoids, colchicine, hydroxychloroquine, and methotrexate was unsuccessful. He had no evidence of common systemic rheumatic diseases.

DIFFERENTIAL DIAGNOSIS

The key symptoms in approaching this case were the coexistence of rash and musculoskeletal pain. While the differential diagnosis of rash and arthritis is broad and has been reviewed elsewhere (1), the diagnostic possibilities in the setting of urticarial rash, bone pain, arthralgia, and a monoclonal protein are relatively limited. Urticaria and monoclonal proteins are briefly reviewed below.

Urticaria presents with itchy, raised, erythematous, and blanchable skin lesions. The lesions usually last 1 to 24 hours and are commonly known as wheals or hives (2). Urticaria is common, prevalent in 9% of the population, with one-third of patients also having angioedema (3). There are many types of urticaria, but we will focus on spontaneous urticaria (i.e., without an

Table 1. Laboratory testing results*

Test	Normal range	Result
Hemoglobin, gm/dl	13.2–16.6	12.3
White blood cells, 10^9/liter	3.4–9.6	18.6
Neutrophil count, 10^9/liter	1.6–6.5	15.4
Platelet count, 10^9/liter	135–317	450
Creatinine, mg/dl	0.74–1.35	0.83
Alkaline phosphatase, units/liter	40–129	146
Bone alkaline phosphatase, μg/liter	0–20	20
Aspartate aminotransferase, units/liter	8–48	20
Thyroid stimulating hormone, mIU/liter	0.3–4.2	1.8
Creatine kinase, units/liter	39–308	30
C-reactive protein, mg/dl	<8	46
Erythrocyte sedimentation rate, mm/hour	0–22	40
Ferritin, μg/liter	24–337	306
Rheumatoid factor, IU/ml	<15	<15
Anticyclic citrullinated peptide, units	<20	<15.6
Antinuclear antibody, units	<1	0.3
Antineutrophil cytoplasmic antibodies	Negative	Negative
Cryoglobulins	Negative	Trace cryoprecipitate (type I)
Total complements, units/ml	30–75	67
C4, mg/dl	14–40	20
Tryptase, ng/ml	<11.5	2.6
Monoclonal protein study	Negative	Monoclonal IgM kappa in gamma fraction
Monoclonal protein spike, gm/dl	Negative	0.5
HLA–B27 positivity	NA	Negative

* NA = not applicable.

identifiable cause). When spontaneous urticaria persists for more than 6 weeks, it is called chronic spontaneous urticaria, commonly referred to as chronic urticaria (CU). It has a prevalence of 0.8% (4). In CU, the individual hives do not persist for 6 weeks, but rather it is the process of their appearance and disappearance that persists. If individual lesions persist for more than 24 hours, a biopsy should be considered for urticarial vasculitis (UV). Systemic symptoms such as fever, malaise, and musculoskeletal symptoms can be present in 16% of CU patients without any underlying causative disorder (5).

There are some differences in CU and urticarial rashes associated with systemic disorders. In CU, the rash is asymmetric, very pruritic, lasts for minutes to a few hours, often has angioedema, and responds to antihistamines. In CU associated with systemic disorders, the rash is symmetric, minimally pruritic, lasts for several hours, does not have angioedema, and antihistamines are ineffective (6). The diagnostic role of a skin biopsy result is paramount. In CU, a biopsy is not required unless atypical features, systemic manifestations, resistance to standard therapy, or suspicion for another diagnosis is present (7). A biopsy result can help identify conditions such as UV, mastocytosis, connective tissue diseases, cryoglobulinemia, or neutrophilic urticarial dermatosis (NUD).

NUD is different from urticaria and neutrophilic dermatosis; it has the clinical picture of an urticarial eruption, but the histopathology shows an intense neutrophilic infiltration and lacks edema (8). NUD also has a sensitive and peculiar finding of neutrophilic epitheliotropism, a term for neutrophils showing affinity for the epidermis or epithelium of cutaneous adnexa, such as eccrine sweat glands (9). NUD is strongly associated with a small group of systemic diseases, namely adult-onset Still's disease, systemic lupus erythematosus (SLE), Schnitzler syndrome, and cryopyrin-associated periodic syndrome (CAPS), with both Schnitzler syndrome and CAPS belonging to the autoinflammatory syndrome (AIS) category (10). Fever, myalgia, and fatigue are common in NUD even in the absence of an underlying disorder (11).

Aberrant production of immunoglobulins (IGs) or their parts (free light chains) by an abnormal clone of plasma cells is referred to as a monoclonal protein (12). Monoclonal protein–associated disorders are known as monoclonal gammopathies (MGs). Well-known MGs are monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, and Waldenström's macroglobulinemia (WM). Of these, MGUS, a premalignant condition, is the most common, with a prevalence of 3.2% in those individuals older than age 50 years and 5.3% in those older than age 70 years (13). It is important to note that MGUS can be associated with several relatively rare diseases across multiple specialties (14). In rheumatologic examination, testing for MGs is not uncommon, as rheumatic diseases can be associated with MGs (15). However, a polyclonal pattern is more common.

Hematologic disorders

Hematologic malignancies, such as WM or multiple myeloma, are diagnosed after monoclonal protein testing. These malignancies, however, require an abnormal bone marrow biopsy result for diagnosis. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) is a rare paraneoplastic syndrome that mandates the presence of neuropathy and a monoclonal protein for diagnosis (16). The skin changes in POEMS syndrome can include hyperpigmentation, hemangiomas, white nails, and acrocyanosis, but urticarial rash is not one of the skin changes associated with POEMS syndrome. The monoclonal protein is of the lambda subtype. Median age at presentation is 51 years (17).

Dermatologic conditions

CU has a prevalence of 0.26% in the age group of 40 to 49 years (18). MGUS is a relatively common disorder, with increased prevalence with age, as discussed before. IgG is the dominant monoclonal protein (70% prevalence) seen in MGUS (19).

Therefore, the co-occurrence of IgG MGUS and CU does not necessarily indicate an underlying systemic inflammatory disorder.

UV is a disease generally affecting young to middle-aged women. It is characterized by an urticarial rash that lasts for more than 24 hours and can be painful rather than itchy. Individual lesions may have central purpura and can cause hyperpigmentation. UV can be associated with systemic symptoms such as fever, arthralgia or arthritis, and lymphadenopathy. This disorder has 3 forms: normocomplementemic UV, hypocomplementemic UV, and hypocomplementemic UV syndrome (20). Normocomplementemic UV is primarily a cutaneous manifestation with normal complement levels, while hypocomplementemic UV has more systemic symptoms, elevated inflammatory markers, and low complement levels. Hypocomplementemic UV syndrome is a severe form of UV. These disorders are associated with low C1q levels and/or antibodies to C1q. As the names suggest, skin biopsy results in all these variants show leukocytoclastic vasculitis and positive immunofluorescence. UV can be associated with connective tissue disease and hematologic malignancies as well as MG.

Acquired angioedema due to C1-esterase inhibitor deficiency is a rare disorder strongly associated with MG and hematologic malignancies, but it does not have an urticarial rash (21). Sweet syndrome is a typical neutrophilic dermatosis with acute onset and several systemic symptoms, leukocytosis, and elevated inflammatory markers; it has its own diagnostic criteria (22). It can be associated with infections, certain prescription drugs, rheumatic diseases, hematologic malignancies, and, rarely, MG. It does not exhibit an urticarial rash, is usually not chronic, and is responsive to glucocorticoids. Biopsy findings show a denser, diffuse dermal neutrophilic infiltrate. In addition, Sweet syndrome has prominent subepidermal edema, which helps differentiate it from NUD. Several dermatologic diseases are associated with MG and have been reviewed under the clinically useful concept of monoclonal gammopathy of cutaneous significance (23).

Common rheumatic diseases

In rheumatoid arthritis, symmetric synovitis is expected. Absence of serologic markers and ineffectiveness of prednisone, 60 mg, is atypical. SLE is unusual in older men, and a negative antinuclear antibody test result virtually rules it out. Skin biopsy findings in SLE are expected to show interface dermatitis and characteristic immunofluorescence staining. Both rheumatoid arthritis and SLE can be associated with MG (15), but it is not typical. Rarely, MG can present with inflammatory arthritis as the initial manifestation (24).

When associated with a pure monoclonal IG, cryoglobulinemia is referred to as type I cryoglobulinemia. In contrast, type II cryoglobulinemia is associated with both monoclonal and polyclonal IGs, while type III cryoglobulinemia is associated only with polyclonal IGs. Rash is a major feature of cryoglobulinemias and is characterized by purpura of the lower extremities and ulcers. However, urticarial rashes can occur, particularly in the cold-induced type. Fatigue, joint pain, neuropathy, and nephropathy are common. Type I cryoglobulinemia also presents with hyperviscosity symptoms, such as Raynaud's phenomenon, acrocyanosis, blurry vision, and dizziness. The mean age at diagnosis for type I disease is 65 years (25). Complement levels are usually low. Skin biopsy findings of a purpuric lesion show evidence of an occlusive vasculopathy with intraluminal hyalin deposits. Immunofluorescence demonstrates IG within the vascular lumina.

Adult-onset Still's disease

Adult-onset Still's disease is a diagnosis of exclusion using diagnostic criteria (26). It is classically characterized by an episodic transient rash, which is typically macular. A recent study has reported an NUD prevalence of 22% in adult-onset Still's disease (27). Fevers tend to spike in the early evening. Arthritis or arthralgia involve the wrists, knees, and ankles. Lymphadenopathy and sore throat may be present. Typical laboratory test results include neutrophilic leukocytosis, elevated inflammatory markers, negative test results for antinuclear antibody and rheumatoid arthritis, and markedly elevated ferritin levels, the latter being a hallmark of adult-onset Still's disease, although it can be seen in other conditions. Skin biopsy results indicate a lymphocytic or neutrophilic pattern (28). It is a disease affecting young people, with a median age of 36 years (29), and it does not show genetic clustering. Neither bone pain nor association with a monoclonal protein is expected.

AIS

Periodic fever and rashes along with systemic symptoms always bring forth the consideration of the very rare group of disorders known as periodic fever syndromes or AIS. Underlying pathophysiology involves the innate immune system in contrast to

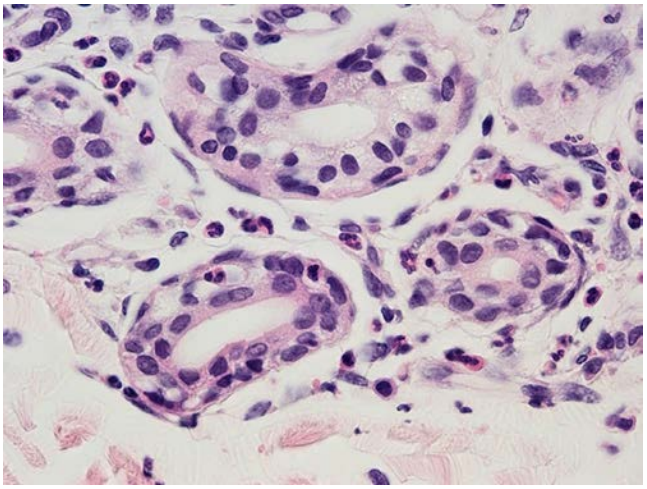

Figure 2. Neutrophilic epitheliotropism on skin biopsy. Neutrophils extend into the epithelium of eccrine sweat glands (hematoxylin-eosin stained; original magnification × 600).

the adaptive immunity of autoimmune diseases (30). Of the ever-increasing number of AIS disorders, Schnitzler syndrome and CAPS are characterized by an urticarial rash in general and NUD in particular.

All CAPS disorders share pathology through the nucleotide-binding oligomerization domain leucine-rich repeats containing pyrin domain 3 (*NLRP3*) gene and the inflammasome. There are 3 main diseases in this group: familial cold AIS, Muckle-Wells syndrome, and neonatal-onset of multisystem inflammatory disease (6). Familial cold AIS symptoms are triggered by exposure to cold. Muckle-Wells syndrome is associated with sensorineural hearing loss. Neonatal onset of multisystem inflammatory disease has a meningitis component. The urticarial rash in these conditions usually occurs daily and may involve the face (31). Ocular involvement such as uveitis can occur. CAPS patients have a strong family history of related disorders due to the mostly autosomal dominant inheritance. They present in infancy or young age and are not associated with a monoclonal protein. Genetic testing plays an important role in diagnosis.

Schnitzler syndrome is the other AIS associated with CU, but it is typically nonpruritic. It is characterized by systemic symptoms such as fever, arthralgia, bone pain, leukocytosis, elevated inflammatory markers, and a monoclonal protein usually of the IgM kappa type. According to a Mayo Clinic study, the odds ratio for a correlation between CU and MGUS with IgM kappa was very high, at 9,801 for Schnitzler syndrome (32). Therefore, in contrast to CU in the setting of IgG MGUS as discussed earlier, such a finding should raise concerns for Schnitzler syndrome. Skin biopsy results indicate NUD. It is slightly more common in men, and the median age at diagnosis is 51 years (10). Unlike the other AIS, family history is usually negative, and genetic testing is not helpful. Testing results for markers of common rheumatologic disorders are negative.

The current patient's previous skin biopsy slides were obtained and reviewed at our institution. A diffuse interstitial and perivascular inflammatory infiltrate composed mostly of neutrophils was identified in the dermis and subcutis. Neutrophils demonstrated a pattern of epitheliotropism with extension into the epithelium of eccrine glands (Figure 2). No subepidermal edema or vasculitis was noted. The histopathologic features were compatible with NUD. A whole-body ^{99m}Tc medronate nuclear bone scan (Figure 3) revealed increased tracer activity in the left tibia and subtly increased tracer activity in the left femoral shaft. Uptake in other articulations was consistent with osteoarthritis.

CLINICAL COURSE

Considering the patient's clinical evaluation and the findings of MG, NUD, and abnormal bone scan results, a diagnosis of Schnitzler syndrome was made. The patient was started on anakinra, 100 mg daily. Within a few weeks, the patient had a remarkable response. His systemic symptoms, rash, and bone pain completely resolved, and only minimal joint pain from osteoarthritis persisted. The importance of the trace cryoglobulins and trace population of abnormal B cells identified on bone marrow aspirate was unclear. He returned to his home state and followed up

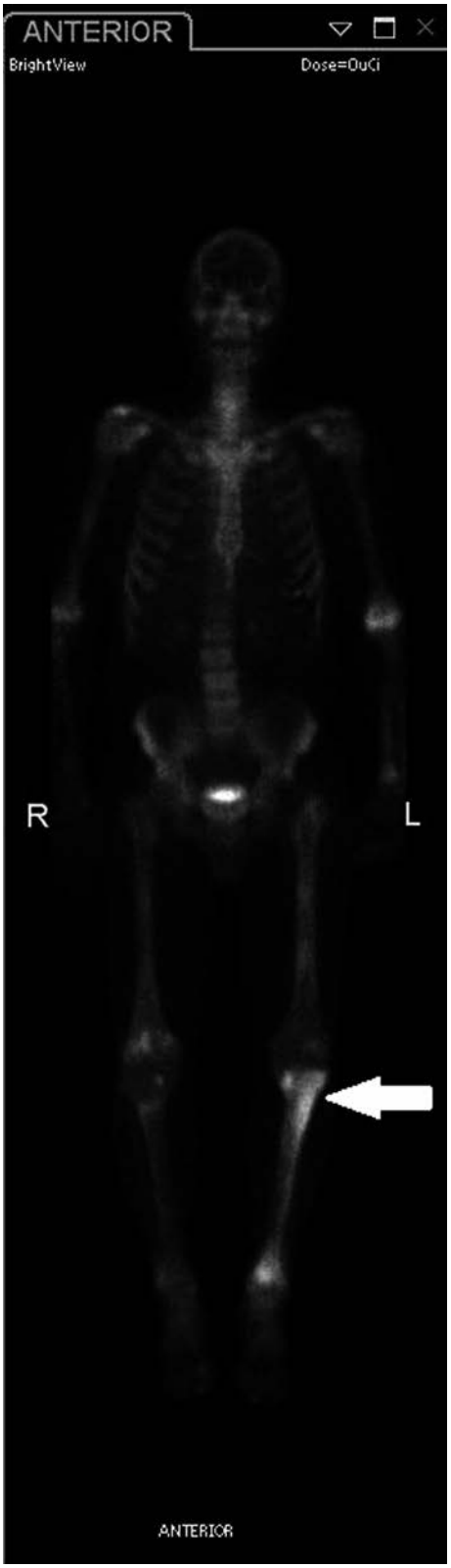

Figure 3. Whole-body ^{99m}Tc medronate nuclear bone scan showing increased tracer activity in the left tibia (arrow).

with local providers, including the hematology department. On a follow-up phone call at the time of this writing, the patient reported that he was doing very well on anakinra.

DISCUSSION

Schnitzler syndrome is rare and different from other AIS, such as CAPS. There have only been 281 cases reported through 2014 (10). It is thought to be an underdiagnosed condition, and a 5-year delay between symptom onset and diagnosis is reported (32,33). The top 5 manifestations are those of rash, fever, arthralgia, bone pain, and lymphadenopathy. Urticarial rash is mandatory for diagnosis and can precede the onset of other symptoms by several years. The rash may occur daily or only a few times a year. It is typically nonpruritic, but rather causes a burning sensation, and is not found on the palms, soles, and face. Individual lesions usually last for a few hours but not more than 24 hours; they almost never persist for more than 48 hours. Antihistamines are usually ineffective. Fevers are usually recurrent, but fever-free periods of 2 weeks or more can occur. Joint pain involves the larger joints (e.g., knees, hip, back). Long-bone pain is present, commonly in the tibia.

ESR or CRP level elevation is seen in 97% of cases, leukocytosis in 75%, and anemia in 63% (10). Serum ferritin levels are usually normal (32). Presence of monoclonal protein is the other mandatory requirement, and all patients will have a monoclonal protein, with 90% being IgM kappa (10). IgG monoclonal protein is much rarer. Once an MG has been found, further testing in collaboration with a hematologist, including skeletal imaging and bone marrow biopsy, should be pursued if patients have high-risk features (14,34). Skin biopsy shows characteristic findings of NUD. While some studies reported vasculitis, later studies and review of some prior ones have cast doubt on this association with vasculitis. The current consensus is that vasculitis is not a typical finding in Schnitzler syndrome (33). Osteosclerosis is seen on radiography findings in 50% of cases. The imaging modality of choice is the nuclear bone scan, as it shows uptake in 85% of cases (35).

Table 2 lists the Strasbourg diagnostic criteria for Schnitzler syndrome. These have been validated and have a sensitivity and specificity of 81% and 100%, respectively (36). An older and original criteria list, known as the Lipsker criteria (37), does not include skin biopsy results. A criticism of the skin biopsy requirement is that diagnosing NUD may require expertise, which may not be available in the community health settings. For example, in our case, the biopsy result that we read as NUD was interpreted as consistent with urticaria in the community setting. However, skin biopsy is an easy and accessible element for diagnosing Schnitzler syndrome, and typical biopsy findings should be easily recognized by experienced dermatopathologists.

The pathophysiology of Schnitzler syndrome remains obscure. It is an AIS related to CAPS by way of clinical symptoms and has an excellent response to treatment with interleukin-1 (IL-1) beta antagonists. Unlike CAPS, it does not have the *NLRP3* mutation (38). *NLRP3* is critically involved in the function of the inflammasome, which regulates IL-1 beta. A recent study has shown the presence of myD88 LP265 mutation in some patients with Schnitzler syndrome (39). Patients with CAPS do not develop MG. To further support this lack of clarity about pathophysiology, an expert panel has proposed changing the name of CAPS to *NLRP3*–associated autoinflammatory disease. However, the term Schnitzler syndrome has not been changed (30). Whether the monoclonal protein in Schnitzler syndrome is a cause or effect of inflammation is unknown. Limited efficacy of rituximab in the treatment of Schnitzler syndrome disputes a pathogenic role of monoclonal proteins (10).

Table 2. Strasbourg diagnostic criteria for Schnitzler syndrome*

Mandatory criteria
Chronic urticarial rash
Monoclonal protein (IgM or IgG)
Minor criteria
Recurrent fevers†
Objective findings of abnormal bone remodeling with or without bone pain‡
Skin biopsy with neutrophilic urticarial infiltrate§
Leukocytosis and/or elevated C-reactive protein¶
Definitive diagnosis
Two mandatory criteria plus at least 2 minor criteria if IgM monoclonal protein and at least 3 minor criteria if IgG monoclonal protein
Probable diagnosis
Two mandatory criteria plus at least 1 minor criterion if IgM monoclonal protein and at least 2 minor criteria if IgG monoclonal protein

* Adapted with permission from ref. 10.
† Unexplained fever >38°C; occurs usually with rash.
‡ Shown by magnetic resonance imaging, nuclear bone scanning, and/or elevated bone alkaline phosphatase test result.
§ Specifically neutrophilic urticarial dermatosis.
¶ Neutrophils >10.0 × 10^9/liters and/or C-reactive protein level >30 mg/dl.

Treatment with anakinra produces a highly efficacious response in 94% of patients, followed by canakinumab in 91%, and tociluzumab in 75% (10). Rilonacept is 50% efficacious in 50% of patients and gives a partially efficacious response in 38% (10,40). If patients do not respond to IL-1 beta antagonists, the diagnosis should be reconfirmed. All other agents have much lower efficacies. However, treatment is not curative, and symptoms recur if treatment is halted.

Hematologic malignancy is the major long-term complication, with a progression rate of 1% per year in MGUS (19). However, MGUS with IgM monoclonal protein, the prevalent type in Schnitzler syndrome, has a higher rate of progression than non-IgM MGUS, especially in the early years after diagnosis (41). WM is the most common hematologic malignancy in Schnitzler syndrome; therefore, rising IgM levels are concerning for WM. Approximately 15% to 20% of patients with Schnitzler syndrome with MGUS will develop a hematologic malignancy. Hemoglobin below 12.2 mg/dl predicts poor survival in Schnitzler syndrome (32). Close coordination with the hematology department is essential

for regular follow-up, as well as laboratory testing based on MGUS risk stratification (14,42). The rarity of the disease and the long-term follow-up required make it challenging to assess the efficacy of IL-1 blockage in preventing WM. In one series with a median follow-up of 3 years, 2 patients developed WM in the no anakinra group, while none did in the anakinra group (43). There is, however, one report of WM development in a patient treated with anakinra (44).

Schnitzler syndrome is a disorder characterized by 2 mandatory findings: urticaria (NUD on histology) and a monoclonal protein. This does not imply that every patient with CU should be screened for MGs. MGs should only be queried if the patient has systemic complaints like those seen in our case, manifests atypical urticarial features, and/or has abnormal laboratory results. The probability of finding an MG in patients with CU under the age of 43 years is very unlikely (45). It is important to remember that a negative serum protein electrophoresis result alone does not exclude an MG, and further testing should follow if clinical suspicion is high (46). This case might seem to suggest that a lot of rare diseases can have associations with monoclonal proteins, which is true. A new syndrome of monoclonal proteins, recurrent fever, and arthralgia without urticaria and bone involvement has been proposed. The authors suggest that a new disease category should be formed: monoclonal gammopathy of inflammatory significance (47), which is along the lines of similar dermatologic and nephrology disorders (48).

Schnitzler syndrome is a disease that crosses the paths of primary care providers, dermatologists, allergists, rheumatologists, and hematologists. Its rarity makes it a challenge to diagnose, but once the relationship between CU and systemic symptoms is known, comprehensive testing to detect a monoclonal protein should easily confirm the diagnosis.

FINAL DIAGNOSIS

Schnitzler syndrome.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Aslam had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Aslam.
Acquisition of data. Aslam, Wiedmeier, DiCaudo.
Analysis and interpretation of data. Aslam, Wiedmeier, DiCaudo.

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Real-World Outcomes Associated With Methotrexate, Sulfasalazine, and Hydroxychloroquine Triple Therapy Versus Tumor Necrosis Factor Inhibitor/Methotrexate Combination Therapy in Patients With Rheumatoid Arthritis

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Objective. Though randomized controlled trials have demonstrated relatively comparable clinical outcomes with triple therapy (methotrexate [MTX], sulfasalazine [SSZ], and hydroxychloroquine [HCQ]) compared to combination therapy (tumor necrosis factor inhibitor [TNFi] and MTX), real-world experiences comparing these strategies have not been well studied.

Methods. We evaluated the clinical effectiveness and effects of medication discontinuation of triple therapy with MTX/SSZ/HCQ versus combination therapy with TNFi/MTX in rheumatoid arthritis (RA) patients enrolled in the Corrona RA Drug Safety & Effectiveness Registry. Propensity score matching was used to match patients up to a ratio of 1:3 to adjust for imbalances between treatment groups, with stratification performed according to biologics-naive or biologics-exposed status of study participants.

Results. Patients eligible for analysis in this study included biologics-naive RA patients (3,926 who received combination therapy with TNFi/MTX and 262 who received triple therapy with MTX/SSZ/HCQ) and biologics-exposed RA patients (3,365 who received combination therapy with TNFi/MTX and 130 patients who received triple therapy with MTX/SSZ/HCQ). Before propensity score matching, numerous factors were imbalanced between the treatment groups, with triple therapy patients generally being older, having a longer disease duration of RA and lower RA disease activity, and more likely having a history of malignancy and other comorbidities. After matching, almost all (93–98%) triple therapy patients could be matched to TNFi/MTX therapy patients, and cohort characteristics were generally well balanced. Discontinuation of medication was greater in triple therapy patients referent to TNFi/MTX therapy patients (adjusted hazard ratio [HR] of 2.17 [95% confidence interval 1.63–2.88] in the biologics-naive group; adjusted HR of 1.51 [95% confidence interval 1.06–2.15] in the biologics-exposed group). At 6 months, the proportion of biologics-naive patients attaining low disease activity was significantly greater in the TNFi/MTX treatment group (49.2% in TNFi/MTX therapy patients versus 33.3% in triple therapy patients), as was the mean change in Clinical Disease Activity Index scores (–9.3 units versus –5.5 [95% confidence interval –1.5, –6.1]). Corresponding results in the biologics-exposed patients numerically favored TNFi/MTX therapy compared to triple therapy but did not reach statistical significance.

Conclusion. Few patients receive triple therapy with MTX/SSZ/HCQ in the US. In the present study, drug persistence and clinical effectiveness outcomes were less favorable in triple therapy patients compared to TNFi/MTX therapy patients.

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SIGNIFICANCE & INNOVATIONS

- While several trials and observational studies have compared triple therapy with methotrexate (MTX), sulfasalazine (SSZ), and hydroxychloroquine (HCQ) to combination therapy with tumor necrosis factor inhibitor (TNFi)/MTX, few studies in the US have investigated the real-world effectiveness of these treatment combinations on drug persistence or clinical effectiveness outcomes.
- Over a 19-year observation period, few combination therapy patients (<3%) received triple therapy. Patients initiating triple therapy were older, had longer disease duration, and had more comorbidities but less active rheumatoid arthritis.
- After propensity score matching was performed to account for imbalances between treatment groups, combination therapy with TNFi/MTX was shown to be significantly more effective than triple therapy with MTX/HCQ/SSZ in regard to drug persistence and improvement in disease activity. Differences were numerically larger but qualitatively similar in patients who were naive to treatment with biologic agents compared to patients who had received treatment with biologic agents.

INTRODUCTION

Several randomized controlled trials (RCTs) conducted in rheumatoid arthritis (RA) patients have shown that at 2 years, clinical outcomes were comparable, or not significantly different, among patients with RA who received triple therapy with methotrexate (MTX), sulfasalazine (SSZ), and hydroxychloroquine (HCQ) compared to patients who received combination therapy with tumor necrosis factor inhibitors (TNFi) and MTX (1–5). These findings were shown in 2 RCTs (Treatment of Early Aggressive Rheumatoid Arthritis [TEAR] and Swedish Farmacotherapy [SWEFOT] trials) in patients with early RA (TEAR) or MTX-naive patients (SWEFOT) (1–3), and in 1 trial in patients with established RA (Rheumatoid Arthritis Comparison of Active Therapies [RACAT] study) (4). Clinical results at 6 months were comparable between triple therapy patients and TNFi/MTX therapy patients in the TEAR trial, though more favorable clinical outcomes were observed at 1 year in the TNFi/MTX treatment group compared to the triple therapy group in the SWEFOT study. A significant radiographic benefit was observed with TNFi/MTX therapy in both the TEAR and SWEFOT trials, although the clinical relevance of the difference (~1–3 units at 2 years) is a topic of debate. Given the substantial differences in cost between MTX/SSZ/HCQ triple therapy and TNFi/MTX combination therapy, triple therapy has shown to be appreciably more cost-effective (5).

Additional evidence has been obtained from real-world settings to evaluate the prevalence of triple therapy use in patients and to investigate whether findings from the RCTs described above can be generalized to routine clinical practice. In one US study based on administrative claims data, treatment intensification to TNFi/MTX therapy was approximately 15-fold more common than intensification to triple therapy with MTX/SSZ/HCQ (6). Based on a US and Veterans Administration electronic health record claims data source, adherence was substantially better, with 13.1% greater adherence (95% confidence interval [95% CI] 9.2–17.0%) to TNFi/MTX therapy than to MTX/SSZ/HCQ triple therapy (7). This finding appeared to be primarily mediated by lower adherence to SSZ (8). However, these data sources were limited due to a lack of information regarding clinical outcomes (e.g., RA disease activity).

Patients might discontinue some of the medications in a TNFi/MTX or MTX/SSZ/HCQ regimen if they attain the treat-to-target goals of low disease activity or remission (9), but data sources (such as administrative claims that lack disease activity information) cannot ascertain whether treatment discontinuation under these circumstances are the underlying reason. Also of importance, these data sources and most other observational data sources are subject to "left censoring" whereby patients receiving prior treatments for RA might not have this information recorded in the data, such that the ability to study both biologics-naive and biologics-exposed patients is limited. Given that clinical outcomes typically are worse when patients do not respond to an increasing number of RA therapies (10), the ability to accurately classify a patient as biologics-naive or biologics-exposed is therefore of importance.

In light of these gaps in medical evidence, the present study was undertaken to compare triple therapy with MTX/SSZ/HCQ to combination therapy with TNFi/MTX in a large US registry of RA patients to evaluate treatment persistence and clinical outcomes. These outcomes included change in RA disease activity, change in physical function, and attainment of the treat-to-target disease activity objectives of low disease activity or remission in a very well-defined population with virtually complete ascertainment of prior treatment regimens.

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PATIENTS AND METHODS

Patient eligibility for study inclusion. The Corrona RA registry (11) was analyzed using data collected from years 2001–2019. All patients provided written informed consent to participate in the study through the New England Independent Institutional Review Board. We identified RA patients in the Corrona registry who were newly started on MTX/SSZ/HCQ triple therapy or TNFi/MTX combination therapy, with medical information contributed by 373 doctors at 131 unique sites across 42 states in the US since registry initiation. Initiation of triple therapies and combination therapies could have been simultaneous or sequential, but patients had to receive all 3 medications (MTX/SSZ/HCQ) for triple therapy or both medications (TNFi/MTX) simultaneously for combination therapy in order to be classified as a member of either cohort. The index date was defined as the date on which first use of triple therapy or TNFi/MTX therapy after enrollment in the Corrona registry occurred.

Study participants were stratified as being biologics-naive or biologics-exposed, or targeted synthetic disease-modifying antirheumatic drugs (DMARDs)–exposed and grouped with the biologics-exposed patients, based upon bespoke registry case report forms that showed lifetime use of biologic DMARDs (bDMARDs) (abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, sarilumab, and tocilizumab), targeted synthetic DMARDs (baricitinib, tofacitinib, and upadacitinib), and conventional synthetic DMARDs (csDMARDs) before or after registry enrollment. Patients could be included once both in the biologics-naive cohort and (at a later time) in the biologics-exposed cohort and were permitted to contribute (at most) only 1 observation to the biologics-naive and to the biologics-exposed cohort. Patients were required to have moderate or high disease activity as measured by the Clinical Disease Activity Index (CDAI) (12) at baseline and ≥1 follow-up visit recorded in the registry. Drug persistence, clinical outcomes, and physical function measured by the Health Assessment Questionnaire (HAQ) were analyzed as described below.

Triple therapy with MTX, SSZ, and HCQ. Triple therapy was defined as combined use of MTX, SSZ, and HCQ with use of no other concurrent csDMARDs (e.g., leflunomide) or bDMARDs. Initiation of triple therapy was defined as the first time that a patient simultaneously used all 3 medications. A patient could have either started all 3 medications simultaneously or could intensify treatment and add other medications sequentially over time. For example, a patient could have been receiving MTX alone, and then have added HCQ and SSZ, either together or separately at subsequent visits. Patients with prior use of triple therapy (e.g., they were enrolled in the registry already receiving triple therapy, and then discontinued but subsequently restarted triple therapy) were excluded from analysis.

Combination therapy with TNFi/MTX. Using a similar approach to the triple therapy patients, the TNFi/MTX treatment group included patients initiating TNFi therapy together with MTX at the same time or patients who added TNFi therapy to background MTX (with no concomitant use of other conventional csDMARDs), and patients must have never previously received a TNFi that was restarted with concomitant use of MTX. Given the expected pattern of treatment escalation in the US, adding MTX to prevalent TNFi use was not classified as TNFi/MTX initiation, and registry patients who received treatments in this order were not included in the present study. Within the biologics-naive and biologics-exposed cohorts, selection of triple therapy exposure was prioritized, given the expectation that there would be fewer individuals receiving triple therapy versus TNFi/MTX therapy.

Definition of treatment discontinuation. Patients were considered to have discontinued (i.e., to not have drug persistence) MTX/SSZ/HCQ triple therapy or TNFi/MTX therapy under any of the following conditions: 1) starting a new bDMARD/targeted synthetic DMARD, 2) addition of a new csDMARD, and/or 3) discontinuation of any of the treatments that comprise triple therapy (MTX, SSZ, or HCQ) and TNFi/MTX therapy (TNFi or MTX) while RA remained in moderate to high disease activity (CDAI >10). Discontinuation of medication if the patient had attained low disease activity (CDAI ≤10) was censored given that it might be clinically reasonable to discontinue some RA medications if the patient attained low disease activity or better.

Clinical outcome measures. For the assessment of clinical response, several outcomes were evaluated, including change in CDAI as a continuous variable, attainment of low disease activity (CDAI ≤10), improvement in CDAI by at least its minimally clinically important difference (6 units for RA patients starting with moderate disease activity, 12 units for RA patients starting with high disease activity) (13), and change in physical function, as assessed using the subgroup of patients who had HAQ data available (14). Change in HAQ analysis was limited to patients with a baseline HAQ score of >0 (the "HAQ subcohort") to avoid a ceiling effect. All clinical outcomes were assessed at the closest clinical visit at ~6 months (range 4–9 months) where CDAI (and HAQ) data were nonmissing. Patients did not have to remain on therapy for these outcomes to be evaluated so as to avoid the bias of a "completer-only" analysis. We compared results for all patients who had a 6-month visit and either imputed nonresponse for the binary outcome if patients stopped therapy or used the last observation carried forward method for continuous outcomes.

Statistical analysis. We evaluated the prevalence of medication use and baseline characteristics at the time of initiation, comparing MTX/SSZ/HCQ therapy patients to TNFi/MTX therapy patients. All descriptive characteristics and subsequent outcome analyses were stratified by whether patients were biologics-naive

Table 1. Baseline comparison of triple therapy with MTX/SSZ/HCQ compared to combination therapy with TNFi/MTX in biologics-naive RA patients*

Baseline characteristics	Triple therapy (MTX/SSZ/HCQ) (n = 262)	Combination therapy (TNFi/MTX) (n = 3,926)	SMD difference	*P*
Female sex	188 (72)	2,906 (74.3)	0.052	0.413
Age, mean ± SD years	60.0 ± 13.2	57.1 ± 13.3	−0.225†	0.000
Race				
White	204 (78.2)	3,150 (80.4)	0.055	0.379
African American	21 (8)	311 (7.9)	0.003	0.957
Asian	2 (0.8)	54 (1.4)	0.059	0.404
Hispanic	22 (9.8)	297 (9.3)	−0.019	0.778
Duration of RA, mean ± SD years	8.4 ± 8.7	6.5 ± 8.5	−0.224†	0.000
History of illness				
Cancer	34 (13.0)	176 (4.5)	−0.304†	0.000
Cardiovascular disease	31 (11.8)	345 (8.8)	−0.100	0.095
Diabetes mellitus	27 (10.6)	331 (8.4)	−0.074	0.233
Serious infection	13 (6.3)	96 (3.4)	−0.138†	0.027
Medical insurance status				
Medicare	88 (35.8)	1,045 (27.4)	−0.181†	0.004
Medicaid	19 (7.7)	242 (6.3)	−0.054	0.390
Private	170 (69.1)	2,892 (75.7)	0.148†	0.020
None	9 (3.7)	86 (2.3)	−0.083	0.157
College education	150 (58.6)	1,985 (52.7)	−0.119†	0.068
Smoking history				
Never smoker	135 (51.7)	2,005 (51.6)	−0.002	0.975
Past smoker	82 (31.4)	1,093 (28.1)	−0.072	0.256
Current smoker	44 (16.9)	786 (20.2)	0.087	0.187
Employment status				
Full-time work	104 (40.8)	1,676 (43.4)	0.053	0.411
Part-time work	23 (9)	358 (9.3)	0.009	0.892
Disabled	18 (7.1)	385 (10)	0.104	0.129
Retired	76 (29.8)	969 (25.1)	−0.105	0.095
Disease activity measures, mean ± SD				
CDAI score, 0–76	15.5 ± 12.1	21.0 ± 14.5	0.412†	0.000
Tender joint count, 0–28	4.4 ± 5.4	6.9 ± 7.1	0.395†	0.000
Swollen joint count, 0–28	4.7 ± 5	6.5 ± 6.3	0.317†	0.000
PtGA score, 0–100 mm	37.9 ± 26.3	41.7 ± 27.3	0.143†	0.039
PhGA score, 0–100 mm	26.7 ± 21.2	35.4 ± 22.9	0.395†	0.000
Pain VAS score, 0–100 mm	43.2 ± 28.4	44.5 ± 28.4	0.045	0.505
HAQ score, 0–3	0.73 ± 0.6	0.91 ± 0.7	0.275†	0.002
Morning stiffness	191 (81.6)	2,938 (83.6)	0.052	0.434
RF or CCP positivity‡	119 (62.6)	1,503 (56.9)	−0.117†	0.122
Treatments received				
No prednisone	186 (71.0)	2,784 (70.9)	−0.002	0.978
Prednisone <7.5 mg	52 (20.2)	719 (18.5)	−0.042	0.511
Prednisone ≥7.5	20 (7.8)	381 (9.8)	0.073	0.279
NSAIDs	150 (57.3)	2,050 (52.2)	−0.101	0.114
Other analgesics	111 (42.4)	1,514 (38.6)	−0.077	0.221
Charlson comorbidity index score				
1	191 (72.9)	3,094 (78.8)	0.138†	0.024
2–3	68 (26)	806 (20.5)	−0.129†	0.036
≥4	3 (1.1)	26 (0.7)	−0.051	0.362
Calendar years of recorded study data				
2001–2007	56 (21.4)	1,034 (26.3)	0.117†	0.076
2008–2012	83 (31.7)	1,465 (37.3)	0.119†	0.067
2013–2016	77 (29.4)	908 (23.1)	−0.142†	0.021
2017–2019	46 (17.6)	519 (13.2)	−0.120†	0.047

* Values are the number (%) unless indicated otherwise. Numbers vary slightly across rows due to missing data for some covariates. List of covariates is shown as partially shortened. Baseline features were defined at time of drug initiation. CCP = citrullinated peptide; CDAI = Clinical Disease Activity Index; HAQ = Health Assessment Questionnaire; HCQ = hydroxychloroquine; MTX = methotrexate; NSAIDs = nonsteroidal antiinflammatory drugs; PhGA = physician global assessment of disease activity; PtGA = patient global assessment of disease activity; SSZ = sulfasalazine; RA = rheumatoid arthritis; RF = rheumatoid factor; TNFi = tumor necrosis factor inhibitor; VAS = visual analog scale.
† Standardized mean difference (SMD) of >0.10 with $P < 0.05$.
‡ Conditional on at least 1 nonmissing value.

(or targeted synthetic DMARDs–naive) or biologics-exposed. A variety of demographic, comorbidity, and RA-related characteristics selected based on clinical knowledge were included in a propensity score model estimated using logistic regression. The propensity score was used to match triple therapy patients to TNFi/MTX combination therapy patients via a variable ratio (up to 1:3), greedy-matching with a maximal caliper width of 0.10, and also matching exactly on CDAI category (moderate versus high disease activity) (15). Across analyses, a small number of patients (<10) were not propensity score matched due to missing data for key covariates. Any characteristics with residual imbalances based on a standardized mean difference (SMD) of >0.10 (after propensity score matching) with a *P* value of <0.05 and prevalence of ≥5% were included in outcome models to provide further confounder control. Because clinical outcomes required data from an additional visit ~6 months later with nonmissing CDAI or HAQ scores, propensity score matching was repeated for clinical outcomes.

Clustered sandwich estimators for variance were used with matched pairs as clusters (16), and the proportional hazards assumption was verified (15). Adjusted mixed effects logistic regression was used to estimate odds ratios (ORs) to evaluate the likelihood of a patient attaining low disease activity according to the CDAI, or change in CDAI score of at least its minimum clinically important difference. Mixed-effects general linear models were used to analyze change in CDAI and HAQ scores, adjusting for covariates with residual and significant imbalance after propensity score matching. Continuous covariates (e.g., patient pain measured on a 0–100–mm visual analog scale [VAS]) were examined in categories based on distributions of the data and also via smoothed scatterplots using loess curves to confirm the linearity assumption. A random intercept (but no other random effects) was estimated to adjust for clustering by matched pairs. Interaction terms were evaluated based on whether drug persistence or 4 clinical effectiveness outcomes results were significantly different for biologics-naive patients versus biologics-exposed patients, with a *P* value of less than 0.10 considered a significant interaction. Stata software was used to perform statistical analyses.

RESULTS

The schema for patient selection is depicted in Supplementary Figures 1 and 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24253/abstract. We identified 392 patients (2.5% of individuals included in this study) who had ever initiated triple therapy with MTX/SSZ/HCQ, of whom only 27% added 2 or more triple therapy medications at the same time, and 15,164 (97.1%) who had ever initiated TNFi use after receiving MTX therapy. In biologics-naive patients (Table 1), there were several differences between the groups prior to propensity score matching. Patients initiating triple therapy (rather than TNFi) were older (mean age of 60 years versus 57 years), had longer RA disease duration (8.4 years versus 6.5 years), were more likely to have a history of malignancy (13% versus 4%) and serious infections (6% versus 3%) yet lower RA disease activity (mean CDAI score of 16 versus 21), and had higher Charlson comorbidity scores. Similarly, of the biologics-exposed patients (Table 2), triple therapy patients were older (mean age of 60.9 years versus 57.1 years), had a longer disease duration (17.0 versus 11.5 years), and experienced a higher frequency of cancer, cardiovascular disease, diabetes mellitus, and serious infections. Triple therapy patients had lower mean scores on the CDAI (17.4 versus 19.9), although both treatment groups still scored on the higher end of the moderate range on the CDAI. There were 22 biologics-naive patients excluded from analysis in the TNFi/MTX therapy group as they were included in the triple therapy group, and 17 biologics-exposed patients who were also excluded from analysis (<1% of patients in each strata were excluded for this reason).

Baseline characteristics of the number of individuals who had at least 1 follow-up visit and who met the additional inclusion criteria for the analysis of discontinuation and clinical effectiveness outcomes before and after propensity score matching are shown in Supplementary Tables 1–4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24253/abstract. Overall, propensity score matching only minimally reduced the size of the triple therapy cohort (with a 98% match and 96% match in the biologics-naive discontinuation cohort and clinical effectiveness cohort, respectively, and a 96% match and 93% match in the biologics-exposed discontinuation cohort and clinical effectiveness cohort, respectively).

Following matching, 118 triple therapy patients were matched to 348 TNFi/MTX therapy patients (Supplementary Table 1), with 95% of triple therapy patients matched at a ratio of 1:3 for the discontinuation outcome, and 92% matched at a ratio of 1:3 for the clinical effectiveness outcome (Supplementary Table 2). After propensity score matching, the groups were generally well-balanced with only small differences. In the triple therapy cohort, the mean age of patients was 61 years, ~75% were women, and >80% were white. The mean CDAI score at the start of treatment was 21, with patients having an average of 6–7 tender and swollen joints. Between 25% and 30% of patients were receiving oral steroids. The corresponding patient characteristics in the biologics-exposed patients yielded 69 eligible triple therapy patients (discontinuation analysis) and 56 eligible triple therapy patients (clinical effectiveness analysis) (Supplementary Tables 3–4 [http://onlinelibrary.wiley.com/doi/10.1002/acr.24253/abstract]), with 90% of patients matched at a ratio of 1:3 for the discontinuation outcome, and 87% of patients matched at a ratio of1:3 for the clinical effectiveness outcome.

In biologics-naive patients, drug persistence (i.e., non-discontinuation) was better in TNFi/MTX therapy patients compared to triple therapy patients (Figure 1). At 12 months specifically, drug persistence with triple therapy was lower compared to the TNFi/MTX therapy group (45% and 69%, respectively).

Table 2. Baseline comparisons of triple therapy with MTX/SSZ/HCQ compared to combination therapy with TNFi/MTX in biologics-exposed RA patients*

Baseline characteristics	Triple therapy (MTX/SSZ/HCQ) (n = 130)	Combination therapy (TNFi/MTX) (n = 3,365)	SMD difference	*P*
Female sex	107 (82.3)	2,693 (80.2)	−0.054	0.553
Age, mean ± SD years	60.9 ± 11.7	57.1 ± 12.9	−0.310†	0.001
Race				
White	108 (83.1)	2,777 (82.7)	−0.011	0.905
African American	8 (6.2)	214 (6.4)	0.008	0.925
Asian	2 (1.5)	39 (1.2)	−0.033	0.693
Hispanic	8 (7.3)	244 (8.8)	0.055	0.586
Duration of RA, mean ± SD years	17.0 ± 11.4	11.5 ± 9.5	−0.522†	0.000
History of illness				
Cancer	20 (15.4)	206 (6.1)	−0.302†	0.000
Cardiovascular disease	18 (13.8)	345 (10.3)	−0.110†	0.188
Diabetes mellitus	20 (15.4)	262 (7.8)	−0.239†	0.002
Serious infection	21 (18.1)	145 (5.3)	−0.405†	0.000
Medical insurance status				
Medicare	53 (41.1)	1,099 (33.3)	−0.160†	0.068
Medicaid	11 (8.5)	193 (5.9)	−0.103	0.209
Private	89 (69)	2,422 (73.5)	0.099	0.258
None	2 (1.6)	60 (1.8)	0.021	0.822
College education	75 (58.6)	1,994 (60.8)	0.045	0.614
Smoking history				
Never smoker	66 (50.8)	1,745 (52.2)	0.029	0.746
Past smoker	45 (34.6)	1,001 (30)	−0.100	0.256
Current smoker	19 (14.6)	596 (17.8)	0.087	0.346
Employment status				
Full-time work	48 (36.9)	1,259 (38.3)	0.027	0.759
Part-time work	15 (11.5)	297 (9)	−0.083	0.329
Disabled	28 (21.5)	523 (15.9)	−0.145†	0.086
Retired	33 (25.4)	830 (25.2)	−0.004	0.966
Disease activity measures, mean ± SD				
CDAI score, 0–76	17.4 ± 11.5	19.9 ± 14.3	0.188†	0.065
Tender joint count, 0–28	5.4 ± 6	6.8 ± 7.2	0.206†	0.041
Swollen joint count, 0–28	4.7 ± 4.2	5.3 ± 5.7	0.121†	0.247
PtGA score, 0–100 mm	42.2 ± 25.5	45 ± 27.3	0.104	0.279
PhGA score, 0–100 mm	30.9 ± 22.5	32.8 ± 22.7	0.081	0.386
Pain VAS score, 0–100 mm	43.8 ± 28.1	47 ± 28.3	0.112†	0.232
HAQ score, 0–3	1.01 ± 0.8	0.98 ± 0.7	−0.039	0.713
Morning stiffness	98 (82.4)	2,451 (83.6)	0.032	0.727
RF or CCP positivity‡	47 (58)	1,295 (60.3)	0.046	0.683
Treatments received				
No prednisone	77 (59.2)	2,391 (71.1)	0.250†	0.004
Prednisone <7.5mg	28 (21.7)	620 (18.6)	−0.076	0.383
Prednisone ≥7.5	24 (18.6)	314 (9.4)	−0.265	0.001
NSAIDs	69 (53.1)	1,866 (55.5)	0.048	0.593
Other analgesics	63 (48.5)	1,539 (45.7)	−0.055	0.541
Charlson comorbidity index				
1	88 (67.7)	2,532 (75.2)	0.167†	0.051
2–3	40 (30.8)	810 (24.1)	−0.150†	0.081
≥4	2 (1.5)	23 (0.7)	−0.081	0.256
Calendar years of recorded study data				
2001–2007	11 (8.5)	609 (18.1)	0.286†	0.005
2008–2012	43 (33.1)	1,297 (38.5)	0.114†	0.208
2013–2016	55 (42.3)	979 (29.1)	−0.278†	0.001
2017–2019	21 (16.2)	480 (14.3)	−0.053	0.546

* Values are the number (%) unless indicated otherwise. Numbers vary slightly across rows due to missing data for some covariates. List of covariates is shown as partially shortened. Baseline features were defined at time of drug initiation. CCP = citrullinated peptide; CDAI = Clinical Disease Activity Index; HAQ = Health Assessment Questionnaire; HCQ = hydroxychloroquine; MTX = methotrexate; NSAIDs = nonsteroidal antiinflammatory drugs; PhGA = physician global assessment of disease activity; PtGA = patient global assessment of disease activity; SSZ = sulfasalazine; RA = rheumatoid arthritis; RF = rheumatoid factor; TNFi = tumor necrosis factor inhibitor; VAS = visual analog scale.
† Standardized mean difference (SMD) of >0.10 with $P < 0.05$.
‡ Both RF- and CCP-negative, negative for 1 antibody and missing data on 1 antibody, or conditional on at least 1 nonmissing value.

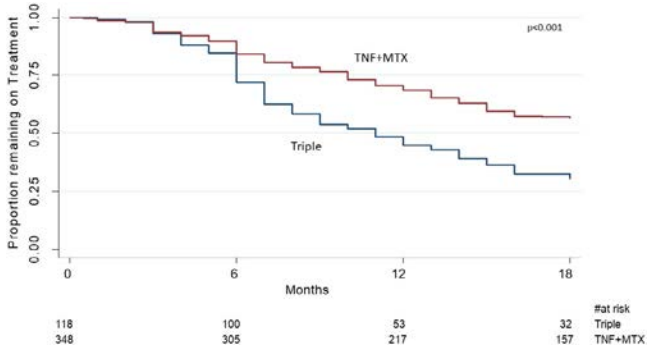

Figure 1. Discontinuation of triple therapy with methotrexate (MTX), sulfasalazine, and hydroxychloroquine in 118 patients with rheumatoid arthritis (RA) and combination therapy with tumor necrosis factor (TNF) and MTX in 348 patients with RA in biologics-naive, propensity score–matched cohorts, with patient matching performed at a ratio of 1:3.

Following multivariable adjustment that accounted for an imbalanced history of medical insurance status, smoking status, and seropositivity as well as the clustered nature of the data, discontinuation of treatment was significantly greater in the triple therapy group compared to the TNFi/MTX therapy group, with an adjusted hazard ratio (HR) of 2.17 (95% CI 1.63, 2.88). Drug persistence was also lower in the MTX/SSZ/HCQ therapy group compared to the TNFi/MTX therapy group among biologics-exposed patients at 12 months (48% and 57%, respectively). The triple therapy group had a higher adjusted risk for discontinuation of medication compared to the TNFi/MTX therapy group (adjusted HR 1.51 [95% CI 1.06, 2.15]) (Figure 2).

Clinical outcomes of propensity score-matched patients are shown in Table 3. In biologics-naive patients, the likelihood that patients attained low disease activity (CDAI of ≤10) at 6 months was higher in the TNFi/MTX therapy group than in the triple therapy group (49.2% and 33.3%, respectively) (OR 0.50 [95% CI 0.31, 0.82]) after consideration of matched pairs and adjusting for patient pain, diabetes mellitus, cardiovascular disease, and calendar year). Similarly, the likelihood of achieving a change in CDAI greater than its minimally clinically important difference was lower in triple therapy patients compared to TNFi/MTX therapy patients (33.3% versus 56.9%, respectively) (adjusted OR 0.38 [95% CI 0.23, 0.62]). The mean reduction in CDAI was –5.5 units in triple therapy patients versus –9.3 units in TNFi/MTX therapy patients, with a significant difference of –3.8 units (95% CI –1.5, –6.1). Change in HAQ score was numerically different, favoring in the TNFi/MTX group by –0.18 units. Results in the smaller cohort of biologics-exposed patients were consistently more favorable in the TNFi/MTX treatment group, though none reached statistical significance. No interaction terms for drug persistence outcomes or clinical effectiveness outcomes were significant, indicating that findings observed in the biologics-naive patient group were not significantly different compared to those in the biologics-exposed patient group.

DISCUSSION

Based on real-world evidence from a large US registry of RA patients collected over 19 years from a large number of sites and physicians, few patients with RA (2.5%) initiated triple therapy with MTX/SSZ/HCQ compared to patients who initiated combination therapy with TNFi/MTX. The paucity of triple therapy in this registry is notable given the fact that the timespan covered by these observational data corresponds to a historic timeframe that began after the publication of the first trial on triple therapy with MTX/SSZ/HCQ (17) and the publication of several highly visible "head-to-head" MTX/SSZ/HCQ therapy versus TNFi/MTX therapy trials (1–4). Patients who received triple therapy had several differences at baseline from those who received TNFi/MTX therapy. Indeed, patients who received triple therapy were older, had longer RA disease duration, and had more comorbidities. We speculate that this may be the reason that clinicians are more comfortable with prescribing biologics to younger patients with fewer comorbidities given safety concerns over their use in older, more ill patients, a fear that may or may not be grounded in evidence. Triple therapy patients also had lower RA disease activity and less impaired functional status than patients starting TNFi/MTX therapy. These differences in baseline status were both statistically significant and clinically meaningful.

After propensity score matching was performed to balance patient characteristics in both biologics-naive and biologics-exposed cohorts, the rate of drug persistence in triple therapy patients was lower at 6 months. Moreover, clinical outcomes of low disease activity as measured by the CDAI, improvement in CDAI score beyond a minimally important difference, change in CDAI score as a continuous variable, and change in HAQ score were more likely to occur in the TNFi/MTX therapy group. Differences between TNFi/MTX therapy patients and triple therapy patients were smaller in magnitude in biologics-exposed patients, and perhaps in part related to the smaller sample size, and did not reach statistical significance; however, based on nonsignificant

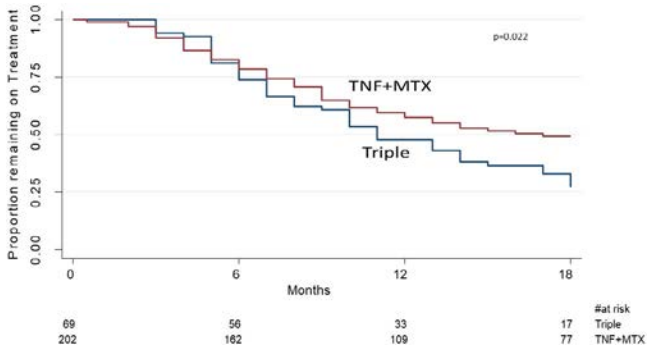

Figure 2. Discontinuation of triple therapy with methotrexate (MTX), sulfasalazine, and hydroxychloroquine in 69 patients with rheumatoid arthritis (RA) and combination therapy with tumor necrosis factor (TNF) and MTX in 202 patients with RA in biologics-exposed, propensity score–matched cohorts, with patient matching performed at a ratio of 1:3. See Figure 1 for definitions.

Table 3. Clinical effectiveness outcomes in propensity score–matched patients at 6 months*

	Triple therapy (MTX/SSZ/HCQ)	Combination therapy (TNFi/MTX)	Adjusted OR or difference of CDAI/HAQ scores (95% CI)†
Biologics-naive patients	(n = 102)	(n = 297)	
Low disease activity on the CDAI, %	33.3	49.2	OR 0.50 (0.31, 0.82)
Change in CDAI > MCID, %	33.3	56.9	OR 0.38 (0.23, 0.62)
CDAI	−5.5 ± 10.0	−9.3 ± 11.4	−3.8 (−1.5, −6.1)
HAQ‡	−0.08 ± 0.49	−0.26 ± 0.63	−0.18 (0.02, −0.38)
Biologics-exposed patients	(n = 56)	(n = 161)	
Low disease activity on the CDAI, %	26.8	31.7	OR 0.75 (0.36, 1.56)
Change in CDAI > MCID, %	26.8	41.6	OR 0.49 (0.24, 1.02)
CDAI	−3.8 ± 14.0	−7.6 ± 12.7	−3.5 (−0.4, 7.3)
HAQ‡	0.02 ± 0.53	−0.09 ± 0.44	−0.11 (0.09, −0.30)

* Values are the mean ± SD except where indicated. No interaction terms were significant for any outcome in the patients naive to treatment with biologics compared to the patients who received treatment with biologics. 95% CI = 95% confidence interval; CDAI = Clinical Disease Activity Index; HAQ = Health Assessment Questionnaire; HCQ = hydroxychloroquine; MCID = minimal clinically important difference; MTX = methotrexate; OR = odds ratio; SSZ = sulfasalazine; RA = rheumatoid arthritis; TNFi = tumor necrosis factor inhibitor.
† Adjusted for patient pain, diabetes mellitus, cardiovascular disease, and calendar year, in addition to the factors that were controlled via propensity score matching.
‡ Analysis restricted to patients who had a baseline Health Assessment Questionnaire (HAQ) score of >0 (n = 45 and 130 in biologics-naive patients in the triple therapy group and combination therapy groups, respectively; n = 30 and 81 in biologics-exposed triple therapy patients and combination therapy patients, respectively).

interaction terms, results in biologics-exposed patients were qualitatively similar to the biologics-naive patients.

The results of the present study are important in the context of findings observed in other clinical trials, such as TEAR (1), SWEFOT (at the 2-year time point [3], but not at the 1-year time point [2]), and RACAT (4), wherein clinical outcomes were shown to be similar between triple therapy patients and TNFi/MTX therapy patients (Table 4). We found that both drug persistence and clinical outcomes were significantly worse in the triple therapy group. Patients participating in a clinical trial may have different motivations, and perhaps fewer alternative treatment options, than those receiving care in real-world settings. Indeed, medication persistence can be influenced by several factors, including patient expectations. For example, if patients expect that triple therapy is less effective than TNFi/MTX therapy, then treatment discontinuation might be differentially increased in the triple therapy arm. In fact, this was observed in the SWEFOT trial in which patients were unblinded with regard to treatments received (2), but was not seen in the TEAR trial in which patients were blinded with regard to treatments received (1).

Because of factors such as direct-to-consumer advertisements, it is possible that patients, or providers, may anticipate greater efficacy from TNFi/MTX therapy than triple therapy. However, our observations were not conducted in a head-to-head setting, as would be the case in an RCT, but prospectively collected in a real-world setting. In addition, many of the patients included in previously published triple therapy trials were started on all 3 medications simultaneously (Table 4). In this observational study, we counted both simultaneous and sequential addition of medications as qualifying as triple therapy. It is possible that patients started on 2 triple therapy drugs, or all 3 medications simultaneously, might have clinically better outcomes than patients adding each of the drugs sequentially to their medication regimen. However, the pattern of patients adding multiple drugs to their treatment regimen at the same time was relatively uncommon in this cohort (only 27% of triple therapy initiations), which did not permit us to investigate this small subgroup of patients separately, and is a recognized limitation of the present study. In addition, analyses from the TEAR trial that explicitly investigated this hypothesis provided evidence against the possibility that patients starting 2 or 3 triple therapy medications simultaneously could have improved clinical outcomes as compared to patients who added each triple therapy drug sequentially, albeit with limitations common to clinical trials (1).

We believe that it is important to note that all of the RCTs comparing triple therapy to TNFi/MTX therapy (except for 1 trial [RACAT]) were conducted in MTX-naive and/or patients with early RA (Table 4). It is well-established that patients with early RA disease respond better to most interventions (18–20), which is perhaps related to a window of biologic opportunity in early disease (21). Study patients had a median disease duration of 6–8 years in the biologics-naive cohort and 12–17 years in the biologics-exposed cohort at the time of treatment initiation, a notable contrast to even the RACAT trial, which had a substantially shorter mean disease duration of ~5 years. The extended disease duration prior to starting biologics noted in our study could be partially explained by our observation period that began in 2001, in which biologics were used less frequently compared to the present day. During the first years of the Corrona registry, patients with longstanding disease were first being prescribed biologic agents.

Additionally, differences in disease activity at baseline differ between the patients assessed in the RCTs and the patients included in the present study. Although all patients in both groups assessed in the present study had to have at

Table 4. Trials and studies with clinical outcomes for triple therapy with MTX/SSZ/HCQ compared to combination therapy with TNFi/MTX in patients with rheumatoid arthritis*

Trial name	Author, year (ref.)	Mean disease duration	Mean disease activity	Length of observation	Blinded	Results of MTX/SSZ/HCQ therapy versus TNFi/MTX therapy	Randomized
TEAR	Moreland et al, 2012 (1)	2.9–4.5 months	DAS28 of 5.8 (high)	2 years	Yes	TNFi/MTX showed improvement on radiographs, but no difference in clinical outcomes.	Yes
SWEFOT							
Year 1	Van Vollenhoven et al, 2009 (2)	6.2–6.3 months	DAS28 of 5.98 (high)	1 year	No	TNFi/MTX showed improvement on radiographs and in clinical outcomes.	Yes
Year 2	Van Vollenhoven et al, 2012 (3)	6.2–6.3 months	DAS28 of 5.98 (high)	2 years	No	TNFi/MTX showed improvement on radiographs, but no difference in clinical outcomes.	Yes
NOR-DMARD	Lie et al, 2011 (22)	1.06–1.22 years	DAS28 of 4.9 (moderate)	6 months clinical, 2 years persistence	No	TNFi/MTX showed improvement on radiographs and in clinical outcomes.	No
RACAT	O'Dell et al, 2013 (4)	4.9–5.5 years	DAS28 of 5.8 (high)	48 weeks	Yes	No difference in clinical outcomes or radiographs shown.	Yes
METEOR	Bergstra et al, 2019 (23)	5–12 months	DAS of 2.58 (moderate)	6.9–9.0 months	No	TNFi/MTX showed improvement on radiographs and in clinical outcomes.	No

* DAS28 = Disease Activity Score in 28 joints; NOR-DMARD = Norwegian Antirheumatic Drug Register; RACAT = Rheumatoid Arthritis: Comparison of Active Therapies in Patients With Active Disease Despite Methotrexate Therapy; SWEFOT = Swedish Farmacotherapy; TEAR = the Treatment of Early Aggressive Rheumatoid Arthritis (see Table 1 for other definitions).

least moderate disease activity as defined by a CDAI score of >10, their mean CDAI score was in the high moderate range (mean CDAI score of 21), which is in contrast to the RCTs where nearly all patients started treatment while experiencing high disease activity. This difference could influence the outcomes that we observed in that patients starting with somewhat lower disease activity may experience a possible floor effect and may have a different likelihood of attaining low disease activity. For this reason, all patients were by design selected for the present study if they were in at least moderate disease activity as defined by the CDAI.

While few other observational studies have investigated the real-world comparative effectiveness of triple therapy versus TNFi/MTX combination therapy, results from the NOR-DMARD cohort are also consistent with our findings and showed that effectiveness was improved with TNFi/MTX combination therapy compared to combination csDMARD therapy (Table 4) (22). More recently, these findings are consistent with the METEOR observational study that found that TNFi/MTX therapy had more improved clinical outcomes as compared to triple therapy (23). In our analysis, the magnitude of improvement in CDAI score was relatively modest (–5.5 units with triple therapy and –9.3 units with TNFi/MTX therapy) compared to that expected from an RCT of biologics-naive RA patients with high disease activity initiating treatment.

Among biologics-exposed patients, treatment responses were similar in the triple therapy arm but somewhat attenuated in the TNFi/MTX therapy arm, such that differences between the treatment arms were no longer significantly different. Numerous RCTs have shown that treatment response is diminished in patients with an inadequate response to TNFi (24), which has also been shown in observational RA data. None of the interaction terms were significant in the TNFi/MTX therapy patients, supporting the finding that the incremental benefit of TNFi/MTX therapy versus triple therapy was not qualitatively different for biologics-naive patients compared to biologic-exposed patients, which is consistent with 2015 American College of Rheumatology guidelines for treatment of RA (9) following failed response to a TNFi.

Strengths of our study included examination of clinical outcomes from a large US registry in which patients analyzed had initiated therapy at a time that their RA was active, as opposed to initiating a therapy due to other reasons, such as safety/tolerability or nonmedical reasons (e.g., medical insurance change). Our use of propensity score matching maximized the use of the available data and attained relatively good balance between exposure groups, despite some meaningful and initial differences between the patients receiving triple therapy with MTX/SSZ/HCQ and those receiving combination therapy with TNFi/MTX prior to matching. Propensity score matching only slightly reduced the size of the triple therapy cohort (2–7%, depending on the analysis performed).

Our results must be interpreted in light of our study design. The number of patients initiating MTX/SSZ/HCQ triple therapy relative to TNFi/MTX combination therapy (2.5% and 97.5%, respectively) was relatively small and reflects the apparent uncommon use of triple therapy in routine clinical practice. Corrona registry visits are spaced approximately every 6 months, which is comparable to other national RA registries. While this frequency likely does not capture every clinical visit, it seems improbable that it would be meaningfully differential between patients who received TNFi/MTX therapy and those who received triple therapy. Additionally, despite use of propensity score matching and controlling for the few remaining imbalanced covariates in outcome models, the potential for residual confounding in these observational data still remains, as treatment was not randomized. We also note that data from the Corrona registry have previously been shown to have good generalizability in the US compared to other population-based data sources (e.g., the US Medicare program) (25). Finally, the registry implements specific case report forms that record the use, start/stop dates, and reasons for initiation and discontinuation of all RA medications. While we recognize the potential for misclassification of the use of medications studied, past work has shown high concordance (97.4% overall agreement) between the data captured regarding MTX use as reported in the registry and independently queried confirmation as reported by patients in regard to their actual medication use (26).

In conclusion, the frequency of triple therapy with MTX/SSZ/HCQ utilization in this large US registry covering a wide sample of healthcare providers and different sites from 42 different US states was quite low. Baseline characteristics of triple therapy patients versus TNFi/MTX therapy patients had many meaningful differences, and in general, triple therapy users experienced more illness with comorbidities, but had somewhat less active RA. After accounting for these differences through propensity score matching, biologics-naive TNFi/MTX patients had increased drug persistence and clinical effectiveness outcomes compared to triple therapy patients. These trends were numerically similar in the biologics-exposed population, although the sample size was smaller and not all findings were significant. These real-world findings add to our understanding of the benefits and disadvantages of triple therapy with MTX/SSZ/HCQ versus combination therapy with TNFi/MTX in the treatment of RA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Curtis had full access to all the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Curtis, Reed, Greenberg, Pappas, Harrold, Kremer.

Acquisition of data. Curtis, Greenberg, Pappas, Harrold, Kremer.

Analysis and/or interpretation of data. Curtis, Palmer, Reed, Greenberg, Pappas, Harrold, Kremer.

ADDITIONAL DISCLOSURES

Authors Palmer, Reed, Greenberg, Pappas, Harrold, and Kremer are employees of the Corrona Research Foundation.

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Shared Decision-Making Applied to Knee Arthroplasty: A Systematic Review of Randomized Trials

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Objective. Shared decision-making (SDM) is a strongly endorsed approach by which patients and clinicians work together to formulate a sensible care plan. The present study was undertaken to conduct a systematic review of SDM trials in patients considering knee arthroplasty (KA) to characterize how SDM was supported and the impact on care received.

Methods. We searched multiple bibliographic databases from inception to December 31, 2019. A pair of reviewers working independently selected studies for inclusion, extracted data, and evaluated each trial's risk of bias.

Results. We found 6 eligible randomized trials (4 included KA and hip arthroplasty), all of which tested the same proprietary decision aid (DA) (Treatment Choices for Hip or Knee Osteoarthritis), with some adding other materials to support SDM. These trials, all of which had moderate-to-high risk of bias, focused on assessing the effect of the DA on patient knowledge about the options while not explicitly supporting other aspects of SDM, such as choice awareness, deliberation, or decision-making. One trial found an increase in the number of African American patients undergoing KA in the 12 months following the intervention. No other trials found that SDM impacts clinical outcomes.

Conclusion. Evidence for SDM in patients considering KA is mostly limited to a single DA. While use of this DA improves patient knowledge about their treatment options, this tool has not been shown to promote SDM, impact treatment decisions, or satisfaction with care. Future work should seek to support SDM directly and assess effects on treatment decisions, functional outcomes, and satisfaction.

INTRODUCTION

Knee arthroplasty (KA) is the most common major surgical procedure conducted in the US, with ~1 million KAs conducted in 2015 (1). Demand has doubled since 2005 and is likely to continue to increase given the increased demand for KA, particularly for patients <60 years of age (2,3). Given that KA is a major elective surgical procedure with substantial benefits, rare but serious risks, and viable treatment alternatives (4,5), a shared decision-making (SDM) approach is recommended by the American Academy of Orthopaedic Surgeons (AAOS). The AAOS position statement reads as follows: "The orthopaedic surgeon should engage in informed shared decision-making with the patient using the patient's values and respect the patient's decision even if it is in disagreement with the physician's recommendation" (6).

SDM describes the work that patients and clinicians do together to co-create a sensible treatment plan that responds well to the patient's situation. Along the trajectory of care, patients with symptomatic knee arthritis may end up considering KA as a treatment option. In these instances, SDM may take place in the clinical encounter, and in the US, typically between the patient and the orthopedic surgeon. SDM involves determining what aspect of the patient situation demands action and what action the situation demands. Here, they may explore together the extent to which knee problems impair the patient's daily life and discuss how each of the sensible alternatives can address those impairments along with their potential harms, costs, and burdens to the patient. Together, the patient and surgeon arrive at the best course of action and set out to implement it.

The SDM interaction between the patient and clinician (i.e., in this case, the surgeon) is grounded in 6 key elements, which are considered critical steps when providing care using SDM (7,8). Table 1 provides a summary of these elements and shows how they might be addressed during an SDM interaction between a

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SIGNIFICANCE & INNOVATIONS

- Patient knowledge about treatment options prior to knee arthroplasty (KA) is enhanced with the use of a decision aid.
- Current evidence in the KA clinical trial literature examining shared decision-making does not directly support key elements critical to shared decision-making.
- With the exception of one study demonstrating an increased uptake of KA among African American patients, evidence indicated that shared decision-making does not impact clinical outcomes.
- Future trials evaluating interventions that directly support shared decision-making may identify innovative approaches that may translate into improved patient care and outcomes.

patient considering KA surgery and the consulting orthopedic surgeon. SDM tools can assist this process. Encounter tools or conversation aids are designed for use during the clinical encounter with the patient and care provider to support the discussion and offer a presentation of the available options and their relative pros and cons. On the other hand, patient decision aids (DAs) are tools designed for patient use and seek to describe the problem and the available options, and to clarify the relevant patient values and preferences. DAs have been shown to enhance patient knowledge about the options and to reduce decisional conflict (9) but have an unclear effect on SDM per se, and they have variable effects on treatment selection.

To our knowledge, the impact of interventions to promote SDM in the care of patients with knee arthritis considering KA has not been systematically summarized. Therefore, we set out to conduct a systematic review of the extant literature on the features and impact of SDM interventions tested in randomized trials, as described in our published protocol (10).

MATERIALS AND METHODS

Protocol and registration. The protocol was previously published (10) and registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42019123586).This report adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (11).

Eligibility criteria. Eligible studies were any randomized controlled trials (RCTs) enrolling patients considering KA for management of any type of knee arthritis (including osteoarthritis, rheumatoid arthritis, or posttraumatic arthritis) and who were randomized to receive either an intervention to promote SDM versus usual care or another active control (10).

Information sources and search strategy. We applied a search strategy developed in collaboration with an experienced research librarian (TT) to find potentially eligible RCTs in Medline (PubMed), Web of Science (Web of Science Core Collection), Embase (Ovid), the Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCO), PsycInfo (APA PsycNET), and the Cochrane Library (Central) from each database's inception until

Table 1. Six key shared decision-making elements*

Situation diagnosis	Conversation with the patient to determine the patient's situation, to determine what specifically requires action, and that the patient's opinion is important in making the decision. In knee arthroplasty, there must be a conversation with the patient to: 1) determine what is bothering him/her about the knee(s), (most commonly related to knee pain and knee function); 2) what they cannot do now; and 3) what they want to be able to do. The importance of the patient's opinion as to how to resolve the problems should be reinforced.
Choice awareness	When >1 reasonable alternative option is available, the clinician should clearly indicate this and highlight that the preferences of the patient are important in deciding on the course of action. In knee arthroplasty, this involves making the patient aware that more than 1 option is available. These choices may be either knee arthroplasty, injections, physical therapy, medication, weight loss, and combinations of these nonsurgical options, as well as which are the initial priorities for the patient. The patient must be made aware that >1 option is available.
Option clarification	Subsequently, the clinician and the patient discuss how each option fits with and accommodates each patient's situation. In knee arthroplasty, this would involve a discussion of each intervention and how each one might fit with the patient's situation, including, but not limited to, considerations of work, home life, conveniences and burdens, and prior treatment.
Discussion of harms and benefits	In knee arthroplasty, this would include estimates of the likely benefits and burdens of each treatment in terms of pain relief and functional improvement as well as risks of each. The most common harms and benefits that should be discussed include but are not limited to complication risks, out-of-pocket cost estimates, time off work, and time demands of rehabilitation.
Deliberation of patient preferences	This involves a conversation about the treatment options and how they fit with patient preferences while supporting the patient in the deliberation. In knee arthroplasty, this would require a conversation with the patient about which of the treatment options is best for addressing the patient's problems and figuring out which option makes the most intellectual, emotional, and practical sense to the patient.
Making the decision	The clinician and patient make the decision, choosing the most appropriate treatment for the patient's knee problem, with the patient's decisional preference weighing most heavily in the decision. The decision of which treatment to try is the result of a well thought-out and discussed process resulting in a consensus decision between patient and surgeon.

* See references 7 and 8. The descriptions applying the elements to knee arthroplasty were conceptualized and written by the authors of the current study.

December 31, 2018 (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24240/abstract). An additional search using the same search strategy for RCTs published in 2019 was added. No language restrictions were applied.

Study selection. Two reviewers (DLR and TS) working independently and in duplicate screened all titles and abstracts; except for records in which both reviewers agreed to exclude, all other records were retrieved in full text. Again, these reviewers screened full-text articles using the same procedure, with acceptable reproducibility for all decisions ($\kappa = 0.51$). Disagreements were resolved by consensus.

Data collection process and summary measures. Two reviewers (DLR and TS) extracted data from all eligible studies using a standardized data extraction form (see Supplementary Appendix B, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24240/abstract). The data form included the following: publication details; study design; populations of interest; sociodemographic characteristics of the sample; inclusion and exclusion criteria; study setting; details of experimental intervention and comparison intervention; commercial availability of the DA/SDM; duration of follow-up and outcomes studied; and extent of effectiveness for both cognitive and clinical outcomes of the DA/SDM approach in relation to the comparator. Information on the presence of the 6 elements of SDM was collected. The definitions for each of the 6 elements of SDM used in this study are presented in Table 1.

Between-arm differences across all reported outcomes (cognitive/affective and clinical, proximal and distal to the treatment decision) and a measure of their precision (e.g., 95% confidence intervals [95% CIs]) were extracted. Outcomes could include the following: decision conflict; content knowledge regarding osteoarthritis; treatment decision preference; satisfaction with surgical outcomes; patient-reported pain; or surgical versus nonsurgical treatment decisions made during the encounter. For continuous outcomes, mean difference or mean changes between the DA/SDM group and the usual care/active control groups, as well as 95% CIs and *P* values, were extracted. For dichotomous and categorical outcomes, risk ratios or odds ratios with 95% CIs were extracted or calculated.

The corresponding author of each study was contacted by email in order to: 1) verify that we characterized their studies correctly; 2) provide missing or incomplete information; and 3) request separate analyses for the KA participants. A second email notice was sent 2 weeks after the initial request if no response was received. Authors of all 6 studies responded to the requests and provided additional information when needed to correctly characterize each study. Study authors either indicated that they were unable to provide KA-specific data or they did not respond to the request. In one case (12), a subgroup analysis of KA participants compared those treated in a community site to those treated in an academic site (13). While the study was not powered for this analysis, the investigators found that fewer subjects experienced decisional conflict at the academic site.

Risk of bias and quality assessment. Two reviewers (DLR and TS) working independently and in duplicate assessed the risk of bias for each study and for each outcome, with disagreement solved by consensus. The risk of bias analysis was conducted using the Cochrane Collaboration's Risk of Bias 2 tool (14). The tool was used to evaluate the potential for bias and to rate this risk as low, some concerns, or high in 5 domains: the randomization process; deviations from intended interventions; outcome data missingness; outcome measurements; and selection of reported results. Using published criteria, we also judged the overall risk of bias for each outcome (14) and rated the overall quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (15). In addition to risk of bias, this rating considers inconsistency of results, indirectness of evidence, imprecision, and risk of publication bias. The quality of evidence ratings include high, moderate, low, and very low ratings.

RESULTS

Study selection and characteristics. As depicted in Figure 1, our search strategy identified 21,632 references up to the end of 2018 and an additional 2,897 in 2019 from the 6 databases. The web-based primary screening tool (i.e., Covidence) removed 6,143 duplicates. A total of 18,386 studies were screened for inclusion in the systematic review based on title and abstract. Of these, 59 studies were selected from this screening to be included in the full-text review. A total of 53 studies were excluded due to either an incorrect study design (n = 51), 1 duplicate manuscript (n = 1), or a conference abstract (n = 1). A total of 6 studies met all the inclusion criteria for this systematic review. Supplementary Appendix C, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24240/abstract, describes the characteristics of the 6 included RCTs. All were conducted in North America, and all used a proprietary DA developed by the Foundation for Informed Medical Decision-Making, and subsequently by Health Dialog (16). This DA included both text and DVD-based content describing osteoarthritis diagnosis and surgical treatment and recovery, evidence-based treatment options, and benefits and risks of joint arthroplasty. A second DA by Healthwise was used in 1 trial (17,18) and was available as an online or hardcopy version with similar content. Four of the 6 trials reported combined results for both hip and knee arthroplasty cases (12,17,19,20). We chose to include the 4 combined hip and KA trials despite our original plan, as defined in our PROSPERO registry, to focus solely on KA. In our view, these combined hip and KA trials contribute important

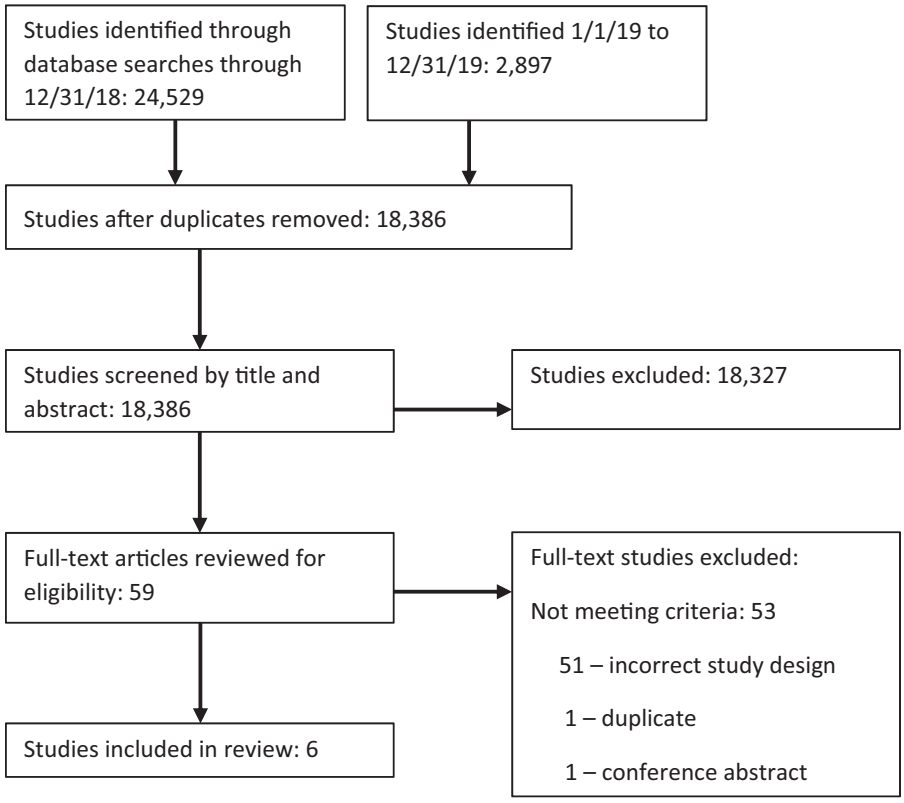

Figure 1. Flow chart of the study selection.

information regarding the outcome measures used and the extent to which SDM elements were incorporated into the SDM tools tested. Because only 6 studies met our inclusion criteria and these trials examined different outcomes over different study periods, we did not conduct a meta-analysis but instead conducted a narrative review with emphasis on individual study quality and the extent to which each trial instrument included the 6 key elements of SDM summarized in Table 1.

SDM elements supported by the Das. All trials (12,17,19–22) tested a similar patient DA, while 3 trials (12,17,22) also included a patient-reported questionnaire provided to the orthopedic surgeon prior to the encounter. The questionnaire detailed patient preferences and, in 2 studies (12,22), Western Ontario and McMaster Universities Osteoarthritis Index self-reported pain, stiffness, and function scores (23) prior to the encounter. We found no RCTs testing encounter-based SDM tools. Table 2 presents the reviewers' decisions on how well the DA supported each of the 6 key elements of SDM described in Table 1. Although choice awareness and a discussion of harms and benefits were partially addressed in all the RCTs, no RCT fully considered all 6 elements; 3 did not include clarification of or deliberation based on patient preferences (19–21). It was judged unclear whether any of the trials addressed making the decision.

Impact of the SDM intervention on patient care. The primary outcomes investigated in the selected papers were varied, with some trials using several primary outcomes (see Supplementary Appendix C, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24240/abstract). The more common examples were as follows: arriving at an informed decision after the first meeting

Table 2. Results of ratings of shared decision-making elements by reviewer 1 (R1) and reviewer 2 (R2)*

	Situation diagnosis		Choice awareness		Option clarification		Discussion of harms and benefits		Deliberation of patient preferences		Making the decision	
Author, year (ref.)	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2
Bozic et al, 2013 (20)	No	No	Partial	Yes	No	No	Partial	Partial	No	No	Unclear	Unclear
Ibrahim et al, 2017 (21)	No	No	Partial	Yes	No	No	Yes	Yes	No	No	Unclear	Unclear
Shue et al, 2016 (19)	No	No	Partial	Yes	No	No	Partial	Partial	No	No	Unclear	Unclear
Stacey et al, 2104 (22)	Partial	Yes	Partial	Yes	No	Unclear	Partial	Yes	No	Unclear	Unclear	Unclear
Stacey et al, 2016 (12)	Partial	Yes	Partial	Yes	No	Unclear	Partial	Yes	No	Unclear	Unclear	Unclear
Sepucha et al, 2019 (17)	Unclear	Partial	Partial	Unclear	No	No	Partial	Partial	No	No	Unclear	Unclear

* Ref. = reference.

with a surgeon (20); receipt of a recommendation for KA within 6 or 12 months of a surgical consult (21); change in patient knowledge (17,19,22); and time from consultation to the patient making a definitive treatment choice (12). Supplementary Appendix C, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24240/abstract, describes the estimates of effect for all primary and secondary outcomes. Outcomes that were significantly impacted by the SDM interventions were reduction in decisional conflict (12,22), patient self-efficacy with developing questions to ask the surgeon (20), stage of decision-making after the consult (20), and measures of decision quality and knowledge (12,17,22), as well as surgeon-reported ratings of the appropriateness and

Table 3. Results from the Risk of Bias 2 tool for all outcomes reported in the included studies*

Author, year (ref.) and outcome	Randomization process	Deviations from intended intervention	Missing outcome data	Measurement of outcome	Selection of reported result	Overall risk of bias
Studies with intent-to-treat						
Bozic et al, 2013 (20)						
Informed decision at first visit	?	?	–	–	–	–
Preconsultation: question self-efficacy	?	?	–	+	?	–
Preconsultation: treatment preference	?	?	–	+	?	–
Preconsultation: stage of decision-making	?	?	–	?	?	–
Patient satisfaction with consultation with surgeon	?	?	–	–	?	–
Postconsultation: MD rating of the number of patient questions	?	?	–	–	?	–
Postconsultation: MD rating of appropriateness of patient questions	?	?	–	–	?	–
Postconsultation: MD overall satisfaction with consultation	?	?	–	–	?	–
Length of time of entire consultation	?	?	–	+	?	–
Time of surgeon visit	?	?	–	+	?	–
Ibrahim et al, 2017 (21)						
Receipt of recommendation for TKA within 6 months	+	+	+	+	?	?
Receipt of TKA within 12 months of consultation	+	+	+	+	?	?
Shue et al, 2016 (19)						
Total change in patient knowledge	?	+	+	+	?	?
Willingness to participate in pain management decisions	?	+	+	+	?	?
Willingness to participate in surgical decisions	?	+	+	+	?	?
Satisfaction with osteoarthritis education	?	+	+	+	?	?
Change in treatment preference	?	+	+	+	?	?
Stacey et al, 2014 (22)						
Time-to-treatment decision	+	+	+	+	?	?
Decision quality	+	+	+	?	?	?
Preparation for decision-making	+	+	+	?	–	–
Stacey et al, 2016 (12)						
Wait time to definitive decision	+	+	+	+	?	?
Good decision quality	+	+	+	?	?	?
Realistic expectations of outcomes	+	+	+	+	?	?
Surgical rates within 2 years	+	+	+	+	?	?
Perceptions of decision-making process/ decisional conflict	+	+	+	?	–	–
Sepucha et al, 2019 (17)						
Patient knowledge	+	?	+	+	+	+
Received preferred treatment	+	?	+	+	+	+
Shared decision-making survey	+	?	+	+	–	–
Decisional conflict	+	?	–	–	–	–
Overall quality of life	+	?	–	–	–	–
Disease-specific quality of life	+	?	–	–	–	–
Surgical rate 6 months post visit	+	?	+	+	+	+
Study with per protocol						
Ibrahim et al, 2017 (21)						
Receipt of recommendation for TKA within 6 months	+	+	+	+	?	?
Receipt of TKA within 12 months of consultation	+	+	+	+	?	?

* Risk of bias ratings: + = low risk; ? = some concerns; – = high risk. TKA = total knee arthroplasty.

number of patient questions (20). One trial found an increase in the uptake of KA among African American patients in the DA arm at 12 months (21); otherwise clinical outcomes (e.g., surgery rate, quality of life) were similar across arms in the remaining trials.

Risk of bias and quality of evidence. Table 3 summarizes the risk of bias analyses, and Tables 4 and 5 summarize the quality of evidence analysis. Most outcomes were judged either to have some concerns or to be at high risk of bias. Reviewers judged this body of evidence to warrant very low to moderate confidence depending on the trial and primary outcome.

DISCUSSION

Our systematic review found 6 RCTs testing 1 patient DA along with some additional patient data in some studies, and an additional brief DA in 1 study (17). Because of the potential relevance of the studies to SDM in KA, we included 4 RCTs presenting the result of patients considering either hip or knee arthroplasty. Few key elements of SDM were addressed in these trials. None tested interventions directly supporting SDM, i.e., interventions used during the clinical encounter and supporting both patient and surgeon. None evaluated SDM directly by observing the clinical encounter. This evidence, which mostly warrants low to very low confidence in the results, shows favorable effects on patient knowledge and confidence in the treatment decision and surgeon satisfaction, and with 1 exception (21), no effect on KA uptake in the DA compared to the control. One RCT enrolling African American patients, a population in which the rates of KA tend to be low, found a higher uptake of KA in the DA arm (21). Scarce evidence prevented our review of KA in RCTs (the first of its kind for KA) from exploring interactions between evidence quality or SDM modalities and care outcomes.

The exclusive use of patient DAs summarized in our systematic review is consistent with the AAOS recommendation of informed decision-making, which refers to a decision made by the patient after being informed of the available options, a key goal of these DAs. The recommendation goes on to indicate that surgeons should go along with the patient decision even when the surgeon disagrees with what the patient wants. SDM is seen as a collaborative arrangement with the patient and clinician working together to arrive at a sensible response to the patient situation. The AAOS recommendation, in our view, is in fact not supportive of SDM because it does not endorse a collaborative, consensus-based approach. In our view, SDM is a superior approach to care but one that awaits further development and evaluation in the KA literature. Future work should therefore emphasize direct SDM support and assessments during the consultation.

One trial included in our review was fundamentally different that the other 5 trials. Sepucha and colleagues published the largest SDM-based RCT in patients considering either hip or knee arthroplasty (17). The study was a 2 × 2 factorial RCT with 1,911 participants randomized to either a short DA or a long DA, along with either patient preference report provided to the surgeon prior to the consultation or no preference report. The patient self-reported preference report summarized the patient's activity limitations, treatment preferences, and expected outcomes of the consultation. The investigators found that participants using the short DA demonstrated greater knowledge regarding arthritis and arthroplasty compared to participants assigned to the long DA. This was the case whether or not the surgeon received a patient preference report. There was no difference between DA arms or between surgeon groups in the percentage of participants receiving their preferred treatment 6 months after the consultation. Because all participants were randomized to a type of DA (i.e., there was no control or usual care arm), the study does not inform the added value of a DA to usual care.

A frequently cited study by Arterburn and colleagues, a nonrandomized quasi-experimental study of patients with hip and knee arthroplasty, indicated a 38% decrease in arthroplasty utilization with use of a DA (24). However, DA usage coincided with an economic downturn in 2008 and 2009, while the non-DA group was recruited prior to the downturn. The timing of the economic downturn, which likely impacted arthroplasty utilization (1), combined with the nonrandomized study design, along with the findings reviewed in the current study, raise substantial concerns about the validity of the findings reported by Arterburn et al (24).

Investments in SDM in KA research and practice can be easily justified by a lack of RCT-based evidence using SDM tools applied during the patient encounter, and by the high volume and costs of KA, with upwards of 1 million procedures per year (1), in combination with the availability of effective nonoperative approaches (4,25,26). Additional research, including the development and testing of clinical encounter-based SDM tools powered by probability-based estimates of KA outcomes and risks (27–29), could impact orthopedic practice and improve the care of patients with knee arthritis.

Our review appears to be the first not only to focus on DA/SDM effects in KA, but also to examine whether the current evidence addresses key SDM elements as well as actual effects of care received. Our review has some limitations, including the small number of studies with varied outcomes that required a narrative review in lieu of a meta-analysis. Additionally, because of the small number of included trials, we included 4 trials of participants with either hip arthroplasty or KA, but without stratification by joint; while the surgical risks are somewhat similar, outcome trajectories (30) and revision risks (28) are different for KA versus hip arthroplasty. Finally, our judgments of the presence of key SDM elements were limited because we did not observe the application of these tools during patient care. We could only judge the presence or absence of these elements based on written descriptions available in the published studies.

In conclusion, the extant evidence for SDM for patients considering KA is very scant, includes trials of patient DAs, and provides little information about the impact of the interventions on

Table 4. Grading of Recommendations Assessment, Development and Evaluation (GRADE) rating for the primary outcome of each trial that was included in the review and that included a usual care group*

Outcomes	Anticipated absolute effects (95% CI)†		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with usual care	Risk with shared decision-making via DA				
Arrived at informed decision after visit with surgeon (basic OA knowledge); assessed with hip/knee OA decision quality instrument	33 per 100	59 per 100 (40–75)	OR 2.89 (1.33–5.88)	120 (1 RCT)	very low‡	Knowledge was improved, but the impact of this OA-related knowledge on the decision and whether patient preferences were considered were not addressed. (ref. 20)
Recommendation by surgeon for TKA 6 mos after intervention (TKA recommendation in 6 mos); assessed with medical record review follow-up: mean 6 mos	15 per 100	20 per 100 (13–31)	OR 1.39 (0.79–2.44)	336 (1 RCT)	moderate§	Use of the DA had no effect on surgeon recommendations for TKA for African American patients 6 mos after the intervention. (ref. 21)
Underwent TKA 12 mos after intervention (12 mos postintervention TKA recommendation); assessed with medical record review follow-up: mean 12 mos	8 per 100	15 per 100 (8–26)	OR 2.10 (1.04–4.27)	336 (1 RCT)	moderate¶	Shared decision-making via use of a DA results in a slight increase in African American patients who underwent TKA 12 mos after intervention. (ref. 21)
OA knowledge assessment (OA knowledge); assessed with customized OA knowledge assessment questionnaire; scale 0–5; follow-up: mean 3 wks	The mean OA knowledge assessment was 0.48	Mean 0.02 higher (0.21 lower to 0.25 higher)	–	132 (1 RCT)	very low#	Knowledge was not improved with use of the DA, and study certainty was very low; the knowledge assessment scale lacked validity evidence. (ref. 19)
Decision-making participation in surgical decision (surgical decision questionnaire); assessed with customized questionnaire follow-up: mean 3 wks	The mean decision-making participation in surgical decision was 0.14	Mean 0.1 higher (0.16 lower to 0.36 higher)	–	132 (1 RCT)	very low**	Participation in the surgical decision was not improved, and certainty was judged to be very low given the lack of evidence provided to support the outcome measure. (ref. 19)
Days from screening to treatment choice (days to decision); assessed with medical record review follow-up: mean 1 yr	79 per 100	79 per 100 (78–79)	HR 0.99 (0.98–1.00)	140 (1 RCT)	moderate††	Days from intervention delivery to the treatment decision was not affected by use of the DA. (ref. 22)
Hip–knee OA decision quality instrument (decision quality); assessed with hip–knee OA decision quality instrument follow-up: mean 2 wks	21 per 100	51 per 100 (32–70)	OR 3.88 (1.73–8.68)	132 (1 RCT)	moderate‡‡	Decision quality was improved, but whether this outcome relates to whether patients' preferences were considered as part of the treatment decision was not addressed. (ref. 12)
Time to implementation of treatment choice; assessed with medical record follow-up: 2 yrs	85 per 100	91 per 100 (85–95)	HR 1.25 (0.99–1.60)	313 (1 RCT)	low§§	The relevance of a time to decision outcome is not clear when applied to use of a DA.

* GRADE working group grades of evidence: high certainty (we are very confident that the true effect lies close to that of the estimate of the effect); moderate certainty (we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); low certainty (our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect); very low certainty (we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect). HR = hazard ratio; OR = odds ratio; RCT = randomized controlled trial; TKA = total knee arthroplasty.
† The risk in the intervention group (and its 95% confidence interval [95% CI]) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
‡ There is a 40% loss to follow-up after randomization in this study. Evidence regarding osteoarthritis (OA) knowledge does not necessarily reflect a clinical decision that aligns with a patient's preferences.
§ The variation around the point estimate is substantial.
¶ The variation around the point estimate indicates substantial error.
# A total of 15 participants were not included in the analyses. The questionnaire was not validated. The finding was not consistent with other trials examining a similar outcome. The link between OA knowledge and a treatment decision that aligned with patient preferences was not made.
** The questionnaire used to measure the outcome was not defined and not referenced. The finding is inconsistent with other trials.
†† The association between day-to-treatment choice and patients making a preference-based treatment decision is unclear.
‡‡ The relevance of the outcome measure to whether patient preferences were met or considered during the encounter is unclear.
§§ The relevance of time-to-treatment decision is not clear when using a decision aid (DA). The width of the confidence interval is somewhat wide.

Table 5. Grading of Recommendations Assessment, Development and Evaluation (GRADE) summary of findings for primary outcomes in the trial by Sepucha et al (ref. 17)*

Outcomes	Anticipated absolute effects (95% CI)†		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with long DA and usual care or preference report‡	Risk with short DA and usual care or preference report‡				
Shared decision-making using a long DA and usual surgeon care compared to a short DA and usual surgeon care for knee replacement candidacy§						
Knowledge score from the Hip/Knee OA Decision Quality Instrument and scored as % of items correct; assessed with questionnaire	Mean knowledge score from the Hip/Knee OA Decision Quality instrument and scored as % of items correct was 71%	Mean 8% higher (3.9 higher to 12.1 higher)	–	550 (1 RCT)	moderate¶	Knowledge scores were higher for the short DA coupled with usual care as compared to the long DA coupled with usual care.
Percentage of patients receiving preferred treatment; assessed with questionnaire	Mean % of patients receiving preferred treatment was 73.1%	Mean 0.7% higher (7.2 lower to 8.5 higher)	–	486 (1 RCT)	moderate#	There was no difference in preferred treatment choice, and this outcome was measured 1 week after the surgeon visit.
Shared decision-making via short DA and surgeon preference report compared to long DA and surgeon preference report for knee replacement candidacy						
Knowledge score from the Hip/Knee OA Decision Quality Instrument and scored as % of items correct; assessed with questionnaire	Mean patient knowledge measured with the Hip/Knee OA Decision Quality Instrument was 75%	Mean 9% higher (5.25 higher to 12.75 higher)	–	532 (1 RCT)	moderate¶	Knowledge scores were higher for the short DA coupled with preference report as compared to the long DA coupled with preference report.
Percentage of patients receiving preferred treatment; assessed with questionnaire	Mean % of patients with preferred treatment 1 week after visit to surgeon was 74.4%	Mean 2.8% higher (0.05 lower to 0.11 higher)	–	470 (1 RCT)	moderate#	There was no difference in preferred treatment choice, and this outcome was measured 1 week after the surgeon visit.

* GRADE Working Group grades of evidence: high certainty (we are very confident that the true effect lies close to that of the estimate of the effect); moderate certainty (we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); low certainty (our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect; very low certainty (we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect). 95% CI = 95% confidence interval; DA = decision aid; OA = osteoarthritis; RCT = randomized controlled trial.
† The risk in the intervention group (and its 95% confidence interval [95% CI]) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
‡ Usual care applies to the category "Shared decision-making using a long decision aid (DA) and usual surgeon care compared to a long DA and surgeon usual care for knee replacement candidacy." Preference report applies to the category "Shared decision-making via short DA and surgeon preference report compared to long DA and surgeon preference report for knee replacement candidacy."
§ Patient or population: knee replacement candidacy. Setting: an academic medical center, a community hospital, and a specialty orthopedic hospital. Intervention: short DA and usual care. Comparison: long DA and usual care.
¶ Consistency varied depending on whether the registry or the main paper was reviewed, and this variation sometimes existed for the same outcome measure.
# Risk of bias was considered serious because the choice of reported outcome varied between the clinical trial registry and the main paper.

SDM, care, and outcomes. Future research should consider methods to further enhance SDM tools to engage both patient and surgeon during the health care consultation and evaluate their impact on care and patient outcomes.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Riddle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Riddle, Montori.
Acquisition of data. Riddle, Sando, Tarver.
Analysis and interpretation of data. Riddle, Sando, Slover, Sierra, Brito, Montori.

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BRIEF REPORT

Association of Quadriceps Adiposity With an Increase in Knee Cartilage, Meniscus, or Bone Marrow Lesions Over Three Years

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Objective. To evaluate the association of fatty infiltration of the quadriceps and vastus medialis (VM) with an increase in knee cartilage, meniscus, or bone marrow lesions, using magnetic resonance imaging (MRI) in knee osteoarthritis (OA) over 3 years.

Methods. Participants (n = 69) with and without radiographic knee OA underwent MRI at baseline and 3 years later. Chemical shift–based water/fat MRI was used to quantify the intramuscular fat fraction and the lean anatomical cross-sectional area (ACSA) for the VM and entire quadriceps muscles. MRI images of the knee were analyzed using the semiquantitative modified whole-organ MRI score (mWORMS) grading to assess change in lesions in the articular cartilage, meniscus, and bone marrow. Logistic regression was used to assess whether baseline quadriceps and VM fat fraction and lean ACSA were associated with an increase in mWORMS scores. Odds ratios (ORs) were adjusted for age, sex, and body mass index.

Results. Overall, of the 69 subjects, 43 (62%) had an increase in cartilage lesions (26 of 43), meniscus lesions (19 of 43), or bone marrow lesions (22 of 43) scores. The quadriceps (OR 2.13 [95% confidence interval (95% CI) 1.09–4.15]) and VM (OR 2.05 [95% CI 1.25–3.36]) fat fraction were both associated with an increase in cartilage, meniscus, or bone marrow lesion scores over 3 years. The association of quadriceps or VM lean ACSA with the outcomes was not significant.

Conclusion. These longitudinal findings using quantitative MRI methods for assessment of muscle adiposity highlight the role of quadriceps adiposity, specifically in the VM, in knee OA progression. However, studies in larger cohorts are needed to confirm these findings.

INTRODUCTION

Intramuscular quadriceps adiposity is increasingly being recognized as an important component of knee osteoarthritis (OA) pathogenesis (1–3). The mechanisms are likely related to release of inflammatory cytokines from the adipose tissue and their effects on the knee joint, as well as the effects of muscle adiposity on muscle function (4). Quadriceps adiposity might be responsive to exercise interventions (5) and, therefore, its effects on knee joint health and OA need to be determined. Chemical shift–based water/fat separation magnetic resonance imaging (MRI) techniques allow for quantification of intramuscular adipose tissue (i.e, fat stored within the muscle fibers) and show very good agreement with MRI spectroscopy (6–8). These techniques provide higher spatial resolution for quantification of adiposity than is available from conventional T1-weighted MRI images (9).

Using quantitative and validated chemical shift–based water/fat MRI techniques, we previously observed that people with knee OA have an increased intramuscular fat fraction in the quadriceps muscle compared to people without knee OA, even after adjusting for age, sex, and body mass index (BMI) (10). Fat fraction refers to the ratio of separated fat signal over the sum of separated water and fat signals from the chemical shift–based water/fat MRI. We also observed that intramuscular fat fraction

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SIGNIFICANCE & INNOVATIONS

- Fatty infiltration of the quadriceps is implicated in pathogenesis of knee osteoarthritis (OA). However, prior studies have not used validated quantitative measures of muscle adiposity. Chemical shift–based water/fat magnetic resonance imaging provides an objective and valid measurement of muscle adiposity.
- The results from this longitudinal study show that fatty infiltration of the quadriceps muscle, particularly the vastus medialis, is related to greater odds of increase in knee cartilage, meniscus, or bone marrow lesions over 3 years.
- The results also demonstrate that loss of quadriceps or vastus medialis anatomical cross-sectional area is not associated with an increase in knee cartilage, meniscus, or bone marrow lesions over 3 years.
- These findings further highlight the role of changes in quadriceps muscle adiposity in knee OA and, if confirmed in larger cohorts, could be used to guide interventions.

of the quadriceps, and not the lean anatomical cross-sectional area (ACSA), was associated with clinical outcomes of knee OA (10). Other studies have reported that fatty infiltration of the vastus medialis (VM) might be implicated in changes in cartilage lesions and bone marrow lesions (BMLs) (2,3). However, whether quadriceps adiposity using chemical shift–based water/fat MRI is associated with longitudinal changes in knee OA is not known.

Intramuscular adiposity of the quadriceps could lead to knee lesions that worsen over time, leading to OA. Our objective was to assess whether intramuscular fat fraction of the quadriceps (i.e., VM, vastus lateralis [VL], vastus intermedius [VI], and rectus femoris [RF]) is associated with an increase in knee cartilage lesions, meniscus lesions, or BMLs over 3 years in adults with and without knee OA. Since prior studies have identified VM adiposity as being related to knee OA (2,3), and since the chemical shift–based water/fat MRI allows for quantification of adiposity within the individual quadriceps muscles at high-resolution, the second objective was to assess whether the intramuscular fat fraction of the VM is associated with an increase in knee cartilage lesions, meniscus lesions, or BMLs over 3 years in adults with and without knee OA. As exploratory analyses, we also investigated the role of other individual quadriceps muscles, i.e., VL, VI, and RF, because this role has not been studied previously.

SUBJECTS AND METHODS

Participants. Data for this study were collected as part of a longitudinal observational study in individuals with and without knee OA. The study was conducted at an urban academic research institution. Participants were recruited from the community using advertisements and flyers. The inclusion criteria for individuals with knee OA were age >35 years, knee pain, aching, or stiffness on most days per month during the past year, or use of medication for knee pain on most days per month during the past year, and radiographic signs of OA. The inclusion criteria for controls were age >35 years, no history of diagnosed OA or OA symptoms, previous knee injuries, or signs of OA on radiographs. The exclusion criteria were concurrent use of an investigational drug, history of intraarticular fracture or surgical intervention in the study knee, conditions other than OA that limit lower-extremity function and mobility and/or would confound the evaluation of function, and contraindications to MRI. A musculoskeletal radiologist with over 22 years of experience (TML) determined radiographic OA using the Kellgren/Lawrence (K/L) grade from bilateral weight-bearing posteroanterior radiographs using the fixed-flexion protocol with a Synaflexor device. Radiographic OA was defined as K/L grade ≥2. All participants who had baseline muscle MRI measurements and 3-year MRI measurements were included in these analyses. The Knee injury and Osteoarthritis Outcome Score pain subscale and the stair climbing test were used to assess pain and physical function, respectively. All subjects signed a written informed consent prior to participation; procedures were approved by the Institutional Committee on Human Research.

MRI. All participants underwent MRI 3T (GE Signa HDx) with an 8-channel transmit-receive knee coil (Invivo). MRI sequences have been described previously (10). High-resolution images were acquired for semiquantitative scoring of knee OA. A modified whole-organ MRI score (mWORMS) was used to assess cartilage, meniscus, and bone marrow lesions by 3 experienced board-certified musculoskeletal radiologists (11). Cartilage lesions and BMLs were assessed over 6 subregions (medial and lateral femur, medial and lateral tibia, patella, and trochlea). The meniscus was assessed over 6 subregions (anterior horn, posterior horn, and the body of medial and lateral menisci). We have previously reported high reproducibility (intraclass correlation coefficient of 0.98, 0.97, and 0.97 for cartilage, meniscus, and bone marrow lesions, respectively) for these measures (11,12). The radiologists were blinded to subject information and performed separate readings with a consensus in case of disagreement. Paired readings were performed to assess longitudinal changes in MRI scores from baseline to 3 years. Individuals were categorized into those with and without an increase in cartilage, meniscus, or bone marrow lesion scores. The score at 3 years had to be >1 for cartilage or meniscus lesions to identify only subjects with morphologic lesions rather than signal change.

Details of quantification of intramuscular fat fraction and lean ACSA have been published previously (10). All images were acquired from a volume that was 14 cm (28 slices) proximal to the superior pole of the patella. For muscle adiposity, an investigational version of the chemical shift–based water-fat separation (7), implemented in a multishot multi-echo 3-dimensional spoiled

Table 1. Demographic information distribution of radiographic and MRI scores, and baseline muscle fat fraction and lean ACSA of the study participants (n = 69)*

Characteristic	Value
Age, years	53.3 ± 10.1
Weight, kg	66.9 ± 9.7
Height, meters	1.7 ± 9.1
Body mass index, kg/m^2	24.3 ± 3.25
Females, no. (%)	36 (55.2)
KOOS pain	90.4 ± 13.0
Stair climbing test	11.4 ± 1.9
Had radiographic OA, no. (%)	24 (34.8)
Kellgren/Lawrence grade, no. (%)	
0	27 (39.1)
1	18 (26.1)
2	6 (8.7)
3	15 (21.7)
4	3 (4.3)
Had lesions in cartilage, meniscus, or bone marrow, no. (%)	52 (75.4)
Had cartilage lesion (mWORMS >1 in any compartment), no. (%)	44 (63.8)
Had meniscus lesion (mWORMS >1 in any compartment), no. (%)	26 (37.7)
Had BML (mWORMS >0 in any compartment), no. (%)	34 (49.3)
Intramuscular fat fraction percentage	
Quadriceps	5.2 ± 1.9
Vastus medialis	7.0 ± 2.3
Vastus lateralis	7.5 ± 2.7
Vastus intermedius	6.8 ± 2.9
Rectus femoris	9.0 ± 6.2
Lean ACSA, cm^2	
Quadriceps	31.7 ± 7.8
Vastus medialis	11.4 ± 3.5
Vastus lateralis	9.5 ± 2.6
Vastus intermedius	9.5 ± 2.6
Rectus femoris	1.4 ± 0.7

* Values are the mean ± SD unless indicated otherwise. ACSA = anatomical cross-sectional area; BML = bone marrow lesion; KOOS = Knee injury and Osteoarthritis Outcome Score; MRI = magnetic resonance imaging; mWORMS = modified whole-organ MRI score; OA = osteoarthritis.

gradient-echo acquisition was used (13). The separation of water and fat signal was based on the iterative decomposition of water and fat with echo asymmetry and the least-squares estimation (IDEAL) algorithm (7), with the multipeak fat spectrum model and single T2* correction (14). In-phase images were calculated by taking the sum of the separated water and fat images. Out-of-phase images were also calculated by taking the absolute value of the difference of the separated water and fat images. Fat fraction images were generated by computing the ratio of the separated fat signal over the sum of the separated water and fat signals. Individual quadriceps muscles (VM, VL, VI, and RF) were segmented on 4 slices (2-cm region of interest between 10 and 12 cm proximal to the superior pole of the patella) on axial T1-weighted images by trained researchers in a custom written Matlab (Mathworks) program. These segmentations were transferred to the fat fraction maps from the IDEAL images. The intramuscular fat fraction (in percentage, fatty infiltration within an individual muscle) and lean ACSA (in cm^2, area of the muscle minus the area of the intramuscular fat) were then calculated for each muscle (10). The average over the 4 slices for both of these measures was used in the analyses. We have previously reported the high reproducibility for intramuscular fat measurements (10).

Statistical analysis. Logistic regression was used to evaluate the association of baseline quadriceps intramuscular fat fraction and lean ACSA, as well as baseline VM intramuscular fat fraction and lean ACSA, with an increase in MRI scores for lesions in cartilage or meniscus or BMLs. Effect measures for potential associations were expressed as odds ratios and the corresponding confidence intervals. The analyses were adjusted for baseline age, sex, and BMI. A secondary set of regression models was developed to assess the associations of other intramuscular fat fraction and lean ACSA for VL, VI, and RF, with an increase in MRI scores. Reproducibility of K/L grade was assessed using a weighted kappa statistic with quadratic weighting from a subset of 20 knees that were graded 2 weeks apart.

RESULTS

Of the 96 participants at baseline, 72% (n = 69) returned for the 3-year visit. Baseline characteristics of the study participants are shown in Table 1. Compared to participants retained, the participants who were lost to follow-up were not statistically different in age (50.8 ± 9.5 years; P = 0.262) and BMI (24.7 ± 3.9 kg/m^2; P = 0.630), and distribution of sex (65% female; P = 0.224), K/L

Table 2. Distribution of increase in MRI scores across subregions, showing frequency of increase in each subregion*

Cartilage/ bone marrow subregions	Frequency of increase for cartilage lesions	Frequency of increase for BML	Meniscus subregion	Frequency of increase for meniscus lesions
Medial femur	6	3	Medial, anterior horn	5
Medial tibia	4	4	Medial, body	7
Lateral femur	3	5	Medial, posterior horn	8
Lateral tibia	4	4	Lateral, anterior horn	4
Patella	18	8	Lateral, body	4
Trochlea	3	7	Lateral, posterior horn	5

* BML = bone marrow lesion; MRI = magnetic resonance imaging.

Table 3. Distribution of increase in MRI scores across subregions showing frequency of increase by number of subregions*

Subregions with increase, no.	Cartilage	Bone marrow	Meniscus
1	19	15	11
2	3	5	3
3	3	2	4
4	1	0	0
5	0	0	1
6	0	0	0

* MRI = magnetic resonance imaging.

grade (21% K/L grade >2; $P = 0.177$), and the presence of cartilage lesions, meniscus lesions, or BMLs at baseline (69% with lesions; $P = 0.513$). Overall, 62% of subjects (43 of 69) had an increase in either cartilage (26 of 43), meniscus (19 of 43), or BML (22 of 43) scores over 3 years. The frequency of increase in each subregion as well as the frequency of increase by the number of subregions for cartilage lesions, meniscus lesions, and BMLs are shown in Tables 2 and 3. The majority of the participants showed an increase in <4 subregions for each MRI feature. The kappa statistic was $\kappa = 0.96$, showing high reproducibility of the K/L grading.

Results from the logistic regression analyses on the association of baseline VM fat fraction and lean ACSA with the study outcomes are shown in Table 4. Greater quadriceps and VM intramuscular fat fraction were associated with a greater odds of increase in MRI scores over 3 years. Quadriceps and VM lean ACSA were not associated with the outcome of interest. Additionally, older age (both models) and female sex (VM model) were associated with greater odds of increase in MRI scores over 3 years. Overall, 28 of 36 women (78%) and 15 of 33 men (45%) showed an increase in lesions. VL, VI, or RF fat fraction were not found to be associated with an increase in MRI scores after adjustment (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24232/abstract).

DISCUSSION

We found that an increase in the intramuscular fat fraction of the quadriceps, particularly the VM, was associated with greater odds of MRI degeneration over 3 years in the knee. Our effect measures relied on a quantitative MRI measure of muscle adiposity that has been validated and has been shown to provide a more reliable assessment than alternative MRI or computed tomography measures. Our results highlight the importance of muscle adiposity in the knee OA disease process and offer a potential target for therapeutic interventions. However, considering the attrition among participants and the relatively small sample size, these findings should be confirmed in larger studies.

We observed that a greater quadriceps and VM intramuscular fat fraction was associated with a greater risk of MRI degeneration of the knee over 3 years. In a study by Raynauld et al that used data from a clinical trial in people with knee OA, the researchers showed that an increase in VM intramuscular fat over 2 years was associated with worsening of cartilage loss and BML scores (2). In another study by Teichtahl et al among healthy adults trying to lose weight, and excluding people with diagnosed knee OA, a reduction in VM fat infiltration over 1.5 to 4 years was associated with a reduced annual loss of medial tibial and patella cartilage (3). Our results support these previous findings, but there are important differences in the studies that should be noted. These previous studies used an MRI measure that has not been validated against established gold standard techniques like MRI spectroscopy. We have used a measure of intramuscular adiposity that has been validated and used in multiple research studies, including measurements of fat fraction in the liver (8). Raynauld et al assessed concomitant changes in VM fat and cartilage and BML scores over 2 years. Hence, whether an increase in VM fat was a cause or consequence of worsening MRI OA is unclear. Teichtahl et al excluded people with knee OA, limiting interpretations about the role of VM adiposity in people with knee OA. However, our study and these previous findings do suggest that therapies targeted at reducing fatty infiltration of thigh muscles need to be explored in people with knee OA. For instance, increasing physical activity can increase lean muscle mass and decrease fatty infiltration of muscles (15). A recent clinical trial reported that periodized circuit training resulted in reductions in thigh intermuscular fat in people with knee OA when compared to strength training and education groups (5).

The mechanisms underlying the role of VM fat fraction in knee OA progression are not clear. An increase in intramuscular fat fraction and/or decrease in lean ACSA leads to weakness that could in theory reduce the stability of the knee during dynamic activities and cause abnormal loading. Quadriceps weakness has been shown to be a risk factor for knee OA progression (16). Possibly

Table 4. Results from logistic regression models for classification of participants into those with and without increase in MRI scores over 3 years*

Variable	OR (95% CI)
Model with quadriceps intramuscular fat fraction and lean ACSA	
Quadriceps intramuscular fat fraction as percentage	2.13 (1.09–4.15)
Quadriceps lean ACSA, cm	1.07 (0.96–1.20)
Age, years	1.11 (1.04–1.19)
Sex (reference female)	0.15 (0.03–0.76)
Body mass index, kg/m^2	0.93 (0.72–1.19)
Model with VM intramuscular fat fraction and lean ACSA	
VM intramuscular fat fraction as percentage	2.05 (1.25–3.36)
VM lean ACSA, cm	1.21 (0.94–1.55)
Age, years	1.13 (1.04–1.22)
Sex (reference female)	0.17 (0.03–0.91)
Body mass index, kg/m^2	0.88 (0.68–1.13)

* For all variables except sex, odds ratios are per 1-unit increase in the exposure. ACSA = anatomical cross-sectional area; VM = vastus medialis.

adipose tissue in the thigh muscles, which shares a direct vascular connection with the muscle it infiltrates, is associated with impaired fat oxidation (17) and unfavorable lipoprotein profiles (18). Further research is needed to clarify the metabolic activity of the intramuscular fat depots of the VM in people with knee OA. The VM may also be preferentially involved in knee OA. A recent study compared VM biopsy results from patients with end-stage knee OA who underwent arthroplasty with patients without OA (19). The authors reported a significantly lower myofiber-occupied area and greater ectopic interstitial adipogenesis in the perimysium and endomysium of people with OA. Individuals with OA had 30.4% of the VM area occupied with adipose tissue versus 4% for people without OA. The authors did not evaluate other quadriceps muscles. Assuming a similar amount of fatty infiltration in all quadriceps muscles, the VM may be most affected earlier, being the smallest of the uni-articular quadriceps muscles. However, the findings may also be related to our measurement of adiposity and lean ACSA. We used a region of interest consisting of a 2-cm section of the thigh 10–12 cm proximal to the superior pole of the patella. Perhaps our method captured fatty infiltration of the VM more than the other quadriceps, which are larger and extend significantly more in the proximal direction.

There are limitations of this study that should be considered. Our cohort consisted of community-dwelling active and high-functioning individuals. Hence, the results may not be generalizable to individuals with more advanced OA or greater functional limitations. We defined our outcome as an increase in scores for either cartilage or meniscus or bone marrow lesions. This definition does not allow for interpretations regarding associations of quadriceps adiposity and individual features of knee OA or individual subregions within the knee joint. Our study also included a relatively small sample, and these results should be confirmed in larger cohorts.

In conclusion, we observed that greater fatty infiltration of the quadriceps muscle, and particularly the VM muscle, were related to an increased risk of worsening knee OA assessed using MRI. These results suggest that quadriceps adiposity could be a target for therapeutic interventions. However, these findings need confirmation in larger cohorts.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Kumar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Kumar, Link, Majumdar, Souza.
Acquisition of data. Kumar, Link, Majumdar, Souza.
Analysis and interpretation of data. Kumar, Link, Jafarzadeh, LaValley, Majumdar, Souza.

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BRIEF REPORT

Effectiveness of Hip Arthroscopy on Treatment of Femoroacetabular Impingement Syndrome: A Meta-Analysis of Randomized Controlled Trials

Nicola C. Casartelli,[1] Pedro L. Valenzuela,[2] Nicola A. Maffiuletti,[3] and Michael Leunig[3]

Objective. To appraise the highest available evidence provided by randomized controlled trials (RCTs) on the effectiveness of hip arthroscopy versus physical therapy in patients with femoroacetabular impingement syndrome (FAIS).

Methods. Four databases (Medline, Embase, Web of Science, and Scopus) were systematically searched until October 1, 2019. Eligible studies were RCTs in which patients with FAIS underwent hip arthroscopy or physical therapy. The study outcome was the International Hip Outcome Tool, 33 Items (iHOT-33) score, a measure of hip pain, function, and quality of life, assessed at baseline and at the follow-up closer to 12 months after randomization. The pooled mean difference in iHOT-33 scores within and between the treatment arms was computed using a random effects model. The minimum clinically important difference in the iHOT-33 scores was set at 10 points.

Results. Three RCTs evaluating iHOT-33 scores between 6 and 8 months after the interventions were included. Significant increases in iHOT-33 scores were observed from baseline to follow-up for both hip arthroscopy (22.3 points [95% confidence interval (95% CI) 17.3–27.4]) and physical therapy (13.0 points [95% CI 9.5–16.4]). Hip arthroscopy demonstrated significantly higher iHOT-33 scores at follow-up compared with physical therapy (10.9 points [95% CI 4.7–17.0]).

Conclusion. Both hip arthroscopy and physical therapy resulted in statistically and clinically significant short-term improvements in hip pain, function, and quality of life in patients with FAIS. Hip arthroscopy was statistically superior to physical therapy in improving the outcome at follow-up even if improvement may not be detected by patients.

INTRODUCTION

Femoroacetabular impingement syndrome (FAIS) is a condition induced by abnormal morphology of the proximal femur and/or acetabulum (1). FAIS causes hip pain and functional limitations in young adults and is a risk factor for developing hip osteoarthritis (OA) (1). Approximately 25% of the White population presents FAIS-related morphology (2), and up to 25% of these individuals develop hip OA (3). In the last decade, hip arthroscopy has matured to the standard of surgical care to manage the complications associated with FAIS. Despite the number of arthroscopic procedures for the treatment of FAIS increasing by ~450% from 2005 to 2013, with >50,000 procedures performed annually in the US (4), the level of evidence supporting the effectiveness of hip arthroscopy for FAIS was low because it is mostly limited to case series (5).

In these studies, patients with FAIS reported significant improvements in hip pain and function during daily activities and sport following hip arthroscopy as compared to their preoperative status (5). Nevertheless, patients also had, on average, residual mild hip pain and/or an impaired hip function following surgery compared to their healthy counterparts (5). At the same time, case

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SIGNIFICANCE & INNOVATIONS

- Both hip arthroscopy and physical therapy led to significant and clinically relevant improvements in hip pain, function, and quality of life in patients with femoroacetabular impingement syndrome (FAIS) in the short-term (6–8 months postintervention) compared to baseline.
- Hip arthroscopy was statistically superior to physical therapy in improving hip pain, function, and quality of life in patients with FAIS, but the clinical difference between the 2 treatment effects at short-term follow-up may not be detected by patients.

series and pilot randomized controlled trials (RCTs) indicated that supervised exercise therapy can also improve hip pain, function, and quality of life in some patients with FAIS (6,7). In the last few years, some RCTs have been published on the effectiveness of hip arthroscopy for FAIS as compared with physical therapy. Because of the highly frequent use of hip arthroscopy for the management of patients with FAIS, there is considerable clinical interest in summarizing the current available evidence on its actual effectiveness. The aim of this study was to identify, appraise, and combine RCTs that investigated the effectiveness of hip arthroscopy in patients with FAIS as compared to physical therapy.

MATERIALS AND METHODS

Study selection. We performed a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was registered in the PROSPERO database with the following identification number: CRD42019139284. We conducted a systematic electronic search in Medline, Embase, Web of Science, and Scopus to identify studies published before October 1, 2019 using the following strategy: ("femoroacetabular impingement syndrome" OR "femoroacetabular impingement") AND ("hip arthroscopy" OR "arthroscopic surgery" OR "arthroscopic hip surgery") AND ("physical therapy" OR "physiotherapy") AND ("randomized controlled trial" OR "randomized controlled trial"). Systematic reviews were additionally screened to detect eligible studies that were not identified by the electronic search. Eligible studies were RCTs in which patients with FAIS underwent hip arthroscopy and physical therapy as intervention and control arms, respectively. Two authors (NCC and PLV) independently screened study titles and abstracts and assessed study eligibility by reading the full text, with disagreement resolved by consensus.

Data extraction. Data were independently extracted by 2 authors (NCC and PVL), with disagreement resolved by consensus. The study outcome was the International Hip Outcome Tool,

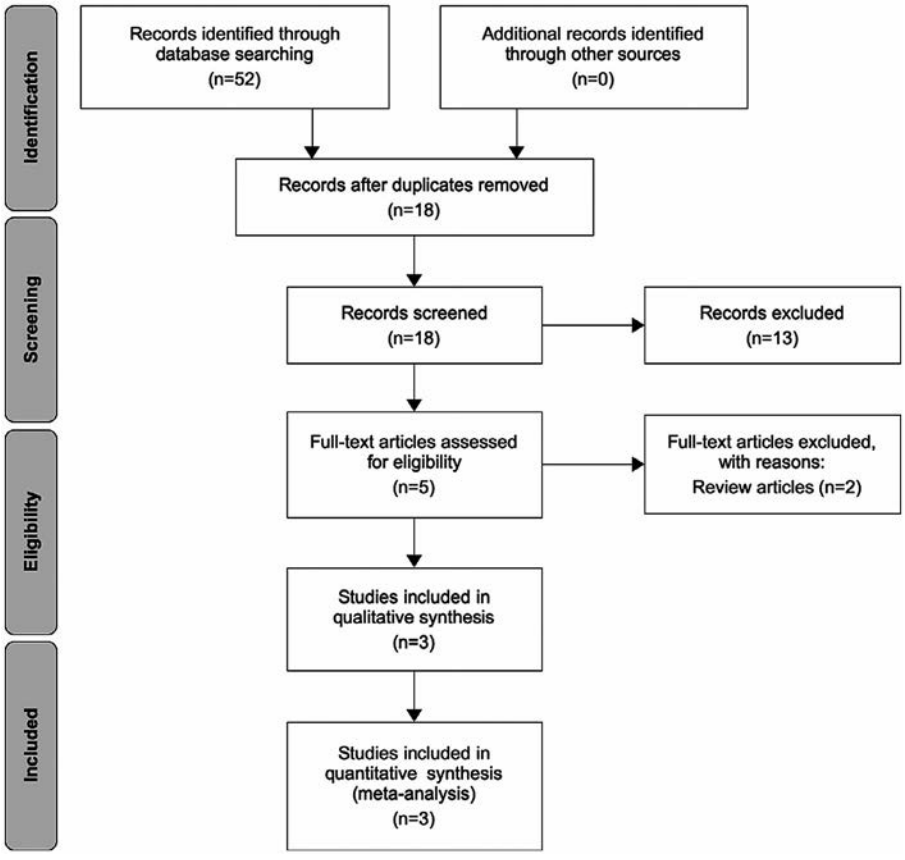

Figure 1. Flow chart of the study selection process.

33 Items (iHOT-33) score, as it was the unique outcome assessed in all the included RCTs. The iHOT-33 is a measure of hip pain, function, and quality of life specifically developed for young and active patients with hip disease (8). Means and SDs of iHOT-33 scores were extracted at baseline and at follow-up closer to 12 months (time from randomization to follow-up) and were analyzed as intent-to-treat. We contacted the authors of one study (9) in which the means and SDs of iHOT-33 scores at both baseline and follow-up were not reported in the original publication.

Methodologic quality. The methodologic quality of the included studies was independently evaluated by 2 authors (PLV and NAM) using the Cochrane Risk of Bias tool, with disagreement resolved by consensus. The Cochrane Risk of Bias tool assesses 6 different domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias (10). Within these domains, the following 7 items were assessed: random sequence generation; allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and crossover rate between treatment arms (other bias). For each item, a judgment as low, high, or unclear risk was provided with reasons. Because the study outcome used for the meta-analysis was a patient-reported score (i.e., the iHOT-33 score), the items that assess the use of blinding procedures for patients and personnel (performance bias), as well as the blinding of outcome assessment (detection bias), were of particular interest for this methodologic evaluation together with the risk of bias associated with the crossover between treatment arms (other bias).

Statistical analysis. The mean difference in iHOT-33 scores within and between the treatment arms was computed using a random effects model. The minimum clinically important difference (MCID) in iHOT-33 scores was set at 10 points (11). Heterogeneity across studies was assessed using Q and I^2 statistics, and the presence of publication bias was verified with Begg's tests. Statistical analyses were performed using MIX, version 2.0 Pro (BiostatXL), with significance level at 0.05.

RESULTS

Three RCTs met the inclusion criteria and were included in the meta-analysis (Figure 1) (9,12,13). Study characteristics are reported in Table 1. All included studies demonstrated high risk of performance and detection bias because patients and clinicians could not be blinded, and outcome was assessed using a patient-reported score (iHOT-33 score; see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24234/abstract). In addition, the study of Mansell et al (13) introduced another bias due to the very high crossover rate from the physical therapy to the surgery treatment arm. A total of 650 patients (48% women) with a weighted mean age of 35 years were included. In 2 studies (9,12), patients in the surgical arm were operated on by various surgeons in multiple hospitals, while in 1 study (13), patients were operated on by a single surgeon in a single hospital. In the surgical arm of all studies, patients had femoral and/or acetabular osteotomies as well as labral repair and/or debridement. Cartilage treatment was only reported in 2 studies (9,12). In the nonsurgical arm of all the

Table 1. Characteristics of the included studies*

Authors, year (ref.)	Trial name	Participants		Interventions		
		Number (% women)	Mean age, years	Hip arthroscopic procedures	Physical therapy protocols	Crossover rate, %
Griffin et al, 2018 (12)	UK FASHIoN	348 (39)	35	Multiple hospitals/multiple surgeons; femoral and/or acetabular osteotomies; labral repair/debridement; cartilage treatment	Personalized, impairment-based; supervised/home-based sessions; 12–24 weeks/6–10 supervised sessions; education/activity modification, stretching, hip and functional strengthening, core stability, self-mobilization	8
Mansell et al, 2018 (13)	US MHS	80 (41)	30	Single hospital/single surgeon; femoral and/or acetabular osteotomies; labral repair/debridement	Personalized, impairment-based; supervised/home-based sessions; 6 weeks/12 supervised sessions; manual therapy, stretching, hip and functional strengthening, core stability	70
Palmer et al, 2019 (9)	FAIT	222 (66)	36	Multiple hospitals/multiple surgeons; femoral and/or acetabular osteotomies; labral repair/debridement; cartilage treatment	Personalized, impairment-based; supervised/home-based sessions; 5 months/1–8 supervised sessions; education/activity modification, muscle strengthening	3

* FAIT = Femoroacetabular Impingement Trial; ref. = reference; UK FASHIoN = Full UK RCT of Arthroscopic Surgery for Hip Impingement versus Best Conservative Care; US MHS = United States Military Health System FAI Trial.

studies, patients received supervised, personalized, impairment-based physical/exercise therapy. Therapy doses (i.e., frequency, volume, intensity) varied between studies. The crossover rate from the nonsurgical to the surgical arm was low (<10%) in 2 studies (9,12) and very high (70%) in the other study (13). The time from randomization to follow-up was 12 months for 2 studies (12,13) and 8 months for 1 study (9). Considering the mean time from randomization to surgery reported in the studies, the actual evaluation time after surgery was ~8 months for 2 studies (12,13) and 6 months for 1 study (9). Significant increases in iHOT-33 scores were observed from baseline to follow-up for both hip arthroscopy (22.3 points [95% confidence interval (95% CI) 17.3–27.4]) and physical therapy (13.0 points [95% CI 9.5–16.4]) (Figure 2). Hip arthroscopy demonstrated significantly higher iHOT-33 scores at follow-up compared with physical therapy (10.9 points [95% CI 4.7–17.0]) (Figure 2). Low-to-moderate heterogeneity and no publication bias were observed.

DISCUSSION

Hip arthroscopy and physical therapy both appeared to improve hip pain, function, and quality of life statistically and clinically in patients with FAIS at ~6–8 months after the interventions. Hip arthroscopy was statistically superior to physical therapy, but the clinical relevance of these findings remains to be elucidated.

For the clinical interpretation of our results, we used a larger MCID in the iHOT-33 score (10.0 points) (11) than the one initially proposed by Mohtadi et al in their development and validation study (6.1 points) (8), which was later also adopted in the RCT of Griffin et al (12). Interestingly, patients with FAIS achieved, at the group level, statistically and clinically relevant improvements in iHOT-33 scores following both hip arthroscopy and physical therapy (22.3 and 13.0 points, respectively). These results are further supported when considering as critical benchmarks the lower limits of the 95% CI for iHOT-33 score improvements following hip arthroscopy and physical therapy (17.3 and 9.5 points, respectively), even if the improvement following physical therapy remains slightly below 10 points. At the individual level, however, it seems that a large proportion of patients showed no improvements at follow-up compared to baseline, as Palmer et al indicated that only ~50% and 30% of patients achieved a clinically relevant outcome improvement following hip arthroscopy and physical therapy, respectively (9). Even if the mean iHOT-33 score change from baseline to follow-up was significantly greater following hip arthroscopy compared to physical therapy, the clinical relevance of these differences remains unclear. Indeed, although the mean

Changes in iHOT-33 score from baseline to follow-up

Study	Baseline		Follow-up		Weight	MD (95% CI)	*P* value
	Mean ± SD	n	Mean ± SD	n			
Hip arthroscopy							
Griffin et al. 2018	39.2 ± 20.9	171	58.8 ± 27.0	158	47%	19.6 (14.4 - 24.8)	<0.001
Mansell et al. 2018	28.5 ± 15.5	37	48.9 ± 27.9	37	19%	20.4 (10.1 - 30.7)	0.001
Palmer et al. 2019	35.2 ± 21.9	112	62.4 ± 28.4	93	34%	27.2 (20.3 - 34.1)	<0.001
Total					**100%**	**22.3 (17.3 - 27.4)**	**<0.001**
Heterogeneity: Q=3.09, I^2=35%; Publication bias: Begg's *P*=1.000							
Physical therapy							
Griffin et al. 2018	35.6 ± 18.2	177	49.7 ± 25.0	163	56%	14.1 (9.5 - 18.7)	<0.001
Mansell et al. 2018	29.4 ± 15.5	37	43.9 ± 22.0	37	16%	14.5 (5.8 - 23.2)	0.001
Palmer et al. 2019	35.7 ± 21.4	110	45.5 ± 25.2	86	28%	9.8 (3.3 - 16.3)	0.003
Total					**100%**	**13.0 (9.5 - 16.4)**	**<0.001**
Heterogeneity: Q=1.25, I^2=0%; Publication bias: Begg's *P*=1.000							

Differences in iHOT-33 score between hip arthroscopy and physical therapy at follow-up

Study	Hip arthroscopy		Physical therapy		Weight	MD (95% CI)	*P* value
	Mean ± SD	n	Mean ± SD	n			
Griffin et al. 2018	58.8 ± 27.0	158	49.7 ± 25.0	163	45%	9.1 (3.4 - 14.8)	0.002
Mansell et al. 2018	48.9 ± 27.9	37	43.9 ± 22.0	37	21%	5.0 (-6.5 - 16.5)	0.392
Palmer et al. 2019	62.4 ± 28.4	93	45.5 ± 25.2	86	34%	16.9 (9.0 - 24.8)	<0.001
Total					**100%**	**10.9 (4.7 - 17.0)**	**0.001**
Heterogeneity: Q=3.62, I^2=45%; Publication bias: Begg's *P*=1.000							

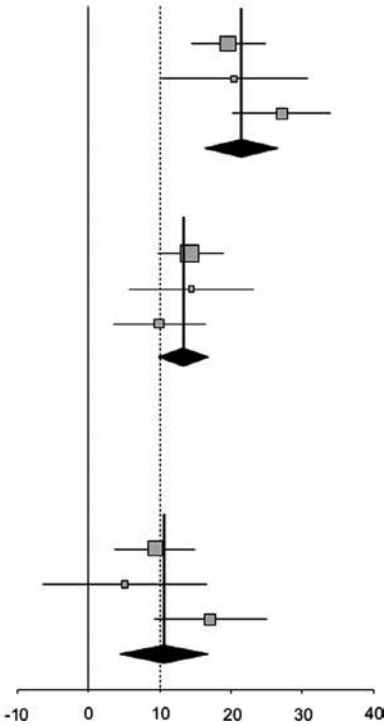

Figure 2. Meta-analysis of outcomes. Gray squares and horizontal lines represent, respectively, the mean difference (MD) and 95% confidence interval (95% CI) for the individual studies. Vertical bold lines and black diamonds represent, respectively, the MD and 95% CI for the pooled results. The vertical broken line indicates the minimum clinically important difference/change of the International Hip Outcome Tool, 33 Items (iHOT-33) score, which was set at 10 points.

difference in iHOT-33 score change between hip arthroscopy and physical therapy was slightly above the MCID (10.9 versus 10.0 points), the lower limit of the 95% CI was well below the MCID (4.7 versus 10.0 points). The fact that the difference in treatment effect between hip arthroscopy and physical therapy may not be detected by patients needs to be considered, especially in light of the superior cost-effectiveness of physical therapy versus hip arthroscopy at short-term follow-up (12).

The primary study of Mansell et al (13) was the only RCT included in the meta-analysis in which hip arthroscopy was not statistically superior to physical/exercise therapy (Figure 2). This RCT evaluated the effectiveness of arthroscopy for FAIS in a specific cohort of patients (i.e., military service members), who were all operated on by a single surgeon in a single hospital. All these factors significantly limit the generalizability of this study's results. Most importantly, 70% of the patients randomized to physical/exercise therapy at baseline in the primary study of Mansell et al ended up having hip arthroscopy during the study period (13), a factor that influenced our intent-to-treat analysis.

Several other factors need to be considered for a cautious interpretation of our results. Only FAIS patients with an indication for surgery and likely severe and prolonged symptoms were included in the primary studies. This sampling bias reduces the generalizability of the findings to all patients with a diagnosis of FAIS. In addition, since patients with FAIS were not blinded to treatment and the main outcome was assessed using a patient-reported questionnaire, a placebo effect of the study intervention (i.e., hip arthroscopy) should not be disregarded. Two ongoing RCTs (FIRST [NCT01623843] and HIPPARTI [NCT02692807] trials) comparing hip arthroscopy to sham surgery are expected to reveal the actual effectiveness of hip arthroscopy for FAIS in a blinded study design. Another limitation is that the physical/exercise therapy protocols adopted as control interventions in the primary studies might not represent the current best practice for nonsurgical management of FAIS (14). Indeed, the implemented therapy doses (i.e., frequency, volume, and intensity) might not adequately target the muscular and functional deficits of patients with FAIS (14). In this regard, an ongoing RCT (the Physio-FIRST trial) comparing 2 different nonsurgical therapy programs (ACTRN12617001350314) is expected to yield information on the most effective nonsurgical therapy protocol for FAIS (15). In addition, longer follow-ups are required to evaluate the effectiveness of hip arthroscopy and physical/exercise therapy not only in improving hip pain, function, and quality of life, but also in preventing hip OA in FAIS patients.

The strength of this meta-analysis is that we did not only evaluate the difference in iHOT-33 score between the treatment arms at follow-up, as did the authors of a previous similar systematic review and meta-analysis (14), but we also investigated the changes in iHOT-33 score within each treatment arm. These additional analyses were possible because we used the unadjusted means and SDs of iHOT-33 scores at baseline and follow-up for our calculations instead of the differences in treatment effect, which were differently adjusted in the original studies. A limitation of our meta-analysis is that only a total of 3 RCTs could be included. However, 2 of these studies were large multicentric RCTs published in high-impact medical journals (9,12). Unfortunately, only data from a single study outcome measure (i.e., the iHOT-33) were collected in all the 3 RCTs.

In summary, evidence to date suggests that hip arthroscopy, but also a more conservative approach such as physical therapy, improves hip pain, function, and quality of life in FAIS patients with severe and prolonged symptoms at short-term follow-up (6–8 months postintervention). The superiority of hip arthroscopy as compared to physical therapy was statistically proven, but the clinical relevance of these findings remains unclear, as the difference between the effects of hip arthroscopy and physical therapy may not be clinically detected by patients. One of the main future research challenges is to identify which patients could best benefit from each of these interventions.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Casartelli had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Casartelli, Valenzuela.

Acquisition of data. Casartelli.

Analysis and interpretation of data. Casartelli, Valenzuela, Maffiuletti, Leunig.

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AMERICAN COLLEGE of RHEUMATOLOGY
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BRIEF REPORT

Impact of the COVID-19 Pandemic on the Employment of Canadian Young Adults With Rheumatic Disease: Findings From a Longitudinal Survey

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Objective. The COVID-19 pandemic has had considerable economic repercussions for young workers. The current study was undertaken to examine the impact of the pandemic on the employment of young adults with rheumatic disease and on perceptions of work and health.

Methods. Surveys were administered to young adults with rheumatic disease prior to and following the onset of the COVID-19 pandemic. Surveys asked about employment status and collected information on sociodemographic, disease/health, and work-context factors. Items also asked about the perceived impact of the COVID-19 pandemic on work and health. A generalized estimating equation model was fitted to examine the effect of the pandemic on employment.

Results. In total, 133 young adults completed the pre–COVID-19 pandemic survey (mean age 28.9 years, 82% women). When compared to the pre–COVID-19 pandemic period, employment decreased from 86% to 71% following the pandemic, but no other changes were identified in sociodemographic, disease/health, or work-context factors. The time period following the COVID-19 pandemic was associated with a 72% lower odds of employment compared to the pre-pandemic period (odds ratio 0.28 [95% confidence interval 0.11–0.71]). Those with a postsecondary education or who reported more mental job demands were more likely to be employed following the onset of the pandemic. Also, a majority of participants reported that the pandemic affected health care (83%), treatment access (54%), working conditions (92%), and occupational health and safety (74%).

Conclusion. The onset of the COVID-19 pandemic had socioeconomic implications for young people with rheumatic disease. To support economic recovery for individuals with rheumatic disease, strategies to promote employment should be designed that account for the young adult life phase and occupational characteristics.

INTRODUCTION

The COVID-19 pandemic has had significant economic and health consequences for the working population. In the early spring of 2020, policies and programs were implemented in Canadian provinces that aimed to address the rising community and occupational spread of SARS–CoV-2 and to minimize cases of COVID-19, including but not exclusive to the closure of nonessential business, social distancing measures, and changes to health care delivery. Canadian labor force data from the general working population showed a sharp drop in the employment rate (–15.4%) following the start of the pandemic (1). Data also show that youth and young adults were 2 times more likely to report job loss than older age groups (1). While the reopening of the economy was accompanied by an economic rebound, paid work remains lower than pre-pandemic levels and is susceptible to disruption from additional waves of disease transmission. Of concern, COVID-19–related employment interruptions have implications for the mental health of young adults (2).

Preliminary studies show that individuals with autoimmune rheumatic diseases could be at an elevated risk of infection from COVID-19 when compared to those not living with

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SIGNIFICANCE & INNOVATIONS

- Using a longitudinal data set, we show a significant reduction in the frequency of young adults with rheumatic disease who were employed after the onset of the COVID-19 pandemic.
- Highlighting occupational inequities in the impact of COVID-19, participants with a higher education or working in jobs with greater mental demands were less likely to report employment loss.
- A majority of participants indicated that the COVID-19 pandemic affected their health care and medical treatment as well as their working conditions and occupational health and safety.

a rheumatic disease (3). Also, studies of individuals with rheumatic disease reported gaps in the delivery of rheumatology care and treatment and worsening health when compared to pre-pandemic levels (e.g., greater fatigue, worsening musculoskeletal and cognitive function, and psychological stress) (3,4). For workers with rheumatic disease, COVID-19 could pose a specific risk of infection for those in occupational settings that require client-facing job tasks or where social distancing measures are more challenging (e.g., nursing, teaching, factory work) (5). Workers with rheumatic disease may have experienced changes to their employment attributed to policies aimed at addressing COVID-19 spread or may have adapted their working situation to address the perceived risk of disease transmission or to cope with psychosocial stressors attributed to the pandemic (4).

Our study focused on young adults with rheumatic disease (ages 18–35 years) who were in the early stages of their working lives. Research conducted prior to the COVID-19 pandemic indicated that young adults with rheumatic disease face challenges finding and sustaining paid work and are more likely to report barriers to accessing modifications to the work environment to support work and health needs (6,7). These employment challenges have the potential of being more pronounced during a period of economic disruption and, for young adults, have the potential to impact work experiences across the life course and affect pathways to health (2,8).

Using longitudinal survey data, we sought to determine changes to employment in a sample of young adults with rheumatic disease in the period following the implementation of policies and programs to address COVID-19 spread (i.e., post COVID-19 pandemic onset) when compared to the period prior to the COVID-19 pandemic. Secondly, we examined the sociodemographic, disease/health, and work-context factors related to employment following the onset of the COVID-19 pandemic. Cross-sectional data collected after the onset of the pandemic examined a third objective: to describe the impact of COVID-19 on perceptions of work and health.

MATERIALS AND METHODS

In a cohort of Canadian young adults with rheumatic disease, a survey was administered at 2 time points separated by 9 months: prior to policies and programs being widely applied to address the spread of COVID-19 (December 1, 2019 to March 31, 2020); and after restrictions related to the COVID-19 pandemic being widely applied (last survey completed December 12, 2020). The study included individuals between the ages of 18–35 years with a self-reported diagnosis of rheumatic disease from a doctor (e.g., juvenile arthritis, systemic lupus erythematosus, rheumatoid arthritis) and having held paid employment (in the past year) or looking for work. Past studies note challenges of recruiting young adults with rheumatic disease to participate in surveys (9). Accordingly, we used 3 purposive recruitment approaches to maximize engagement. First, participants were recruited from specialty clinics in 3 Canadian provinces (British Columbia, Ontario, and Quebec). Eligible participants recruited through clinics were provided with a study invitation that included a link to the survey. Second, eligible participants were identified and recruited through an existing panel of Canadians maintained by a research firm that is nationally representative according to region and income (9). Third, community-based recruitment was conducted through 3 patient-led organizations of individuals with rheumatic disease that shared study advertisements through their listservs or social media accounts. All interested eligible potential participants were provided with detailed study information; informed consent was obtained, and eligibility was confirmed. A 30-minute online English- or French-language survey was administered to participants at each time point. University of Toronto's Research Ethics Board approved study procedures (REB number 36588).

Survey. The survey was informed by previous qualitative research (7). Items and measures were selected according to past studies of people with rheumatic disease in which validity, reliability, and associations with employment were established (6,10).

Employment status as outcome. At each time point, respondents were asked about their current employment status. Respondents were classified as employed or not employed (i.e., student, short-term leave, furloughed or temporarily laid off, on long-term leave, unemployed but looking for work, unemployed, and not looking for work).

Covariates. Participant details were collected at each time point, including age (years), sex/gender, educational attainment, and marital status. Information on diagnosis of rheumatic disease, age at disease onset, and self-rated health (1 = poor, 5 = excellent) was obtained. Self-reported pain, fatigue, and disease activity were measured using 11-point scales (0 = no pain/fatigue/disease activity, 10 = worst possible pain/fatigue/disease activity) (11). The 10-item Center for Epidemiological Studies Depression Scale (CESD-10) was used to measure frequency of current depressive symptoms (e.g., depressed mood

Table 1. Sociodemographic, disease/health, and work-context factors reported by young adults with rheumatic disease prior to and after the onset of the COVID-19 pandemic*

Characteristic	Prior to COVID-19 pandemic (n = 133)	After onset of COVID-19 pandemic (n = 110)	*P*
Employment status			
Employed	114 (85.7)	78 (70.9)	0.01
Not employed	19 (14.3)	32 (29.1)	
Sociodemographic factors			
Age, mean ± SD years	28.7 ± 4.9	29.6 ± 4.8	0.17
Sex/gender			0.97
Women	109 (82.0)	91 (82.7)	
Men	23 (17.3)	18 (16.4)	
Non-binary	1 (0.75)	1 (0.91)	
Educational attainment			
Less than postsecondary education	17 (12.8)	14 (12.7)	
Postsecondary education or more	116 (87.2)	96 (87.3)	
Married/living as if married	57 (42.9)	50 (45.5)	0.68
Primary childcare responsibilities	19 (14.9)	17 (15.5)	0.92
Disease/health factors			
Rheumatic disease diagnosis			0.61
Juvenile arthritis	37 (27.8)	33 (30.0)	
Lupus	16 (12.0)	16 (16.4)	
Rheumatoid arthritis	48 (36.1)	32 (29.1)	
Other rheumatic disease diagnosis	32 (24.1)	27 (24.6)	
Pediatric disease onset, age <18 years	90 (69.0)	76 (69.7)	0.86
Pain score, mean ± SD (range 0–10)	4.3 ± 2.4	4.30 ± 2.6	0.96
Fatigue score, mean ± SD (range 0–10)	5.8 ± 2.6	5.31 ± 2.6	0.14
Disease activity score, mean ± SD (range 0–10)	3.8 ± 2.5	3.6 ± 2.5	0.53
Flare severity			0.29
No flares	28 (21.1)	31 (28.2)	
1–2 flares	66 (49.6)	51 (46.4)	
≥3 flares	36 (27.1)	27 (24.5)	
Do not know	3 (2.3)	1 (0.9)	
Self-rated health			0.86
Poor	14 (10.5)	6 (5.5)	
Fair	37 (27.8)	35 (31.8)	
Good	48 (36.1)	45 (40.9)	
Very good	30 (22.6)	18 (16.4)	
Excellent	4 (3.0)	6 (5.45)	
Depression			
Depressed, CESD-10 score ≥10	84 (63.2)	67 (60.9)	0.72
Not depressed, CESD-10 score <10	49 (37.8)	43 (39.1)	
Workplace activity limitations mean ± SD (WALS score range 0–36)	9.9 ± 5.9	9.5 ± 6.3	0.57
Work-context factors†			
Employment type			0.24
Full-time work hours, ≥30 hours/week	87 (76.3)	65 (83.3)	
Part-time work hours, <30 hours/week	27 (23.7)	13 (16.7)	
Employment contract			0.92
Permanent contract	84 (73.7)	58 (74.4)	
Temporary contract	30 (26.3)	52 (25.6)	
Job tenure, mean ± SD years	3.4 ± 3.4	3.9 ± 3.8	0.29
Job control, mean ± SD (range 1–5)	2.9 ± 1.2	2.9 ± 1.2	0.74
Workplace physical activity requirement, mean ± SD (range 1–5)	3.0 ± 1.4	2.7 ± 1.5	0.13
Perceived mental job demands, mean ± SD (range 1–5)	3.8 ± 1.1	3.7 ± 1.2	0.58
Perceived job stress, mean ± SD (range 1–5)	3.1 ± 0.9	3.1 ± 1.1	0.72
Perceived organizational support, mean ± SD (range 1–5)	3.2 ± 1.3	3.3 ± 1.3	0.31
Job sector			0.48
Trades/transportation	29 (21.8)	20 (25.6)	
Sales/services	12 (9.02)	3 (3.9)	
Professional services/technology	15 (11.3)	14 (17.9)	
Health care/social services	57 (42.9)	41 (52.6)	

* Values are the number (%) unless indicated otherwise. CESD-10 = 10-item Center for Epidemiological Studies Depression Scale; WALS = Workplace Activity Limitations Scale.
† Percentage calculated for those reporting paid employment.

and feelings of guilt) using a 5-point ordinal scale (0 = rarely/none of them time, 4 = all of the time) (12). A CESD-10 score ≥10 indicated depression. Participants completed the 12-item Workplace Activity Limitation Scale (WALS) to measure difficulties with workplace acts and tasks (i.e., problems with lower mobility, upper mobility, and concentration) (0 = no difficulty/not applicable to job, 3 = unable to do). Items were summed to produce a score ranging from 0 to 36 (10).

Participants were asked about whether they held part-time (<30 hours/week) or full-time employment (≥30 hours/week) or held a permanent or temporary contract, their job tenure (years), and the job sector worked (trades/transportation, sales/services, professional services, health care/social services, technology). Participants were asked about the physical activity requirements of their workplace and mental job demands (1 = not at all, 5 = a great deal). Additionally, participants were asked about their perceptions of job control, job stress, and organizational support (1 = not at all, 5 = a great deal).

Perceptions of COVID-19 impact. Descriptive items were developed that asked about the perceived impact of the COVID-19 pandemic on work and health and were measured after the onset of the pandemic. Two questions asked about the extent to which the COVID-10 pandemic interrupted access to health care providers and medical treatment (1 = not at all, 5 = a great deal). Also, 2 questions asked about the extent to which the COVID-19 pandemic affected workplace health and safety and working conditions (1 = not at all, 5 = a great deal).

Statistical analysis. Descriptive statistics (i.e., percentages, means) were used to examine variable distributions. Chi-square tests and *t*-tests were conducted to compare employment status and sociodemographic, health/disease, and work-context factors using observations collected for each participant prior to the COVID-19 pandemic and after the onset of the pandemic. Univariable logistic regression models were conducted to examine the individual relationship between each study variable collected prior to the COVID-19 pandemic and the odds of employment following the onset of the pandemic. We fitted a multivariable generalized estimating equation (GEE) model to examine change in employment status in the time period after the onset of the COVID-19 pandemic when compared to the period prior to the pandemic. Our model also enabled the examination of relationships between study variables and employment after the onset of the COVID-19 pandemic. The GEE model was fitted with a logit link and exchangeable correlation structure to account for the relationship between observations within participants over time. Analyses were conducted using SAS, version 9.30 (13).

RESULTS

Overall, 133 young adults with rheumatic disease completed the survey prior to the COVID-19 pandemic. Of those, 83% completed the survey after the onset of the COVID-19 pandemic. No significant difference was identified between participants who completed both surveys and those lost to follow-up. A majority of participants were women (82%) and had a postsecondary education (87%). Less than one-half of participants indicated being married/living as if married (43%), and 15% reported having primary childcare responsibilities. Approximately 28% reported having juvenile arthritis, and 36% reported having rheumatoid arthritis; 70% indicated a diagnosis of a pediatric disease. Prior to the COVID-19 pandemic, participants indicated moderate-to-low mean pain (mean ± SD 4.3 ± 2.4), fatigue (mean ± SD 5.8 ± 2.6), and disease activity scores (mean ± SD 3.8 ± 2.5). Also, prior to the COVID-19 pandemic, approximately two-thirds of participants reported good, very good, or excellent health (62%); 63% indicated depressive symptoms. Participants indicated moderate limitations to workplace activity prior to the pandemic (mean ± SD 9.9 ± 5.9) (Table 1).

Of note, 86% of participants held paid employment prior to the COVID-19 pandemic. An examination of information on work-context factors collected prior to the COVID-19 pandemic showed that 76% of participants worked full-time hours, 74% held a permanent job, and just under one-half worked in the health care/social services job sector (43%). Participants reported moderate mean job control (mean ± SD 2.9 ± 1.2), mental job demands (mean ± SD 3.8 ± 1.1), job stress (mean ± SD 3.1 ± 0.9), organizational support (mean ± SD 3.2 ± 1.3), and requirements of workplace physical activity (mean ± SD 3.0 ± 1.4).

Significantly fewer participants were employed after the onset of the COVID-19 pandemic (71%) ($P < 0.01$). Additionally, after the onset of the pandemic, participants did not report significant differences to sociodemographic, disease/health, or work-context factors (Table 1).

When adjusting for study covariates, the time period after the onset of the COVID-19 pandemic was associated with a 72% lower odds of employment when compared to the time period prior to the pandemic (odds ratio [OR] 0.28 [95% confidence interval (95% CI) 0.11–0.71]) (Table 2). Having a postsecondary education prior to the COVID-19 pandemic was associated with a greater odds of employment following the onset of the pandemic when compared to those not holding a postsecondary education (OR 7.2 [95% CI 1.76–26.62]). Those reporting that their job required greater mental demands prior to the COVID-19 pandemic were more likely to report employment after the onset of the COVID-19 pandemic (OR 1.56 [95% CI 1.08–2.25]). Also, the multivariable model indicated an association between being a woman and a lower likelihood of employment when compared to men (OR 0.26 [95% CI 0.11–0.71]). Pediatric onset of rheumatic disease was associated with a greater likelihood of being employed when compared to those with adult-onset rheumatic disease (OR 2.68 [95% CI 1.12–6.43]).

Table 2. Univariable model and multivariable generalized estimating equation (GEE) model examining the effect of the COVID-19 pandemic on the employment of young adults with rheumatic disease*

	Univariable OR (95% CI)†	Multivariable OR (95% CI)‡
Time period		
Prior to COVID-19 pandemic		–
Following onset COVID-19 pandemic		0.28 (0.11–0.71)§
Sociodemographic¶		
Age, years	1.11 (1.01–1.21)§	1.08 (0.99–1.17)
Sex/gender		
Women	0.91 (0.30–2.81)	0.26 (0.11–0.71)§
Men	–	–
Education		
Less than postsecondary education	–	–
Postsecondary education or more	3.94 (1.24–12.52)§	7.2 (1.93–26.62)§
Marital status		
Married/living as if married	1.83 (0.77–4.40)	2.5 (0.99–6.42)
Not married or living as if married	–	–
Childcare responsibilities		
Primary childcare responsibilities	0.29 (0.06–1.47)	0.35 (0.07–1.82)
No childcare responsibilities/not primary caregiver	–	–
Disease/health factors¶		
Disease onset		
Pediatric disease onset, age <18 years	1.3 (0.53–3.11)	2.68 (1.12–6.43)§
Adult onset, age >18 years	–	–
Self-rated health		
Poor/fair	–	–
Good/very good/excellent	2.67 (1.13–6.27)§	1.79 (0.60–5.38)
Pain score (range 0–10)	0.75 (0.62–0.91)	1.08 (0.80–1.46)
Fatigue score (range 0–10)	0.84 (0.70–0.99)	0.93 (0.67–1.28)
Disease activity score (range 0–10)	0.78 (0.65–0.94)§	0.96 (0.68–1.37)
Depression		
Depressed, CESD-10 score ≥10	0.93 (0.87–0.99)§	0.46 (0.15–1.37)
Not depressed, CESD-10 score <10	–	–
Workplace activity limitations (WALS score range 0–36)	0.91 (0.85–0.98)§	1.01 (0.92–1.11)
Work-context factors¶		
Job control (range 1–5)	1.11 (0.77–1.61)	1.38 (0.95–2.00)
Organizational support (range 1–5)	1.37 (0.95–1.98)	0.91 (0.61–1.35)
Physical activity (range 1–5)	0.62 (0.45–0.87)§	1.19 (0.82–1.73)
Mentally demanding job (range 1–5)	1.41 (0.94–2.12)§	1.56 (1.08–2.25)§

* 95% CI = 95% confidence interval; CESD-10 = 10-item Center for Epidemiological Studies Depression Scale; OR = odds ratio; WALS = Workplace Activity Limitations Scale.
† Univariable logistic regression model examining the relationship between study variables and employment after the onset of the COVID-19 pandemic. Due to limitations of sample size, the participant who was non-binary was not included in the model and should be examined in further analyses.
‡ GEE model examined the relationship between study variables and employment following the application of policies and programs to address the spread of COVID-19. Due to limitations of sample size, the participant who was non-binary was not included in the model and should be examined in further analyses.
§ Significant.
¶ Measured prior to the onset of policies and programs to address the spread of COVID-19.

More than 80% of participants indicated that the COVID-19 pandemic affected access to health care, of which just under one-half reported quite a bit/a great deal of impact. Also, 44% of participants reported that the COVID-19 pandemic affected access to medical treatment. More than 90% of participants indicated that the COVID-19 pandemic affected working conditions, of which one-half indicated quite a bit/a great deal of impact. Close to three-fourths of participants indicated that the COVID-19 pandemic affected their perceptions of occupational health and safety (74%) (Figure 1).

DISCUSSION

Young adults with rheumatic disease are a labor market group with vulnerability to the economic impact of the COVID-19 pandemic. Utilizing a longitudinal survey of a purposively recruited sample of Canadian young adults with rheumatic disease, we showed a significant decline in employment following the onset of the COVID-19 pandemic when compared to pre-pandemic levels. For the young adults in our study, having a less established employment history, a more recently diagnosed condition,

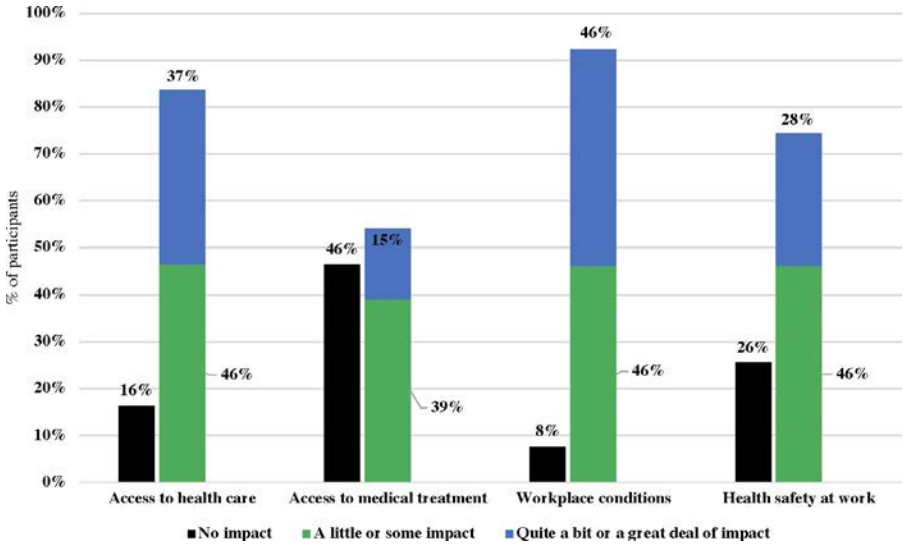

Figure 1. Perceived impact of the COVID-19 pandemic on work and health as indicated in data from young people with rheumatic disease collected after the onset of the pandemic.

or working in entry-level positions could mean that they were particularly susceptible to labor market shocks (7). Scholarship on the social determinants of health indicate that paid work provides pathways to promoting long-term health and quality of life (8). Disruption to employment because of COVID-19 at the early career phase could have significant implications for employment and health outcomes (2). Supporting employment engagement represents a strategy to assist young people with rheumatic disease in recovering from the effects of the COVID-19 pandemic and to promote health.

Descriptive findings highlighted the work and health implications of the COVID-19 pandemic. Participants reported that the pandemic affected health care access and medical treatment as well as working conditions and occupational health and safety. This was not, however, reflected by self-reported disease severity or other health factors that did not differ between pre- and post–COVID-19 periods. The loss of employment identified in our sample could be attributed to labor market policies that addressed occupational spread of COVID-19, which may have affected participants who were at an early career stage, rather than being related to changes to health. Additional research is required to elaborate on the ways in which the COVID-19 pandemic affected employment of young adults with rheumatic disease, as well as short- and longer term labor market outcomes.

Study findings could reflect occupational inequities in the impact of COVID-19. Participants reporting greater educational attainment or those working in jobs with greater mental demands were more likely to be employed following the onset of the COVID-19 pandemic. It may be that educational attainment and mental demands are proxies for those employed in higher skilled jobs that may be performed from home or where there is opportunity to modify work (14). Aligning with labor force data, our study of young adults with rheumatic disease found an association between being a women and not working after the onset of the COVID-19 pandemic (1,15). These preliminary findings may be explained by differences in workplace experiences (e.g., occupation) and roles outside of work (e.g., childcare responsibilities) for female participants that could have contributed to a greater socioeconomic burden of the pandemic (16). Research in a larger sample is required to further examine differences in sex and gender in the impact on employment among young adults with rheumatic disease. Findings pointing to the importance of contextual and personal factors should be considered in the design of policies and programs that support participation in paid work during the COVID-19 pandemic and during periods of economic recovery.

We determined changes in employment resulting from the COVID-19 pandemic that were attributed to the longitudinal design of the study. Our study timeframe was, however, limited, and we were not able to ascertain whether the removal or reapplication of policies addressing additional waves of COVID-19 resulted in employment fluctuations or if other forces may be driving change in paid work. Also, we focused mainly on employment status but did not examine changes in work hours or productivity that could also have been affected by the COVID-19 pandemic. Sample characteristics mirror past studies of young adults with rheumatic disease (17). Participants were purposively recruited, and there may be limitations related to the small sample size and generalizability of findings. Nonetheless, these data provide important preliminary insight into the work and health implications of the COVID-19 pandemic for a vulnerable subgroup of workers.

In conclusion, the COVID-19 pandemic contributed to a significant decrease in the employment of young adults with rheumatic disease. Of concern, for those at the early career phase, the effect of the pandemic on employment could extend across the

course of life and have significant implications for work and health. Employment interventions should be considered for young adults with rheumatic disease to support recovery from the COVID-19 pandemic.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Jetha had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Jetha, Tucker, Gignac.
Acquisition of data. Jetha, Tucker, Gignac.
Analysis and interpretation of data. Jetha, Chen.

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Disruptions in Rheumatology Care and the Rise of Telehealth in Response to the COVID-19 Pandemic in a Community Practice–Based Network

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Objective. The effect of the COVID-19 pandemic on community-based rheumatology care and the use of telehealth is unclear. We undertook this study to investigate the impact of the pandemic on rheumatology care delivery in a large community practice–based network.

Methods. Using a community practice–based rheumatologist network, we examined trends in in-person versus telehealth visits versus canceled visits in 3 time periods: pre–COVID-19, COVID-19 transition (6 weeks beginning March 23, 2020), and post–COVID-19 transition (May-August). In the transition period, we compared patients who received in-person care versus telehealth visits versus those who cancelled all visits. We used multivariable logistic regression to identify factors associated with canceled or telehealth visits.

Results. Pre–COVID-19, there were 7,075 visits/week among 60,002 unique rheumatology patients cared for by ~300 providers practicing in 92 offices. This number decreased substantially (24.6% reduction) during the COVID-19 transition period for in-person visits but rebounded to pre–COVID-19 levels during the post–COVID-19 transition. There were almost no telehealth visits pre–COVID-19, but telehealth increased substantially during the COVID-19 transition (41.4% of all follow-up visits) and slightly decreased during the post–COVID-19 transition (27.7% of visits). Older age, female sex, Black or Hispanic race/ethnicity, lower socioeconomic status, and rural residence were associated with a greater likelihood of canceling visits. Most factors were also associated with a lower likelihood of having telehealth versus in-office visits. Patients living further from the rheumatologists' office were more likely to use telehealth.

Conclusion. COVID-19 led to large disruptions in rheumatology care; these disruptions were only partially offset by increases in telehealth use and disproportionately affected racial/ethnic minorities and patients with lower socioeconomic status. During the COVID-19 era, telehealth continues to be an important part of rheumatology practice, but disparities in access to care exist for some vulnerable groups.

INTRODUCTION

Telehealth use in rheumatology prior to the COVID-19 pandemic was primarily limited to treating patients in rural areas that were medically underserved (1,2). The COVID-19 pandemic, however, has led to substantial health care disruptions and a rapid rise in telehealth use among patients with rheumatic and musculoskeletal diseases (RMDs) (3–6). Many of these patients are at increased risk of infection and may be at increased risk of severe COVID-19 due to immune dysregulation from their rheumatic

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SIGNIFICANCE & INNOVATIONS

- The COVID-19 pandemic has had major impacts on rheumatology care delivery, but most reports have described the experience of single centers or small regional practice networks.
- Within a large, multistate, community rheumatology practice network, follow-up visit cancellations were as high as 60% at the height of the COVID-19 pandemic and were more common in patients who were older, Black, Hispanic, of lower socioeconomic status, and residing in rural areas.
- Telehealth grew from almost no use to >40% of follow-up visits at the height of the COVID-19 pandemic, but older age, lower socioeconomic status, and rural residence were associated with lower use of telehealth.
- Telehealth has partially offset disruptions in care sparked by the pandemic, but lower telehealth use in vulnerable populations threatens to exacerbate existing disparities in rheumatology care.

condition, immunosuppressive medications, or multiple comorbid health conditions (i.e., multimorbidity) (7–9). Concerns about COVID-19 may further exacerbate health care disruptions in this population, yet these patients also require frequent health care visits for the evaluation and management of their conditions. Telehealth, defined as the use of electronic information and telecommunications technologies to support long-distance clinical health care (10), offers an attractive alternative to face-to-face visits for at least a subset of patients, especially for those with an already-established diagnosis from their rheumatology provider.

Little is known, however, about the patterns of health care disruptions and telehealth use in rheumatology practices during the pandemic, or the degree to which vulnerable patient populations have been disproportionately affected. We sought to understand the impact of the pandemic on rheumatology care in the setting of a large rheumatology community practice–based network. We described use of telehealth services within this provider network and tested the hypothesis that social determinants of health, including age, sex, race/ethnicity, socioeconomic status, and geographic location would influence missed rheumatology visits or infusion therapies given at rheumatology offices. We also evaluated whether these same social determinants of health (11–14) were associated with use of telehealth services.

MATERIALS AND METHODS

Definitions of telehealth services. We extracted the analytic cohort from the Columbus electronic health record (EHR) data warehouse of the American Arthritis and Rheumatology Associates (AARA) network, which represents ~300 full-time practicing rheumatology clinicians across 27 states. AARA and its business affiliate, Bendcare, is the largest US super group of rheumatology specialist providers in the US and was founded to promote high-quality, value-based rheumatology care within the context of a community practice-based network. Its providers use a common EHR system with an embedded video-based telehealth platform. Structured and selected unstructured data elements are normalized to a common data model, and the EHR data are augmented by a variety of internal and external data feeds, including patient-reported outcome data from the National Institutes of Health Patient-Reported Outcomes Measurement Information System (15) and linked laboratory, pharmacy, and health plan claims data from several sources. This infrastructure supports both prospective and retrospective clinical projects, quality improvement initiatives, and research studies.

Telehealth services were defined based on billed visits from the Evaluation and Management Current Procedure Terminology (CPT) code set (e.g., 99214) that included the modifiers -95, -GT, and -GQ, reflecting use of synchronous or asynchronous telecommunication services. The CPT codes for phone visits (i.e., 99441-3), and digital evaluation and management services (99421-3), and virtual visits (G2010, G2012) were also included. In-person visits were additionally identified using similar CPT codes without the telehealth modifiers, and visits were stratified as to whether they were for consultations/new patient encounters versus return patient visits for established patients.

Longitudinal trends in telehealth and traditional rheumatology services. We examined calendar trends in the frequency of in-person versus telehealth (video and/or phone) visits in 2020 over all AARA practices. The key intervals of time were subdivided a priori into the pre–COVID-19 time interval (i.e., the first full 10 weeks of 2020), the COVID-19 transition period (i.e., week 12 of 2020, beginning the week of March 23, and the ensuing 6 weeks), and the post–COVID-19 transition interval (i.e., beginning the week of May 4). The transition interval was anchored at week 12, given multiple news and public health authority announcements that recommended social distancing and encouraged restriction of discretionary travel (16). The data were censored at September 1 to allow for complete adjudication of billed visits and health care services. Scheduling data from the EHR were used to examine whether visits were canceled or missed (i.e., no show), or kept, stratified by visit type. Canceled/missed visits that were rescheduled within the same time period (i.e., COVID-19 transition period) were considered kept. We included in this evaluation administration for intravenous (IV) rheumatology therapies typically given in a provider's office, focusing on treatments for rheumatoid arthritis (RA) that included IV abatacept, IV tocilizumab, IV golimumab, and infliximab.

Social determinants of health and other factors potentially associated with telehealth services. In addition to age, sex, and race/ethnicity, we evaluated a number of additional social determinants of health. Factors of interest included

the national percentile ranking of the Area Deprivation Index (ADI) (17). The ADI is based on the American Community Survey (18) and ranks neighborhoods by socioeconomic status disadvantage within either the entire US (used for this analysis), or at a state level. It encompasses domains of income, education, employment, and housing quality and is based on census block group, obtained by use of patients' individual 9-digit zip code. We also evaluated the door-to-door driving distance between each patient's residence and their rheumatologist's office address, computed based on estimates from Google Maps. Rural/urban status was classified according to the categorization developed by the Centers for Disease Control and Prevention National Center for Health Statistics (19), with rural status being assigned as noncore areas. Finally, given the possibility that patients' willingness to receive in-person care would be influenced by local COVID-19 activity, we evaluated the tertile of COVID-19 cases per capita in each patient's county of residence (relative to all other US counties) on May 1 (near the end of the COVID-19 transition period) obtained from USAFACTS.org (20).

COVID-19 as a potential disruptor of clinical management of RA, and the availability of telehealth as a moderating influence. Among the subset of patients with RA who had disease activity measured using the Clinical Disease Activity Index (CDAI) available both in the pre–COVID-19 period and in the post–COVID-19 transition period at in-person visits, we examined the within-person change in CDAI score to assess whether patients experienced disease activity worsening in the COVID-19 transition period. While some practices did collect CDAI scores during telehealth visits, the methods by which these data were collected were highly variable across practices, and these CDAI observations were therefore excluded.

Additionally, to evaluate the hypothesis that COVID-19 reduced clinician and patients' willingness to start a new targeted RA therapy, we examined the likelihood that patients would start a new biologic or JAK inhibitor treatment in the COVID-19 transition period. The analysis was restricted to rheumatology practices that contributed data both in 2019 and 2020, and we compared the likelihood of treatment initiation during that 6-week interval to the corresponding 6-week interval in spring 2019.

Statistical analysis. Given the expectation that the COVID-19 transition period would create the greatest disruption in rheumatology care, we focused on that 6-week interval. Because we observed that telehealth services were minimally deployed for new patients, we compared the characteristics of established rheumatology patients who received in-person care, who received telehealth care, or who canceled any/all scheduled rheumatology visits with their clinician. Categories were mutually exclusive and applied in a hierarchical fashion such that someone who (for example) had a visit canceled but rescheduled it and received both in-person and telehealth care during the 6 weeks period would be counted only in the in-person care category. We compared demographics, main rheumatology diagnosis, and measures of social determinants of health, as described above. Standardized mean differences were used to compare these 3 groups, with values >0.10 indicative of potentially important differences (21).

We used multivariable logistic regression models to identify factors associated with canceled versus any completed visits (i.e.,

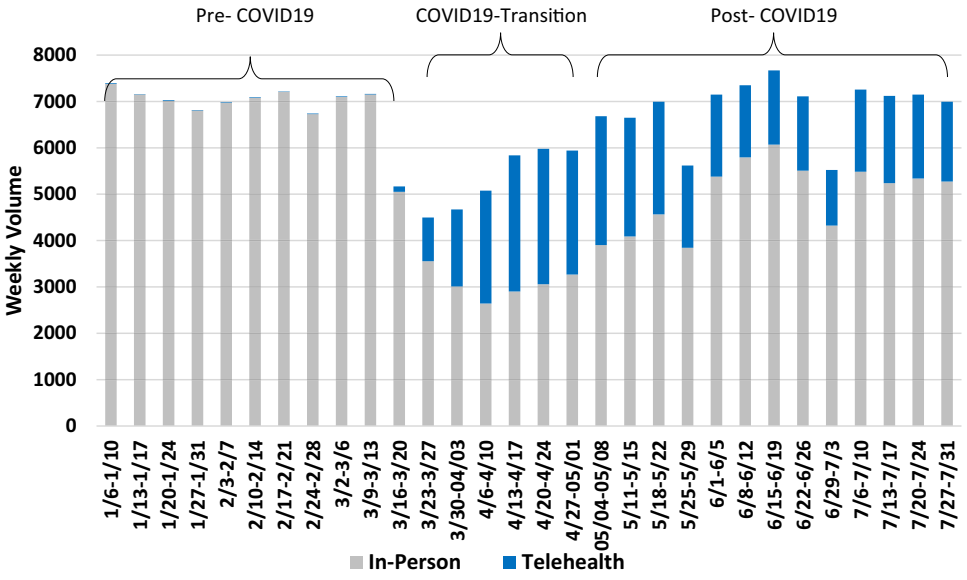

Figure 1. Weekly volume of follow-up clinician visits in the pre–COVID-19, COVID-19 transition, and post–COVID-19 periods. Visits include all evaluation and management clinician visit types other than new patient encounters and consultations. The decrease shown in the final week of May and the first week of July reflect the influence of national US holidays. The national state of emergency was declared on March 13, 2020; that week (full week 11 in 2020) was not included in either the pre–COVID-19 or the COVID-19 transition period, given the state of flux during that week. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24626/abstract.

telehealth or in-person visits). In separate models we compared those who underwent a telehealth versus an in-person visit during the COVID-19 transition period. The main independent variables of interest were the social determinants of health described above. Because some factors related to geography were modestly correlated with one another, not all could be examined in multivariable models; factors of highest interest were retained. Given the clustered nature of the data (patients nested within physician practices), alternating logistic regression was used to adjust for and estimate the effects of practice-level effects. The proportion of all visits conducted as a telehealth visit, rather than an in-person visit, was quantified for each physician practice. To evaluate the hypothesis that greater telehealth volume might somewhat offset reduced total visit volume during the COVID-19 transition period, we plotted the proportion of visits conducted as telehealth, ranging from 0%, reflecting no use of telehealth, to 100%, indicating that all visits during this interval were conducted using telehealth. This proportion was plotted as a function of the mean weekly visit volume during the COVID-19 transition period compared to the pre–COVID-19 period and plotted as a ratio. A ratio close to 1 would indicate that for any given office, visit volume during the COVID-19 transition period was the same as during the pre–COVID-19 interval.

The within-person changes in CDAI scores in the pre–COVID-19 and post–COVID-19 transition periods were evaluated with paired *t*-tests. Logistic regression was used to model the likelihood of treatment initiation in the COVID-19 transition period versus the corresponding interval in 2019, controlling for practice-level clustering as described above. The study received institutional review board approval and patient consent was waived. All data analyses were conducted in SAS 9.4 and R 4.0.3.

RESULTS

A total of 126,550 patients contributed 303,037 unique visit days in which 1 or more encounters occurred in 2020. In the first 10 full weeks of 2020 (pre-COVID), the mean ± SD number of weekly visits across all visit types (e.g., in person, laboratory testing appointments, infusions) in the provider network was 10,806 ± 280, occurring among 73,976 unique rheumatology patients. Restricting to only follow-up visits with clinicians, the mean ± SD weekly visit volume was 7,075 ± 184 visits in the pre–COVID-19 interval,

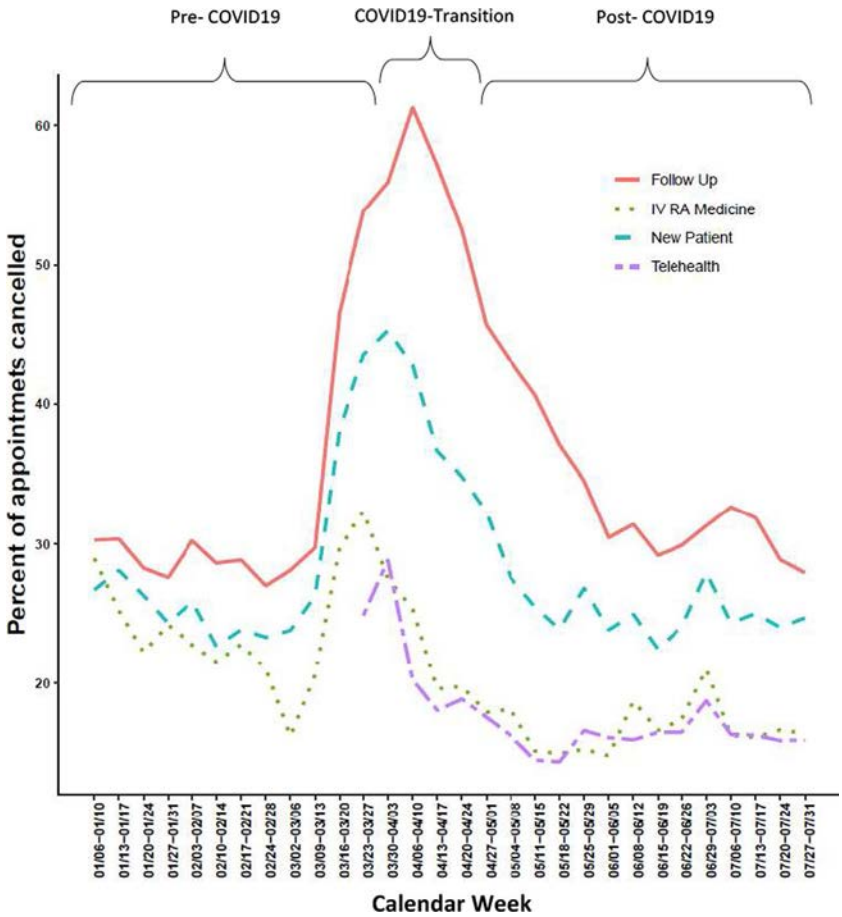

Figure 2. Canceled appointments for new patient visits, follow-up visits, telehealth, and intravenous infusions for rheumatoid arthritis (RA) treatments during 2020. IV = intravenous.

contributed by 60,002 unique patients (Figure 1). Overall follow-up visit volume decreased by 24.6% in the COVID-19 transition period but rebounded within a few months to pre–COVID-19 levels. Telehealth visits pre–COVID-19 were nearly nonexistent and increased to 41.4% and 27.7%, respectively, of all follow-up clinician visits in the COVID-19 transition period and post–COVID-19 period (Figure 1, blue bars). The vast majority of telehealth visits were video-based (91%); the remainder were phone (7%) or digital visits (2%).

Among all follow-up visits and depending on the calendar week, up to 60% of visits were canceled (Figure 2, red line), higher than for new patients and for IV RA medications. In the COVID-19 transition and post–COVID-19 transition periods, telehealth visits (purple broken line) were less likely to be canceled than in-person follow-up (solid red line) or new patient visits (blue broken line).

Table 1 shows characteristics of the 50,988 established rheumatology patients who canceled, had in-person visits, or had telehealth visits during the COVID-19 transition interval. Older patients were more likely to cancel visits and less likely to have telehealth-only care. Non-White race, lower socioeconomic status proxied by the ADI, US region, and greater COVID-19 activity in the patient's county of residence were associated with canceling and having in-person visits rather than telehealth care alone.

Table 1. Characteristics of rheumatology patients with canceled, in-person, and telehealth return visits during the 6-week COVID-19 transition period (n = 50,988 visits)*

Characteristic	Canceled	In-Person†	Telehealth	SMD
Visits, no.	22,237	16,510	12,241	–
Age, mean ± SD years	62.1 ± 15.3	58.8 ± 15.4	57.2 ± 14.9	0.21
Age <65, no. (%)	12,661 (59)	9,960 ± 60.4	8,389 ± 64.4	0.07
Age ≥65, no. (%)	8,803 (41)	6,540 ± 39.6	4,635 ± 35.6	–
Sex				0.07
Female	15,178 (78.4)	12,464 (75.5)	9,757 (79.7)	–
Race‡				0.23
White	14,290 (64.3)	12,612 (76.4)	9,070 (74.1)	–
Black	2,050 (9.2)	1,728 (10.5)	1,192 (9.7)	–
Hispanic	2,539 (13.1)	1,968 (11.9)	1,649 (13.5)	0.05
Area Deprivation Index, national rank				0.10
Quintile 1 (most affluent)	2,473 (12.7)	1,982 (12.0)	1,884 (15.4)	–
Quintile 2	5,370 (27.7)	4,437 (26.9)	3,628 (29.6)	–
Quintile 3	4,842 (25.0)	4,224 (25.6)	3,053 (24.9)	–
Quintile 4	3,946 (20.3)	3,528 (21.4)	2,208 (18.0)	–
Quintile 5 (least affluent)	2,766 (14.3)	2,338 (14.2)	1,468 (12.0)	–
Driving distance, mean ± SD kilometers	25.1 ± 41.6	26.2 ± 50.8	29.3 ± 75.8	0.05
Rural residence	1,612 (8.3)	1,331 (8.1)	676 (5.5)	0.09
Primary rheumatology diagnosis				–
RA	5,765 (29.7)	5,281 (32.0)	4,165 (34.0)	0.06
Osteoarthritis	2,908 (15.0)	2,157 (13.1)	1,493 (12.2)	0.05
PsA/AS/SpA	1,734 (8.9)	1,784 (10.8)	1,584 (12.9)	0.09
Osteoporosis	1,324 (6.8)	888 (5.4)	561 (4.6)	0.06
Systemic lupus erythematosus	1,144 (5.9)	1,196 (7.2)	1,151 (9.4)	0.09
Gout	555 (2.9)	442 (2.7)	240 (2.0)	0.04
Region				0.36
South Atlantic	11,685 (60.2)	8,515 (51.6)	6,934 (56.6)	–
West South Central	2,024 (10.4)	2,144 (13.0)	1,472 (12.0)	–
East North Central	1,648 (8.5)	1,393 (8.4)	1,309 (10.7)	–
Pacific	1,613 (8.3)	1,152 (7.0)	1,323 (10.8)	–
Mountain	1,000 (5.2)	2,048 (12.4)	446 (3.6)	–
East South Central	696 (3.6)	708 (4.3)	151 (1.2)	–
Mid-Atlantic	514 (2.6)	255 (1.5)	427 (3.5)	–
West North Central	82 (0.4)	268 (1.6)	30 (0.2)	–
New England	20 (0.1)	9 (0.1)	134 (1.1)	–
Not available	115 (0.6)	17 (0.1)	15 (0.1)	–
Cases of COVID-19 per capita§				0.18
Lowest tertile	5,625 (29.0)	5,196 (31.5)	3,062 (25.0)	–
Middle tertile	6,601 (34.0)	6,866 (41.6)	4,912 (40.1)	–
Highest tertile	6,964 (35.9)	4,319 (26.2)	4,107 (33.6)	–

* Values are the number (%) unless indicated otherwise. AS = ankylosing spondylitis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SMD = standardized mean difference (differences >0.10 are considered potentially clinically relevant); SpA = spondyloarthritis.
† May also include telehealth visits.
‡ Other category not shown, includes Asian, Native American, and missing race.
§ County-level data linked to the patient through 5-digit zip code; as of May 1, 2020.

Table 2. Factors associated with canceling visits and use of telehealth (versus in-person visits) during the 6-week COVID-19 transition period*

Factor	Canceled all visits versus having in-person or telehealth care (n = 50,988 visits)	Telehealth versus in-person care (n = 28,785 visits)
Age, 5-year interval	1.09 (1.09–1.10)†	0.97 (0.96–0.98)†
Male	0.91 (0.87–0.96)†	0.79 (0.74–0.83)†
Black (versus White)	1.17 (1.10–1.24)†	0.98 (0.90–1.06)
Hispanic ethnicity	1.16 (1.10–1.23)†	1.18 (1.10–1.28)†
Area Deprivation Index (reference to quintile 1, most affluent)		
Quintile 2	1.08 (1.01–1.14)†	0.83 (0.77–0.90)†
Quintile 3	1.09 (1.02–1.16)†	0.74 (0.68–0.80)†
Quintile 4	1.10 (1.03–1.18)†	0.65 (0.60–0.70)†
Quintile 5 (least affluent)	1.12 (1.04–1.20)†	0.66 (0.60–0.72)†
Driving distance from patient's residence to rheumatologist office, per 30-km increment	0.96 (0.93–0.98)†	1.03 (1.01–1.06)†
Rural	1.27 (1.19–1.37)†	0.78 (0.70–0.80)†
Primary diagnosis (reference to RA)‡		
PsA/AS/SpA	0.99 (0.92–1.06)	1.03 (0.89–1.20)
Systemic lupus erythematosus	0.96 (0.89–1.04)	1.03 (0.89–1.19)
Gout	1.39 (1.23–1.57)†	0.88 (0.72–1.07)
Osteoarthritis	1.18 (1.11–1.26)†	0.94 (0.82–1.08)
Osteoporosis	1.32 (1.21–1.43)†	0.83 (0.69–1.08)

* Values are the odds ratio (95% confidence interval). AS = ankylosing spondylitis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SpA = spondyloarthritis.
† Statistically significant.
‡ County-level data linked to the patient through 5-digit zip code.

After multivariable adjustment, the factors independently associated with canceling all return visits in the COVID-19 transition period (Table 2, left column) included older age, female sex, Black race, Hispanic ethnicity, lower socioeconomic status, and rural residence. Compared to patients with RA, patients with gout, osteoarthritis, and osteoporosis were more likely to cancel all visits and not reschedule them. Most but not all these same factors were associated with lesser use of telehealth compared to having an in-person visit (Table 2, right column, Figure 3). Factors associated with a lower likelihood to have a telehealth visit included older age, male sex, lower socioeconomic status, and rural residence. Greater driving distance from the rheumatologists' office was associated with a greater likelihood to have a telehealth visit.

The proportion of all visits delivered via telehealth was highly variable across different rheumatology practices (Figure 4). In some offices, telehealth comprised almost 100% of visits during the COVID-19 transition period (i.e., the highest points on the

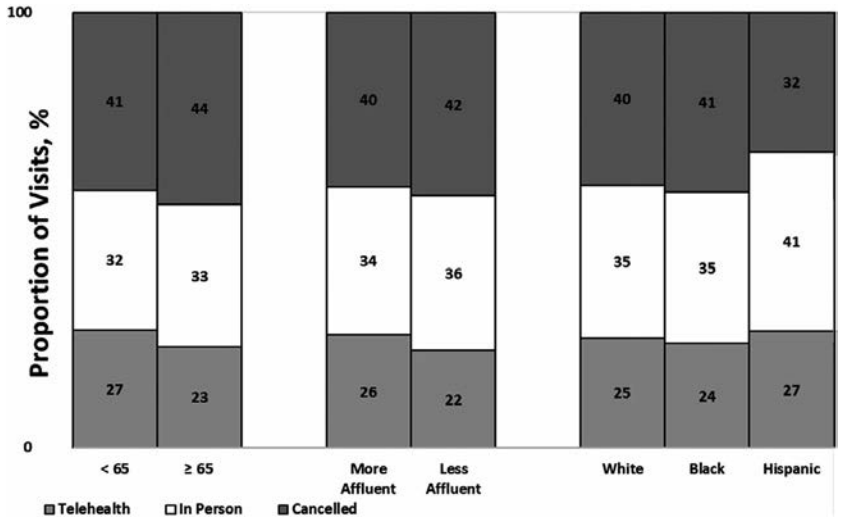

Figure 3. Proportion of telehealth, in-person, and canceled visits by age, Area Deprivation Index score, and race/ethnicity. More affluence is represented by an Area Deprivation Index score ≤80 (i.e., upper 4 quartiles); less affluence is represented by an Area Deprivation Index score >80 (i.e., lowest quartile).

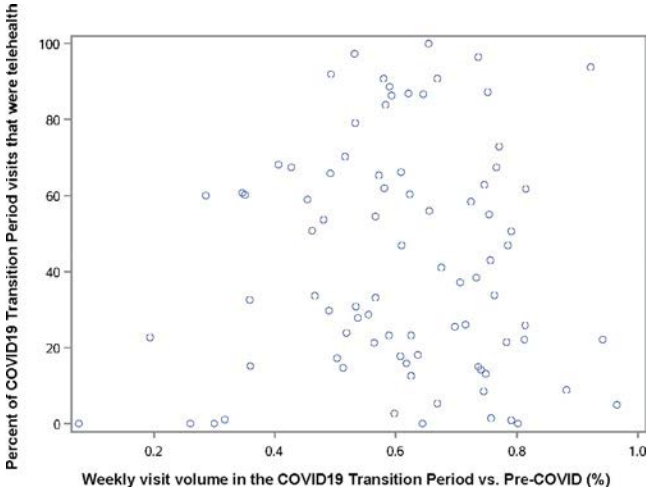

Figure 4. Practice-level variability in the proportion of visits conducted as telehealth visits (rather than in-person follow-up visits) in the COVID-19 transition period (y axis), plotted against the ratio of visit volume in the COVID-19 transition period divided by the pre–COVID-19 period (x axis) (n = 12,241). Every data point represents a unique American Arthritis and Rheumatology Associates rheumatology office (n = 89 offices). Three offices with ratios >1 were omitted for visual consistency. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24626/abstract.

y axis), whereas at other offices, there was no telehealth use. There was no association between the use of telehealth and the reduction in visit volume in the COVID-19 transition period compared to pre–COVID-19 levels (Figure 4, x axis). Likewise, there was no association between use of telehealth and practice size (not shown). After multivariable adjustment for demographics, social determinants of health, and primary rheumatologic diagnosis, patients receiving care at offices with greater telehealth use were 4.32-fold more likely to receive telehealth than at offices with lesser use of telehealth services (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24626/abstract). This practice-level effect was larger in magnitude than all other demographic and social determinants of health-related factors that we studied, although most of these remained significant. Practice site likewise was associated with a greater likelihood that patients canceled visits (adjusted odds ratio [OR] 1.54 [95% confidence interval (95% CI) 1.18–2.02]).

Among people who had both a CDAI score in the pre–COVID-19 and post–COVID-19 transition period (n = 2,741, baseline mean CDAI score = 13.8), the mean within-person change in the CDAI score was <1 unit, reflecting no meaningful change. Related to medication initiation in the COVID-19 transition period, and after controlling for practice-level clustering, the odds of starting a new biologic or JAK inhibitor therapy for an RA patient was substantially lower (adjusted OR 0.55 [95% CI 0.50–0.61]) compared to the corresponding 6-week period of time in 2019.

DISCUSSION

In this analysis of telehealth use in a large, multistate, US community practice–based rheumatology network, we found that telehealth care was essentially nonexistent in the pre–COVID-19 era, grew rapidly to comprise almost half of all follow-up clinic visits as the COVID-19 pandemic evolved, and later stabilized to comprise approximately one-fourth of all follow-up visits. Telehealth appeared to be a substitute for in-person visits, and one of the drivers of more visit cancellations was lower use of telehealth. Of major concern, several important social determinants of health (older age, lower socioeconomic status, and rural residence) were associated with a lower likelihood of having telehealth visits and a greater likelihood of canceling all visits. Further driving distance from the rheumatology office was associated with greater telehealth use, presumably related to the convenience of telehealth for patients with longer driving distances. In this context, the reduced use of telehealth among patients from rural areas is particularly striking and highlights the complex social and socioeconomic factors contributing to inequities among patients in rural areas.

We also identified other factors associated with telehealth use. Patients with certain autoimmune rheumatic diseases (e.g., RA, psoriatic arthritis, systemic lupus erythematosus) were less likely to cancel visits during the COVID-19 transition period compared to patients with gout, osteoarthritis, and osteoporosis, perhaps reflecting the need for close follow-up or medication monitoring among patients with autoimmune conditions. Individual office practice in delivering telehealth also had a large effect on whether patients received these services, suggesting that some rheumatology practices were able to convert and adapt their practices to deliver care via telehealth, while others made minimal use of it. While reasons for this high practice-level variability are unclear, the ratio of office staff to patients, access to telehealth technology within each provider's office and comfort with its use, and the case mix of individual physician practices may all be influential.

Prior to COVID-19, the use of telehealth in rheumatology received limited attention and use was largely confined to highly selected settings such as the Alaska Tribal Health system (1). Since the pandemic began, however, the use of telehealth has emerged as a tool to help mitigate disruptions in health care, with a variety of applications across health care (3,22,23). Several reports have described the impact of the COVID-19 pandemic on patient behaviors and health care delivery. For example, surveys of patients with autoimmune RMDs have shown that approximately 10–15% stopped their rheumatology treatments during the pandemic, usually without the recommendation or knowledge of their rheumatology provider (4,24). At the height of the COVID-19 transition period, the proportion of patients skipping office visits and/or required laboratory monitoring tests was as high as 50% (24). Patients with noninflammatory

RMDs have also been affected by the pandemic, and appear to have similar levels of concern regarding COVID-19 as those with inflammatory and autoimmune RMDs (4). While telehealth has been an important tool in reducing health care disruptions during the pandemic, as shown in our study, it also is likely to serve an important purpose in health care delivery in the future.

How to best deliver telehealth care in outpatient rheumatology practices moving forward remains unclear. Several important features may facilitate best practices. Telehealth care pathways can be used to identify the most appropriate patients to receive telehealth instead of in-office care, identifying which diagnoses and visit reasons are most suitable for telehealth care, which patients are most comfortable and satisfied with telehealth, and screening for access to technology needed to deliver telehealth (25). New provider and patient education may be needed, teaching how to conduct a rheumatology examination over a live video feed and how to best instruct and assist patients in conducting their own standardized self-examination (e.g., a patient joint count for those with RA) (26). Collecting disease-specific and disease-agnostic electronic patient-reported outcomes using a digital platform via a smartphone app and/or passive monitoring (e.g., health tracker device such as a Fitbit or Apple watch) may also be useful complements to delivering high-quality remote patient care (12,27).

The results of this study highlight the importance of ensuring that telehealth does not exacerbate existing disparities in health care access. Recognizing that social determinants of health are associated with visit cancellations, practices should have processes to identify and contact patients with missed or canceled visits. Interventions to improve access to and/or assistance in using telehealth technology is particularly important for vulnerable populations. Additionally, incorporating patient preferences for telehealth versus office visits and providing alternatives for patients who are uncomfortable with standard telehealth visits will be important. Identifying barriers to effective telehealth use and strategies to overcome these barriers is a significant area of need.

Results from this analysis must be contextualized considering its setting. This study reflects the experience of rheumatology providers in this high-volume, community practice–based network of ~300 community rheumatology providers distributed among 92 offices. While diverse, these clinicians' practice characteristics and patterns may not generalize to other community settings, nor to academic medical centers, although our findings appear similar to early reports from smaller rheumatology provider networks (28). Measures of social determinants of health were inferred based on patients' residence using their 9-digit zip code, which maps to census block group. This approach is commonly used in health services research, because this information is often not available directly from patients. The potential biases inherent to collecting socioeconomic status data from individual patients, including the expected nonresponse bias, likely offsets this limitation.

Finally, as a nuance of the single-vendor EHR system used by these clinicians, the scheduling system allows a visit to be rescheduled by changing the date, but this change will not be recognized as a canceled visit. Thus, the actual cancellation rates may be higher than shown in Figure 2, although efforts are underway to remedy this limitation in the future. Finally, we note that telehealth services may be associated with greater (or worse) satisfaction according to patients and providers (11) and may or may not achieve comparable outcomes as in-person visits (29). These topics were out of scope for this analysis but will be fruitful as future directions.

In conclusion, we observed large disruptions in care during the COVID-19 pandemic, partially offset by telehealth use, with evidence that telehealth continues to be an important part of care delivery. Telehealth and other technology-focused tools facilitating remote patient care and monitoring may be valuable to optimize outcomes, but these approaches need to be made more accessible, irrespective of the important social determinants of health that impact access to technology-enabled care. The substantial disparities we found in access to care for rheumatology patients during the pandemic based on age, socioeconomic status, and rural residence should be a call to action for rheumatology providers. Vulnerable populations should be prioritized, with specific strategies developed to reduce disparities in access to rheumatology care and maximize health and quality of life for these patients.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Curtis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Danila, Nowell, Saag, Curtis.
Acquisition of data. Watrous, Reddy, Alper.
Analysis and interpretation of data. George, Danila, Xie, Kallich, Clinton, Saag, Curtis.

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Association of Medication Access Difficulty and COVID-19–Related Distress With Disease Flares in Rheumatology Patients During the COVID-19 Pandemic

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Objective. Due to concerns of infection and medication disruptions during the COVID-19 pandemic, rheumatology patients at the pandemic epicenter were at risk of distress and poor health outcomes. We sought to investigate medication disruptions and COVID-19–related distress in the Bronx, New York shortly after the peak of the pandemic and determine whether factors related to the pandemic were associated with flares, disease activity, and overall health.

Methods. In the month following the epidemic peak, we surveyed adult patients and parents of pediatric patients from rheumatology clinics in the Bronx regarding medication access, medication interruptions, COVID-19 infection, COVID-19 hospitalization, and COVID-19–related distress. We examined which factors were associated with patient-reported flares, disease activity, and overall health scores in regression models accounting for sociodemographic characteristics and rheumatologic disease type.

Results. Of the 1,692 patients and parents of pediatric patients that were contacted, 361 (21%) responded; 16% reported medication access difficulty, 14% reported medication interruptions, and 41% reported experiencing flare(s). In a multivariable logistic regression model, medication access difficulty was associated with increased odds of flare (odds ratio [OR] 4.0 [95% confidence interval (95% CI) 1.5, 10.4]; $P = 0.005$), as was high COVID-19–related distress (OR 2.4 [95% CI 1.2, 4.6]; $P = 0.01$). In multivariable linear regression models, medication access difficulty and high COVID-19–related distress were associated with worse disease activity scores, and high COVID-19–related distress was associated with worse health scores.

Conclusion. Medication access difficulties and flares were common among rheumatology patients from the Bronx, New York in the month following the peak of the epidemic. Medication access difficulty and COVID-19–related distress were highly associated with flare and disease activity. COVID-19–related distress was associated with overall health scores.

INTRODUCTION

As of October 2020, ~8 million cases of COVID-19 and >218,000 related deaths have been reported in the US (1). The first major peak in the pandemic in the US occurred in New York City in the middle of April 2020 (2). Early in the pandemic, the Centers for Disease Control and Prevention widely publicized guidance that immunocompromised individuals were at higher risk for COVID-19 (3). In addition to the stress of being high risk for infection, people with rheumatologic conditions have been subjected to the stress of medication shortages while medications used to treat rheumatologic diseases, such as hydroxychloroquine, were being used for treating COVID-19 (4,5). A recent national survey showed that the COVID-19 pandemic led to disruption in medication therapy and care, as well as increased anxiety among rheumatology patients (6). Some individuals may

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SIGNIFICANCE & INNOVATIONS

- We characterized medication access difficulty, medication interruptions, and flares among minority and low-income rheumatology patients from the epicenter of the COVID-19 pandemic in the month following the epidemic peak; 22% of patients experienced either medication access difficulty or medication interruptions, and 41% experienced flares.
- Medication access difficulty and COVID-19–related distress were highly associated with patient-reported flares and disease activity, and COVID-19–related distress was highly associated with worse patient-reported health scores.
- The findings of this survey underscore the importance of advocating for and providing medication access resources to rheumatology patients.
- Future longitudinal studies of rheumatology patients during the pandemic should investigate the impact of the pandemic on physical and mental health.

be especially vulnerable to the challenges brought upon by the pandemic, including those with low income and those from racial and ethnic minorities (7).

The Bronx, which has the highest density of cases per capita in New York City, has been the borough most affected by COVID-19, with >45,000 cases by June 2020 (8). Demographically, the Bronx is >35% Black and 56% Hispanic/Latinx (9), which are populations that have been disproportionately affected by COVID-19 in New York City (10). The Bronx includes the poorest congressional district in the US and has consistently scored lowest on every health indicator among all 62 counties in New York (11).

Data are lacking on those most vulnerable to the impact of the pandemic on resources, stress, and health. To this end, we surveyed rheumatology patients who were seen at Montefiore Medical Center in the Bronx in the month following the COVID-19 epidemic peak in New York City. Our goals were to identify challenges related to medication disruptions during the pandemic and to determine whether factors related to the pandemic were associated with flares, disease activity, and overall health. Specifically, these factors included medication access difficulty, medication interruptions, COVID-19 infection, and COVID-19–related distress.

PATIENTS AND METHODS

Population. The population that was surveyed comprised rheumatology patients who were treated at Montefiore Medical Center rheumatology clinics. Montefiore Medical Center is the largest medical center within the Bronx, providing care to >2 million people, and is associated with Albert Einstein College of Medicine. Potential participants were identified through Clinical Looking Glass, which is a web-based application developed at Montefiore Medical Center to enable clinician researchers to extract information from the electronic medical record (EMR) (12). Participants were identified based on: 1) the presence of 2 International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, billing diagnosis codes related to rheumatologic diseases (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24531/abstract); 2) 2 visits within 6 months of each other to an adult or pediatric rheumatology clinic at Montefiore Medical Center between March 1, 2018 and March 1, 2020 (beginning 2 years prior to the onset of the COVID-19 epidemic in New York); and 3) a prescription for an immunomodulator (see Supplementary Appendix B, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24531/abstract) within 180 days of the most recent rheumatology visit. This search strategy was based upon validated algorithms to identify patients with rheumatoid arthritis (RA) from administrative data (13). Patients were additionally identified from the Einstein Lupus Cohort Registry, a large cohort of >500 patients with systemic lupus erythematosus (SLE), as well as registries of dermatomyositis and polymyositis patients seen at Montefiore Medical Center clinics. To be eligible for the study, patients had to be ≥18 years of age to respond for themselves; parents of patients ages <18 years were also eligible for the study.

Recruitment. Potential participants were contacted by email, or by phone if no email was included in their EMR. Phone recruitment was conducted by 8 members of the research staff, including 3 native Spanish speakers who called patients with Spanish language preference in their EMR. The recruitment was guided by a script, and those individuals who were interested in participating could either provide an email address for a web link to the consent form and survey or could give consent and take the survey over the phone. Data were collected and managed using Research Electronic Data Capture (REDCap) (14,15). The study was approved by the Institutional Review Board of Albert Einstein College of Medicine (IRB 2020-11330), and all participants consented to be in the study.

The survey was reviewed by a patient and parent from the Rheumatology Patient Advisory Group for content and language. Surveys were conducted between May 8, 2020 and June 1, 2020 in English and Spanish. Surveys took 10–15 minutes to complete online and 20–30 minutes by phone. Surveys included mental health and physical health questionnaires not included in this baseline analysis.

Study variables. *Demographic information and clinical factors.* Race/ethnicity was determined from patient-reported categorization in the EMR. Socioeconomic status (SES) was characterized by an SES index, a census-derived combined Z score reflecting the deviation of a patient's neighborhood SES from the mean of the New York state population (16). For the analyses, rheumatologic disease type was classified as SLE, RA, or other.

Patient-reported data were assessed over the prior 30 days, including COVID-19 symptoms, diagnoses, and care; prescription medication access and/or interruptions, and disruption; and COVID-19–related distress.

COVID-19 symptoms, diagnoses, and care. Participants were asked if they experienced any symptoms not related to their rheumatologic disease (fever, cough, sore throat, diarrhea, muscle aches, headache, fatigue, difficulty smelling/tasting, redness/swelling in toes and/or fingers, or any new rash). We asked if participants were tested for COVID-19, the results of the test (positive, negative, unknown), emergency room or urgent care visits for COVID-19, hospitalizations, and whether they required ventilatory support (in those who reported hospitalization).

Prescription medication access and/or interruptions, and disruption. If participants indicated that they experienced access difficulties and/or interruptions, they were asked to select from a list of reasons (for survey details, see Supplementary Appendix C, available on the *Arthritis & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/art.24531/abstract). If participants indicated that there were medication shortages or interruptions in their medication therapy, they were asked to select those medications from a list, including hydroxychloroquine, chloroquine, interleukin-6 (IL-6) inhibitors, IL-1 inhibitors, JAK inhibitors, or other. These medications were queried because they were being used or considered for the treatment of COVID-19 at the time of survey development. We also included medications suggested in public discussions to be harmful in individuals with COVID-19 (steroids and nonsteroidal antiinflammatory drugs [NSAIDs]). Medication disruption was defined as either medication access difficulty or medication interruption.

COVID-19–related distress. Adult participants were asked to rate their distress related to COVID-19 on a scale of 0–10. Parent participants were asked to rate the distress of their children from 1–10. Child distress questions were part of a questionnaire used in the COVID-19 Exposure and Family Impact Survey (Center for Pediatric Traumatic Stress, 2020; https://www.nlm.nih.gov/dr2/CEFIS_COVID_questionnaire_English_42220_final.pdf). To standardize results on COVID-19–related distress, we used a dichotomized variable for a patient with reported distress (child or adult) based on whether they had scores in the top quartile for either the pediatric or adult patient group. A free-text question was asked in order to collect qualitative data on the impact of the pandemic: "Is there another way that the coronavirus pandemic has affected your ability to care for your (or your child's) rheumatologic or autoimmune condition?" All responses were tabulated and read in their original language (Spanish or English) and were examined for repeating themes; illustrative quotations for each theme were selected by two authors (DM and TBR).

Outcomes. Respondents were asked whether they had a flare in their rheumatologic condition and the level of the intensity (mild, moderate, severe). We assessed disease activity and overall health with a 0–10 scale (0 = least active/most well and 10 = most active/least well).

Statistical analysis. Statistical analysis was performed using Stata, version 14. To assess participation bias in our study sample, we examined differences in sociodemographic and patient characteristics between patients who did and did not respond to the survey. We used Pearson's chi-square test for categorical variables and the Mann-Whitney U test to compare continuous nonparametric variables. Multivariable linear regression models were built to determine which COVID-19–related exposures were independently associated with scores for disease activity and for overall health. Multivariable logistic regression models were used to determine which COVID-19–related exposures were associated with flares. Multivariable models included respondents with complete data. Sociodemographic covariates (age, sex, race/ethnicity, and SES) and disease category (SLE, RA/juvenile idiopathic arthritis [JIA], or other) were included in all multivariable models. COVID-19–related exposure covariates were included if they met a P value of less than or equal to 0.2 threshold in univariable regression models. Variables were tested for collinearity with the Spearman's rank test. We performed a subgroup analysis of pediatric patients. Due to the small sample size, we did not conduct regression analyses of the pediatric subgroup.

There were 15%, 16%, and 23% missing values on scales of overall health, disease activity, and distress scores, respectively, among respondents who completed those questionnaires. Because the REDCap visual analog scale by default had the marker set at 5, we performed sensitivity analyses, where we assigned 5 for these missing values.

RESULTS

Survey response and participant demographics. Of 1,692 identified patients, 1,129 (67%) were sent an email invitation and 563 (33%) were contacted exclusively by phone. We received responses from 361 study participants, of whom 245 (68%) responded via email link. Response rates were higher among women (23%) versus men (15%) (P = 0.001). Response rates were the highest among Hispanic patients (26%) and the lowest among Black non-Hispanic patients (16%). Response rates were higher in Spanish (31%) versus English speakers (21%) (P = 0.001), and in patients with SLE (25%) versus those with RA/JIA (19%) or another disease (17%) (P = 0.002). Age, SES, and the proportion of parents of pediatric patients versus adult patients were similar in the respondent and nonrespondent groups.

Demographic and clinical characteristics of participants are shown in Table 1. Most participants (307 [85%]) were adult

Table 1. Demographic and clinical characteristics of Montefiore Medical Center survey participants (n = 361)*

Characteristic	Value
Respondents	
Patients (ages ≥18 years old)	307 (85)
Parents (for patients ages <18 years old)	54 (15)
Sex	
Female	317 (88)
Male	44 (12)
Age, median (IQR) years	42 (23–58)
Race/ethnicity	
Black, non-Hispanic	93 (26)
Hispanic	175 (49)
White	22 (6)
Other	33 (9)
Unknown/declined	38 (11)
Language	
English	297 (82)
Spanish	64 (18)
Primary rheumatic disease	
Systemic lupus erythematosus	230 (64)
Rheumatoid arthritis/JIA	70 (19)
Dermatomyositis/polymyositis	35 (10)
Sarcoidosis	5 (1)
Other	16 (4)
Rheumatic disease activity	
Flare in the past month†	147 (41)
Mild	51 (14)
Moderate	61 (17)
Severe	34 (10)
Disease activity score (VAS 0–10 cm), median (IQR)‡	3.5 (0.5–6.5)
Overall health score (VAS 0–10 cm), median (IQR)§	3.5 (0.6–6.2)
COVID-19 reported symptom	
≥1 COVID-19 symptom	115 (32)
≥3 COVID-19 symptoms	43 (5)
COVID-19–related care	
Total reported testing	70 (19)
Positive test result	21 (6)
COVID-19 urgent care/ER visits	14 (4)
COVID-19 hospitalizations	7 (2)
COVID-19 required mechanical ventilator	2 (0.6)

* Values are the number (%) unless indicated otherwise. ER = emergency room; IQR = interquartile range; JIA = juvenile idiopathic arthritis; VAS = visual analog scale.
† Data missing for 4 participants.
‡ Data missing for 87 participants.
§ Data missing for 90 participants.

patients, and 54 (15%) were parents responding for pediatric patients. The majority of respondents were female (317 [88%]); 175 (48%) were Hispanic, 93 (26%) were non-Hispanic Black, and 33 (9%) were other races. A total of 230 participants (64%) had SLE. More than 90% of the survey respondents were from the Bronx (Figure 1).

COVID-19 symptoms, testing, and care. Of the 361 survey respondents, 21 (6%) tested positive for COVID-19 (including 2 pediatric patients). A total of 14 of those who tested positive were seen in an emergency room or urgent care center for COVID-19 (1 pediatric patient), 7 were hospitalized (none were pediatric), and 2 required ventilatory support.

Of the 115 survey respondents who reported ≥1 COVID-19 symptom that they thought was unrelated to their rheumatologic condition, 37 were tested (16 were positive for COVID-19). Among the 43 patients who reported ≥3 symptoms, 16 were tested (10 were positive for COVID-19). The most common symptoms were fatigue and muscle aches; both were found in 15% of respondents. Of the 246 survey respondents who did not report any symptoms, 33 were tested (5 were positive for COVID-19, and 4 were unknown).

Medication access difficulty. A total of 56 survey respondents (16%) reported medication access difficulty. Among these respondents who reported difficulties, 27 (48%) had difficulty due to shortages, 15 (27%) had difficulty reaching a prescriber, 9 (16%) had difficulty physically getting to a pharmacy, 6 (11%) had difficulty paying for medication, 5 (9%) had a loss of insurance, and 10 (18%) reported "other" reasons. In free-text responses describing other reasons for access difficulty, 3 respondents mentioned difficulties obtaining the medication from pharmacies (2 because of long lines and 1 because a prior authorization was needed).

Medication interruptions. Forty-nine respondents (14%) reported medication interruptions. Among these respondents, 13 (26%) reported interruptions of <1 week in duration, 11 (22%) reported 1–2 weeks, 8 (16%) 2–4 weeks, and 17 (34%) ≥4 weeks. The 49 respondents who reported medication interruptions selected the following reasons: medication shortages (18 [36%]), difficulty reaching a prescriber (10 [20%]), difficulty physically getting to a pharmacy (9 [18%]), feeling unsafe about the medication (5 [10%]), loss of insurance (5 [10%]), not making medications a priority (3 [6%]), difficulty paying for the medication (3 [6%]), and unable to obtain an infusion (3 [10%]).

A total of 78 respondents (22%) reported a medication disruption, among whom 56 had access difficulty, 50 had a medication interruption, and 28 had both. Medication shortage was the most frequently reported reason for medication disruption, affecting 30 respondents (8%). The most frequent medication that was disrupted was hydroxychloroquine; 23 of 26 respondents who reported hydroxychloroquine disruptions had SLE. Medication interruptions were associated with medication access difficulty; 59% of respondents who reported medication interruptions experienced medication access difficulty, compared to 9% of those who did not have medication interruptions ($P < 0.001$ by chi-square test). Overall medication disruptions, difficulty obtaining medication, and interruptions in medications were not associated with race/ethnicity or SES.

COVID-19–related distress. For adult participants, the median level of COVID-19–related distress was 6 (interquartile range [IQR] 3–8) on a 0–10 scale. For child COVID-19–related distress reported by parents, the median level was 5 (IQR 3–7) on a

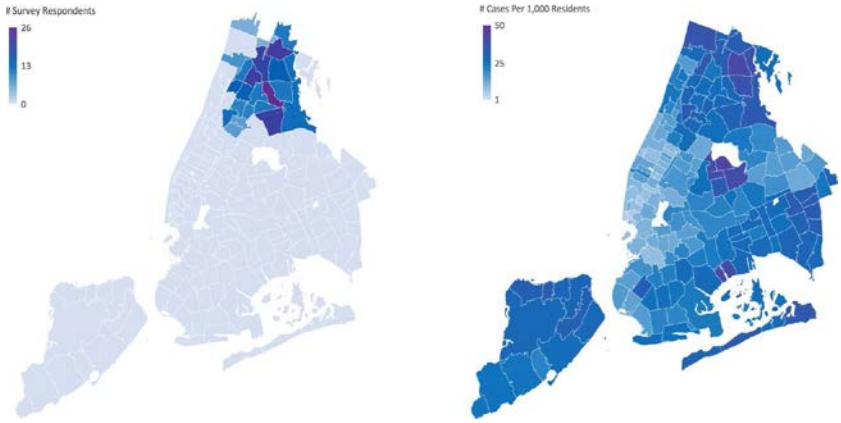

Figure 1. Geographic distribution of COVID-19 survey respondents showing area of highest density of responses (left) versus geographic distribution of confirmed positive COVID-19 case rates as of May 30, 2020 (right) in New York City. Survey responses were collected between May 8, 2020 and June 1, 2020. To protect the privacy of survey respondents, all zip codes with <5 responses were not shaded in the figure.

1–10 scale. Based on top quartiles, high COVID-19–related distress scores were defined as ≥8 for adults and as ≥7 for children. High COVID-19–related distress was not associated with either access difficulty or medication interruptions.

Factors associated with disease flare. In univariable analyses, flare was associated with female sex, high COVID-19–related distress, medication access difficulty, and medication interruption. In the multivariable analysis, flare was associated with female sex, lower SES, high COVID-19–related distress, and medication access difficulty (Table 2). The strongest association was seen with medication difficulty; participants who reported medication access difficulty were 4 times as likely to report flares than those without difficulty.

In a subgroup analysis of parents of pediatric patients, flares were associated with medication access difficulty. All 3 of the respondents who reported access difficulty for their children reported flares versus 22% in those who did not report access difficulty (P = 0.02). Flares significantly correlated to COVID-19–related distress scores in children (Spearman's ρ = 0.3, P = 0.02).

Factors associated with disease activity scores. In univariable analyses, worse disease activity was associated with increasing age, high COVID-19–related distress, medication access difficulty, and medication interruption (Table 3). In the multivariable model, disease activity was associated with increasing age, female sex, having RA/JIA versus SLE, high COVID-19–related distress, and medication access difficulty. The strongest

Table 2. Demographic, clinical, and COVID-19–related factors associated with flare*

	Univariable model			Multivariable model		
	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.0	1.0, 1.0	0.3	1.0	1.0, 1.0	0.1
Sex (male vs. female)	0.23	0.10, 0.54	0.001	0.15	0.042, 0.55	0.004
Race/ethnicity						
Hispanic vs. Black	1.6	0.95, 2.7	0.08	1.4	0.68, 2.8	0.3
White vs. Black	1.1	0.41, 2.9	0.9	2.2	0.59, 8.2	0.2
Other vs. Black	1.4	0.62, 3.2	0.4	1.6	0.57, 4.5	0.4
Unknown vs. Black	1.2	0.55, 2.7	0.6	0.78	0.26, 2.4	0.7
SES	1.0	0.9, 1.0	0.3	0.89	0.80, 1.0	0.05
Rheumatologic disease						
RA vs. SLE	0.79	0.45, 1.4	0.4	0.89	0.39, 2.0	0.8
Other vs. SLE	1.1	0.62, 2.0	0.6	1.4	0.59, 3.1	0.5
COVID-19 positive	2.2	0.89, 5.6	0.1	–	–	–
COVID-19 hospitalized	3.7	0.70, 19	0.1	2.3	0.21, 27	0.5
High COVID-19–related distress†	2.4	1.4, 4.2	0.002	2.4	1.2, 4.6	0.01
Medication access difficulty‡	4.2	2.2, 7.9	<0.001	4.0	1.5, 10.4	0.005
Medication interruption§	2.3	1.3, 4.3	0.007	1.1	0.39, 2.9	0.9

* Among 357 respondents for whom complete flare data were available. 95% CI = 95% confidence interval; OR = odds ratio; RA = rheumatoid arthritis; SES = socioeconomic status; SLE = systemic lupus erythematosus.
† Defined as scoring in the upper quartile of the COVID-19–related distress question.
‡ Defined as difficulty obtaining a prescribed medication.
§ Defined as an interruption in prescribed medication therapy.

Table 3. Demographic, clinical, and COVID-19–related factors associated with disease activity scores*

	Univariable model			Multivariable model		
	β	95% CI	*P*	β	95% CI	*P*
Age	0.027	0.0097, 0.045	0.003	0.023	0.0029, 0.043	0.03
Sex (male vs. female)	−0.65	−1.8, 0.50	0.3	−1.6	−3.0, −0.25	0.02
Race/ethnicity						
Hispanic vs. Black	0.86	−0.030, 1.8	0.06	0.48	−0.50, 1.5	0.3
White vs. Black	−0.72	−2.4, 0.99	0.4	−0.53	−2.4, 1.4	0.6
Other vs. Black	0.71	−0.67, 2.1	0.3	0.28	−1.2, 1.8	0.7
Unknown vs. Black	−0.24	−1.5, 1.0	0.7	−0.84	−2.3, 0.63	0.3
SES	−0.11	−0.25, 0.036	0.1	−0.075	−0.23, 0.083	0.4
Rheumatologic disease						
RA vs. SLE	0.55	−0.42, 1.5	0.3	1.2	0.13, 2.4	0.03
Other vs. SLE	−0.065	−1.1, 0.93	0.9	0.56	−0.61, 1.7	0.4
COVID-19 positive	0.93	−0.64, 2.5	0.2	–	–	–
COVID-19 hospitalized	2.1	−0.69, 4.8	0.1	1.2	−1.7, 4.2	0.4
High COVID-19–related distress†	1.6	0.68, 2.5	0.001	1.2	0.24, 2.1	0.01
Medication access difficulty‡	2.3	1.3, 3.3	<0.001	1.5	0.31, 2.8	0.02
Medication interruption§	1.6	0.53, 2.7	0.004	0.85	−0.47, 2.2	0.2

* Among 271 respondents for whom complete disease activity scores were available. Disease activity scores were rated by participants on a scale of 0–10, where 0 = no activity and 10 = the most activity. 95% CI = 95% confidence interval; RA = rheumatoid arthritis; SES = socioeconomic status; SLE = systemic lupus erythematosus.
† Defined as scoring in the upper quartile of the COVID-19–related distress question.
‡ Defined as difficulty obtaining a prescribed medication.
§ Defined as an interruption in prescribed medication therapy.

association was seen with medication access difficulty, which was associated with an increase of 1.5 units on a scale from 0 to 10 of worsening disease activity scores. In the pediatric subgroup, disease activity was not significantly associated with difficulties in medication access, interruptions in medications, or COVID-19–related distress.

Factors associated with overall health scores. In univariable analyses, worse health scores were associated with increasing age, Hispanic versus non-Hispanic Black race/ethnicity, lower SES, COVID-19–positive status, having been hospitalized for COVID-19, high COVID-19–related distress, and medication difficulty (Table 4). In the multivariable model, worse health scores were associated with increasing age and high COVID-19–related distress. High COVID-19–related distress was associated with an increase of 1.8 units on a scale from 0 to 10 of worsening health scores. In the pediatric subgroup, worse health scores were significantly associated with COVID-19–related distress scores (Spearman's $\rho = 0.5$, $P = 0.001$).

Sensitivity analyses. Sensitivity analyses were performed where missing values were imputed for overall health, disease activity, and COVID-19–related distress visual analog scales. These did not yield significantly different results, except in the case of the relationship between COVID-19–related distress and disease activity. In multivariable models of disease activity, high COVID-19–related distress was no longer a significant predictor ($\beta = 0.6$ [95% CI −0.2, 1.3], $P = 0.1$).

Qualitative responses on the impact of COVID-19 on rheumatologic disease care. Themes in the qualitative responses included those of stress and anxiety over the pandemic, avoiding medical care for fear of exposure to COVID-19, and relative inactivity due to avoidance of leaving the home. Illustrative quotations are presented in Table 5.

DISCUSSION

In this survey of rheumatology patients from the Bronx in New York City in the month following the peak of the COVID-19 pandemic, we identified common challenges that these patients faced. As residents of the hardest-hit borough, our patients were truly at the epicenter of the pandemic in the spring of 2020. We found that approximately 1 in 5 respondents experienced medication disruptions and respondents reported high levels of COVID-19–related distress.

The peak of the COVID-19 pandemic in New York was associated with state shutdowns (termed "NY on PAUSE"), which began in March 2020 as ordered by Governor Andrew Cuomo, followed by additional city restrictions put into place by Mayor Bill de Blasio, which affected transportation and led to business closures (17). Pharmacies were considered essential and were allowed to remain open, but the responses from our study indicate that a proportion of patients had difficulties obtaining medications related to physical access to pharmacies, access to their medications from pharmacies, and long lines at pharmacies.

The most common barrier related to medication disruptions was medication shortages, and this was by far most frequently

Table 4. Demographic, clinical, and COVID-19–related factors associated with overall health scores*

	Univariable model			Multivariable model		
	β	95% CI	*P*	β	95% CI	*P*
Age	0.026	0.010, 0.042	0.001	0.024	0.006, 0.042	0.008
Sex (male vs. female)	−0.26	−1.3, 0.75	0.6	−0.007	−1.2, 1.2	1.0
Race/ethnicity						
Hispanic vs. Black	1.0	0.25, 1.8	0.01	0.60	−0.29, 1.5	0.2
White vs. Black	−0.63	−2.2, 0.92	0.42	−0.36	−2.1, 1.4	0.7
Other vs. Black	0.71	−0.60, 2.01	0.29	1.2	−0.20, 2.6	0.09
Unknown vs. Black	−0.26	−1.4, 0.85	0.64	−0.61	−1.9, 0.71	0.4
SES	−0.14	−0.27, 0.009	0.04	−0.092	−0.24, 0.050	0.2
Rheumatologic disease						
RA vs. SLE	−0.26	−1.1, 0.60	0.55	−0.050	−1.07, 0.97	0.9
Other vs. SLE	−0.020	−0.93, 0.89	0.97	0.28	−0.79, 1.3	0.6
COVID-19 positive	2.1	0.66, 3.5	0.004	1.3	−0.32, 2.9	0.1
COVID-19 hospitalized	3.1	0.63, 5.6	0.01	–	–	–
High COVID-19–related distress†	1.8	1.0, 2.6	<0.001	1.8	0.98, 2.7	<0.001
Medication access difficulty‡	1.2	0.22, 2.2	0.02	0.45	−0.67, 1.6	0.4
Medication interruption§	0.85	−0.15, 1.8	0.1	0.44	−0.76, 1.6	0.5

* Values represent the 275 respondents for whom complete data on health scores were available. Overall health scores were rated by participants on a scale of 0–10 (0 = very well, 10 = very poorly). 95% CI = 95% confidence interval; RA = rheumatoid arthritis; SES = socioeconomic status; SLE = systemic lupus erythematosus.
† High COVID-19–related distress was defined as scoring in the upper quartile of the COVID-19–related distress question.
‡ Medication access difficulty was defined as difficulty obtaining a prescribed medication.
§ Medication interruption was defined as an interruption in prescribed medication therapy.

reported regarding hydroxychloroquine. During the peak of COVID-19 hospitalizations in March, hydroxychloroquine was being used widely across all major New York City hospitals to treat COVID-19. Supplies of hydroxychloroquine were diverted to hospitals from community pharmacies and restrictions were placed on rheumatology patients' access to the medication, including requirements of confirmation of diagnosis and prior use, and even prior authorizations.

Table 5. Illustrative free-text answers on the impact of the COVID-19 pandemic on rheumatologic care from survey participants*

Quotations about impact
Stress and anxiety
"Stress and worry about the pandemic has caused in my opinion my flare ups…"
"I been getting really anxious…"
"I find myself getting panic attacks if I have to go outside."
"Psychological, fear of going out and knowing I have a weak immune system…" (translated from Spanish)
Avoiding medical care for fear of exposure
"Scared of visiting my doctor when I had a flare…"
"I have been forced to stay home and cry myself to sleep from morning to night from the pains due to several severe flares, instead of going to the ER."
"I am less likely to go to the doctor right now out of fear of catching COVID-19."
Avoiding outdoors/being inactive
"Limited ability to go out for light exercise and fresh air due to concerns about exposure…"
"I am more inactive daily."
"Not being able to go out and walk to strengthen my bones, because at the house it's not the same, breathing air, it has not been easy, it gives you depression and anxiety." (translated from Spanish)

* Free-text answers to the question "Is there another way that the coronavirus pandemic has affected your ability to care for your (or your child's) rheumatologic or autoimmune condition?" ER = emergency room.

Our findings are in agreement with a recent national survey of rheumatology patients during the earlier weeks of the pandemic, which also found challenges to medication access and care; 10% of patients were unable to obtain medications and 4% of patients were not able to contact their rheumatologist (6). Respondents of this national study were more likely to have higher education and to be White, and less likely to be from the Northeast US, which during the time of this study had been the hardest hit region from the COVID-19 pandemic. Thus, our study provides insight into a population with demographic characteristics that were not well-represented previously, being largely low income, minority race/ethnicity, and from a highly affected area; this population is likely more vulnerable to the impact of the pandemic. Indeed, the proportion of respondents that were affected by difficulties with medication access appears somewhat higher in our study than that reported by Michaud et al (16% versus 10%) (6). However, this difference may have been driven by the higher proportion of patients with SLE in our study, considering that the most frequently affected medication that we found was hydroxychloroquine (which is used in the majority of patients with SLE).

We found that medication access difficulty and COVID-19–related distress were highly associated with flares and disease activity scores. In particular, we found that in multivariable models accounting for other sociodemographic factors and disease

types, medication access difficulty was associated with a 4-fold increase in odds, and high COVID-19–related distress was associated with a 2-fold increase in odds of reporting flare. COVID-19–related distress was also highly associated with overall health scores. The direction of the associations or causality between COVID-19–related distress or medication access difficulty and health outcomes is not revealed in this study. While distress and challenges with medication access may have helped precipitate flares, it is possible that the association between medication access difficulty and flare was driven by patients with flares being more likely to need or seek out medications and therefore being more likely to experience medication access difficulties. Likewise, patients with flares may be more vulnerable to experiencing stress and thus be more likely to report high levels of COVID-19–related distress. Finally, these associations may not reflect causal links in either direction but may be associated with other markers of mental and physical health. Longitudinal studies in specific disease populations and examination of detailed mental and physical health data are needed to understand these relationships more completely.

Our study found that 6% of rheumatology patients who completed the survey had a COVID-19 positive test result and 2% were hospitalized. During a similar time range in the Bronx, the reported case rate is 3% and the hospitalization rate 0.8% (18). Collaborative global studies are currently underway to better define the COVID-19 disease burden in the rheumatology population (19).

Despite the fact that few pediatric patients were found to be positive for or hospitalized for COVID-19, a relationship between COVID-19–related distress was seen with flares and with overall health scores in the subgroup analysis of parents responding on behalf of pediatric patients. This may have represented parents' distress, and further studies are planned to investigate the relationship between COVID-related parental distress, child distress, and disease outcomes.

Qualitative results from the survey illustrated that patients were anxious about pursuing care and avoided care for their rheumatologic conditions because of fears of infection. These themes were like those found by Michaud et al in their survey (6). These findings, along with the high levels of COVID-19–related distress that we found in rheumatology patients in the Bronx, underscore the importance of further investigation into the impact of the pandemic on the mental health of rheumatology patients and how health behaviors and future disease outcomes may be impacted.

In addition to medication access difficulty, challenges contacting prescribers were identified as a problem for some patients and connected to medication interruptions. During the peak of the pandemic many rheumatologists were deployed to care for COVID-19 inpatients, either as hospitalists or as consultants to help manage cytokine storm and multisystem inflammatory syndrome associated with COVID-19 in children. Outreach programs to rheumatology patients and increased access with telehealth with allied health professionals may help if another wave of escalating COVID-19 cases occurs and rheumatologists are again deployed to inpatient care. Of particular concern are those patients who will be unreachable due to lack or loss of phone or internet service. Deploying mobile health teams to particularly low income and areas heavily affected may help provide access to care.

Important limitations to our study were the low response rate and the bias in respondent sample toward relatively higher SES and non-Black patients. In an effort to reach a population that has been underrepresented in other studies to date, our survey strategy utilized both phone and email; however, several patients were still unreachable and phone numbers were noted to be disconnected. Our data may underrepresent those who were the most affected by the financial repercussions of the COVID-19 pandemic.

Notably, this study only examined patient-reported outcomes. This was intentional, because of the recognized decrease in non–COVID-19–related patient encounters during the surge of the pandemic that made measuring flare and disease activity through other traditional means unreliable. Though these outcomes were obtained using questions from validated measures that correspond to physician-derived disease activity measures commonly used in rheumatology (20,21), future studies during the pandemic that investigate serologic markers of disease activity, health care utilization, and other important health outcomes are needed.

Higher rates of missing responses than expected were seen in distress, disease activity, and health measures. This may be due to the presentation of the visual analog scale through REDCap. Survey directions did not specify that respondents needed to click the marker to record a response in agreement with the default "5," corresponding to a middle level value. We recognize that granularity was lost in the crude grouping of diseases because of small numbers (SLE, RA/JIA, and other), and future studies that assess the impact in specific disease populations are warranted. Finally, in the complex relationship between distress and health outcomes, there are likely additional confounders (including the presence of psychiatric disease and other factors regarding psychosocial health) that were not accounted for in our analyses.

In conclusion, we documented a link between both medication access difficulty and COVID-19–related distress with disease control in rheumatology patients. Medication access to vulnerable patients during the pandemic should be an advocacy priority in the rheumatology community. Future longitudinal studies are needed to understand the long-term impact of challenges related to the COVID-19 pandemic on rheumatology patients living in the Bronx and will aid us in developing strategies to mitigate the adverse effects of the pandemic. Examining the long-term effects of psychological distress related to COVID-19 on disease outcomes will help us better understand the role that psychological stress may play in rheumatologic diseases in general.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Rubenstein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Hypouricemia and Mortality Risk in the US General Population

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Objective. The most recent European Alliance of Associations for Rheumatology (EULAR) recommendations for gout advise against maintaining a serum urate (SU) level of <3 mg/dl for prolonged periods of time. While several Asian cohort studies have shown higher rates of mortality in individuals with extremely low SU levels, data from non-Asian cohort studies are scarce, and the relationship between hypouricemia, cardiovascular risk, and mortality remains unclear.

Methods. Using data collected from the 1988–1994 and 1999–2008 National Health and Nutrition Examination Survey (NHANES), we examined the relationship between SU level and overall and cause-specific mortality in 41,807 adults in the US. We calculated multivariable hazard ratios (HRs) that were compared to a referent SU level of 5–6 mg/dl for SU categories <4, 4–5, 6–7, 7–8, and >8 mg/dl in men and SU categories <3, 3–4, 4–5, 6–7, and >7 mg/dl in women.

Results. A higher mortality risk was not observed in women who had an SU level of <3 mg/dl (HR 1.09 [95% confidence interval (95% CI) 0.92–1.28]). A 28% higher mortality risk was observed in men who had an SU level of <4 mg/dl (HR 1.28 [95% CI 1.13–1.45]), with a nearly three-times higher mortality risk from diabetes mellitus also noted (HR 2.89 [95% CI 1.59–5.23]), but no increase in mortality from any other specific cause.

Conclusion. We found no long-term excess mortality risk among American women with SU levels as low as <3 mg/dl, a finding which is incompatible with the notion of a causal relationship between hypouricemia and premature mortality in women. We found excess all-cause mortality and diabetes mellitus–related mortality among hypouricemic American men, which may in part be attributable to the uricosuric effect of hyperglycemia in fatal uncontrolled diabetes mellitus (analogous to reverse causality).

INTRODUCTION

The potential causal role of hyperuricemia in the risk of cardiovascular disease and premature mortality has long been a topic of clinical and research interest (1). However, the potential effects of hypouricemia on cardiovascular disease and premature mortality has also been investigated in recently published studies (2–6). Although several studies from Japan, the Republic of Korea, and Taiwan have demonstrated an association between very low serum urate (SU) levels (e.g., <3.5 mg/dl in men and <2.5 mg/dl in women) and higher all-cause and cardiovascular-related sex-specific mortality, the overall relationship between hypouricemia, cardiovascular risk, and mortality remains unclear (2–7). Furthermore, the association of hypouricemia with premature mortality in non-Asian cohorts remains poorly understood.

The potential harm of extreme hypouricemia has been speculated to originate from antioxidant properties in SU, potentially contributing to lowering the risk of neurodegenerative conditions. To that end, general population studies (not limited to gout) have shown an inverse association of SU levels with the risk of

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SIGNIFICANCE & INNOVATIONS

- Extreme hypouricemia is suspected to have harmful effects on health, although the nature of the relationship between low serum urate (SU) levels and mortality risk remains unclear.
- In large cohorts representative of the US general population, low levels of SU were shown to be associated with higher mortality in men, but not women.
- In men, presence of diabetes mellitus contributed to higher mortality with low levels of SU, which may be explained by the uricosuric effect of hyperglycemia in uncontrolled diabetes mellitus.
- These findings reduce prior concerns that extreme hypouricemia increases the risk of mortality.

Alzheimer's disease–related dementia (8–10) and Parkinson's disease (11,12). Prompted by these data, the latest European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of gout advise against maintaining an SU level of <3 mg/dl in individuals for prolonged periods (13).

To examine the evidence gap in non-Asian populations and to further clarify the potential risk associated with hypouricemia, we examined all-cause and cause-specific mortality in the US with follow-up data from multiple cycles of the 1988–1994 Third National Health and Nutrition Examination Survey (NHANES-III) and the 1999–2008 NHANES.

PATIENTS AND METHODS

Study population. The NHANES is a nationwide survey in the US that assesses the health and nutritional status of adults and children using interviews, physical examinations, and laboratory data (14,15). The survey uses a complex, multistage probability design to provide a nationally representative sample of the noninstitutionalized US civilian population (16). NHANES was conducted on a periodic basis until 1999, after which they became continuous surveys. For the present study, we analyzed data collected from the 1988–1994 NHANES-III and the 1999–2008 NHANES from human subjects ages 18 years or older who had SU levels measured at enrollment. All procedures in each NHANES were approved by the National Center for Health Statistics Ethics Review Board, and written informed consent was obtained from all subjects at time of enrollment in the NHANES (14,15).

Measurement of SU levels. SU levels were measured at the time that subjects were enrolled in the NHANES using a colorimetric method in which uric acid is oxidized to allantoin and hydrogen peroxide by uricase (Hitachi Model 737 Multichannel Analyzer, Boehringer Mannheim Diagnostics). Details in regard to quality control procedures have been previously described (15). Values are reported in mg/dl and can be converted to μmol/liter by multiplying by 59.48.

Assessment of patient outcomes. Deaths and their underlying causes were obtained from data linkage to the National Death Index until December 31, 2015, which reflects data from death certificate documentation. Death certificates document the immediate cause of death as well as the underlying cause of death, which is the initiating event in the causal sequence leading to the death (17). For example, if a patient with severe uncontrolled diabetes mellitus died from myocardial infarction, the immediate cause may be listed as myocardial infarction and the underlying cause may be listed as diabetes mellitus at the discretion of the certifying physician (17,18). Specific underlying causes of death included cardiovascular disease, malignancies, chronic lower respiratory disease, Alzheimer's disease, and diabetes mellitus. Contributory causes of death were not included in the present analysis.

Statistical analysis. Baseline covariates obtained from the NHANES included age, race (White, Black, other), education level (some high school or lower, high school, college, or graduate school or higher), body mass index (BMI), the presence of hypertension (yes/no), diabetes mellitus (defined according to the 2020 American Diabetes Association [ADA] criteria for the classification and diagnosis of diabetes [19], self-reported diabetes mellitus, or use of an antidiabetic drug), alcohol consumption (drinks per month), smoking status (current, former, or never), estimated glomerular filtration rate (GFR), serum albumin level, and total cholesterol level.

Our analysis was stratified by sex, given the higher levels of SU observed in men compared to women (20). SU levels were categorized into 6 groups among men (<4, 4–5, 5–6, 6–7, 7–8, and >8 mg/dl) and women (<3, 3–4, 4–5, 5–6, 6–7, and >7 mg/dl). More extreme categories (e.g., <3 mg/dl and 3–4 mg/dl in men and 7–8 mg/dl and >8 mg/dl in women) did not provide sufficient sample sizes for analyses. We used a common SU level reference of 5–6 mg/dl in both sexes, analogous to having the same therapeutic target for urate-lowering therapy for gout between sexes. Age was used as a time scale for survival analyses.

We calculated multivariable hazard ratios (HRs) using 3 different models with increasing adjustments for covariates. Our "age-race adjusted model" was adjusted for age, race, NHANES cycle, and competing risk (for cause-specific mortality, using a cause-specific model) (21). Our "primary multivariable model" was also adjusted for the same variables in the "age-race adjusted model" in addition to BMI, education history, smoking status, alcohol consumption, and total cholesterol. The "extended multivariable model" was adjusted for the same variables in the "age-race adjusted model" and "primary multivariable model" in addition to hypertension and estimated GFR, which remain potential causal intermediates in the relationship between SU level and all-cause

and cardiovascular/renal–related mortality. However, as diabetes mellitus–specific mortality was an outcome of interest in our study, our multivariable models did not include diabetes mellitus, an obvious causal intermediate.

We performed several sensitivity analyses to assess the robustness of our findings. First, to account for the known positive correlation between SU level and BMI, the study population was matched to subjects who had a BMI within the same range (±1 kg/m^2) (22). An analysis was also performed according to race, as classified in the NHANES (White, Black, other). To account for variable follow-up time, a sensitivity analysis was performed in which follow-up time was truncated at 10 years. Given the variation in SU level based on menopausal status in women, a subgroup analysis of postmenopausal women was performed. We did not perform analyses in premenopausal women due to a small number of women in that subgroup. Lastly, we performed an additional analysis excluding subjects with diabetes mellitus, defined by the ADA criteria (19), self-reported diagnosis, or use of an antidiabetic drug. For all measures, we calculated 95% confidence intervals (95% CIs). All *P* values were 2-sided, and a significance level was set at 0.05. All statistical analyses were performed using SAS version 9.4.

RESULTS

Baseline characteristics of study population. Among 19,954 men and 21,853 women, there were 5,714 deaths recorded in male subjects and 4,901 deaths recorded in female subjects over a mean follow-up time of 13.7 years in men and 14.6 years in women. Age-adjusted baseline characteristics of the study population are shown for men and women (Tables 1 and 2). Among men, as SU level increased, age-adjusted BMI, hypertension, alcohol use, and total cholesterol tended to increase, whereas estimated GFR and the percentage of men with diabetes mellitus tended to decrease. Among women, as SU level increased, age, levels of age-adjusted BMI, hypertension, alcohol use, and total cholesterol tended to increase, as did the percentage of women with diabetes mellitus, whereas estimated GFR tended to decrease. Serum albumin levels were generally similar across all SU levels in men and women. In men, mean hemoglobin A1c levels were highest at the lowest SU range (mean hemoglobin A1c of 6.3% at SU levels of 0–4 mg/dl), while in women, the mean hemoglobin A1c was highest at the highest SU range (mean hemoglobin A1c of 6.0% at SU levels of >7 mg/dl).

Table 1. Age-adjusted baseline characteristics of 19,954 men ages 18 years or older with serum urate measurement at enrollment in the 1988–1994 NHANES-III and 1999–2008 NHANES*

	Serum urate range, mg/dl					
Baseline characteristics	<4	4–5	5–6	6–7	7–8	>8
Number of subjects	781	3,114	6,083	5,444	2,931	1,601
Age, mean ± SD years	53.9 ± 19.9	47.9 ± 19.9	45.8 ± 20.0	46.4 ± 19.7	48.7 ± 20.0	51.9 ± 19.9
Race†						
White	341 (43.7)	1,330 (42.7)	2,737 (45.0)	2,586 (47.5)	1,413 (48.2)	728 (45.5)
Black	162 (20.7)	688 (22.1)	1,320 (21.7)	1,160 (21.3)	703 (24.0)	463 (28.9)
Other	278 (35.6)	1,096 (35.2)	2,026 (33.3)	1,698 (31.2)	815 (27.8)	410 (25.6)
Education						
Some high school/less than high school	264 (33.8)	959 (30.8)	1,703 (28.0)	1,448 (26.6)	777 (26.5)	456 (28.5)
High school	220 (28.2)	856 (27.5)	1,728 (28.4)	1,492 (27.4)	783 (26.7)	437 (27.3)
College	172 (22.0)	707 (22.7)	1,411 (23.2)	1,366 (25.1)	771 (26.3)	380 (23.7)
Graduate school or higher	125 (16.0)	592 (19.0)	1,241 (20.4)	1,138 (20.9)	600 (20.5)	328 (20.5)
BMI, mean ± SD kg/m^2	25.1 ± 0.2	25.5 ± 0.1	26.7 ± 0.1	28.1 ± 0.1	29.5 ± 0.1	30.7 ± 0.2
Hypertension	158 (20.2)	607 (19.5)	1,338 (22.0)	1,399 (25.7)	929 (31.7)	677 (42.3)
Diabetes mellitus	200 (25.6)	478 (15.4)	664 (10.9)	569 (10.4)	327 (11.2)	251 (15.7)
Alcohol use, mean ± SD times per month	3.9 ± 0.4	3.9 ± 0.1	4.4 ± 0.1	5.1 ± 0.1	5.3 ± 0.2	5.9 ± 0.3
Smoking						
Current	266 (34.1)	984 (31.6)	1,898 (31.2)	1,584 (29.1)	765 (26.1)	413 (25.8)
Former	206 (26.4)	831 (26.7)	1,691 (27.8)	1,557 (28.6)	941 (32.1)	508 (31.7)
Never	309 (39.5)	1,299 (41.7)	2,494 (41.0)	2,303 (42.3)	1,225 (41.8)	680 (42.5)
Estimated GFR, mean ± SD ml/minute	100.6 ± 1.3	96.3 ± 0.5	91.8 ± 0.4	88.6 ± 0.3	86.3 ± 0.5	80.8 ± 0.6
Albumin, mean ± SD mg/dl	4.2 ± 0.02	4.2 ± 0.01	4.3 ± 0.01	4.3 ± 0.01	4.3 ± 0.01	4.2 ± 0.02
Hemoglobin A1c, mean ± SD %	6.3 ± 2.0	5.7 ± 1.4	5.5 ± 1.0	5.5 ± 0.9	5.6 ± 0.9	5.7 ± 1.0
Total cholesterol, mean ± SD mg/dl	191.3 ± 1.9	193.5 ± 0.7	198.5 ± 0.5	202.9 ± 0.6	206.2 ± 0.8	210.5 ± 1.3

* Values are the number (%) unless indicated otherwise. BMI = body mass index; GFR = glomerular filtration rate; NHANES-III = Third National Health and Nutrition Examination Survey.
† Not adjusted for age.

Table 2. Age-adjusted baseline characteristics of 21,853 women ages 18 years or older with serum urate measurement at enrollment in the 1988–1994 NHANES-III and 1999–2008 NHANES*

Baseline characteristics	Serum urate range, mg/dl					
	<3	3–4	4–5	5–6	6–7	>7
Number of subjects	1,156	5,273	7,226	4,666	2,212	1,320
Age, mean ± SD years	39.2 ± 17.2	40.0 ± 17.8	44.5 ± 19.3	50.5 ± 19.9	55.7 ± 19.9	62.9 ± 17.3
Race†						
White	468 (40.5)	2,193 (41.6)	3,237 (44.8)	2,174 (46.6)	1,104 (49.9)	663 (50.2)
Black	442 (38.2)	1,946 (36.9)	2,385 (33.0)	1,395 (29.9)	509 (23.0)	227 (17.2)
Other	246 (21.3)	1,134 (21.5)	1,604 (22.2)	1,097 (23.5)	599 (27.1)	430 (32.6)
Education						
Some high school/less than high school	343 (29.7)	1,392 (26.4)	1,807 (25)	1,241 (26.6)	580 (26.2)	366 (27.7)
High school	327 (28.3)	1,440 (27.3)	2,153 (29.8)	1,386 (29.7)	679 (30.7)	411 (31.1)
College	251 (21.7)	1,339 (25.4)	1,828 (25.3)	1,134 (24.3)	544 (24.6)	381 (28.9)
Graduate school or higher	235 (20.3)	1,102 (20.9)	1,438 (19.9)	905 (19.4)	409 (18.5)	162 (12.3)
BMI, mean ± SD kg/m^2	24.7 ± 0.2	26.0 ± 0.1	27.7 ± 0.1	30.4 ± 0.1	33.0 ± 0.2	34.4 ± 0.4
Hypertension	195 (16.9)	1,039 (19.7)	1,770 (24.5)	1,488 (31.9)	927 (41.9)	725 (54.9)
Diabetes mellitus	143 (12.3)	606 (11.5)	769 (10.6)	583 (12.5)	364 (16.4)	279 (21.1)
Alcohol use, mean ± SD times per month	1.4 ± 0.1	1.6 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	2.4 ± 0.4
Smoking history						
Current	243 (21.0)	1,002 (19)	1,467 (20.3)	1,041 (22.3)	549 (24.8)	317 (24.0)
Former	169 (14.6)	891 (16.9)	1,279 (17.7)	854 (18.3)	438 (19.8)	269 (20.4)
Never	744 (64.4)	3,380 (64.1)	4,480 (62)	2,771 (59.4)	1,225 (55.4)	734 (55.6)
Estimated GFR, mean ± SD ml/minute	109.6 ± 1.5	98.4 ± 0.5	93.0 ± 0.4	87.9 ± 0.5	85.0 ± 0.7	76.9 ± 1.4
Albumin, mean ± SD mg/dl	4.0 ± 0.02	4.1 ± 0.0	4.1 ± 0.01	4.0 ± 0.01	4.0 ± 0.01	4.0 ± 0.02
Hemoglobin A1c, mean ± SD %	5.4 ± 1.3	5.4 ± 1.1	5.5 ± 1.0	5.6 ± 1.0	5.8 ± 1.0	6.0 ± 1.1
Total cholesterol, mean ± SD mg/dl	201.5 ± 1.2	201.7 ± 0.6	205.0 ± 0.5	208.2 ± 0.7	209.0 ± 1.0	214.8 ± 1.8

* Values are the number (%) unless indicated otherwise. BMI = body mass index; GFR = glomerular filtration rate; NHANES-III = Third National Health and Nutrition Examination Survey.
† Not adjusted for age.

Mortality rate in men. The age-race adjusted model showed a 33% higher risk of all-cause mortality in men with a low SU level (<4 mg/dl) (HR 1.33 [95% CI 1.18–1.50]) compared to men with an SU level of 5–6 mg/dl (Table 3). The HR from the primary multivariable model was attenuated slightly as compared to the age-race adjusted model but remained significant (HR 1.28 [95% CI 1.13–1.45]), and the extended multivariable model showed results similar to those observed in the age-race adjusted model (HR 1.33 [95% CI 1.17–1.51]). At a high SU level (>8 mg/dl), there was a 59% higher risk of all-cause mortality in the primary multivariable model (HR 1.59 [95% CI 1.44–1.75]) (Table 3).

For cause-specific deaths at low SU levels, only diabetes mellitus–specific mortality was elevated, with a primary multivariable HR of 2.89 (95% CI 1.59–5.23) and extended multivariable HR of 3.39 (95% CI 1.89–6.09) among men with an SU level of <4 mg/dl compared to men with an SU level of 5–6 mg/dl. In contrast, higher SU levels (>8 mg/dl) were associated with higher mortality from cardiovascular disease (primary multivariable HR 1.39 [95% CI 1.16–1.67]) and chronic lower respiratory disease (primary multivariable HR 1.70 [95% CI 1.10–2.61]) as compared to an SU level of 5–6 mg/dl. Higher SU levels were also associated with higher diabetes mellitus–specific mortality (primary multivariable HR 1.77 [95% CI 1.01–3.10]), although the association was no longer significant following further adjustment for hypertension and GFR (extended multivariable HR 1.60 [95% CI 0.87–2.95]).

Mortality rate in women. In women, lower SU levels were not associated with higher all-cause mortality risk. At an SU level of <3 mg/dl, the age-race adjusted HR was 1.13 (95% CI 0.96–1.32), and the primary multivariable HR was 1.09 (95% CI 0.92–1.28) compared to an SU level of 5–6 mg/dl (Table 4). However, higher SU levels were associated with higher risk of all-cause mortality. At SU levels of >7 mg/dl, the age-race adjusted HR was 1.60 (95% CI 1.46–1.76), and the primary multivariable HR was 1.58 (95% CI 1.43– 1.74) compared to an SU level of 5–6 mg/dl. Compared to the age-adjusted and primary multivariable HRs, the extended multivariable HR was of a slightly lower magnitude but still significant (HR 1.45 [95% CI 1.31–1.61]).

Lower SU levels were not associated with cause-specific deaths in women. However, higher SU levels were associated with a higher risk of cardiovascular deaths (primary multivariable HR 1.38 [95% CI 1.15–1.65]) (Table 4). Similarly, high levels of SU were associated with higher risk of diabetes mellitus–related mortality (primary multivariable HR 1.91 [95% CI 1.23–2.98]).

Sensitivity analysis. To finely adjust for BMI across SU levels given their close association, we conducted a sensitivity analysis that matched the study population to subjects who had a BMI within the same range (±1 kg/m^2), in which our results persisted with higher overall mortality and diabetes mellitus–related mortality

Table 3. All-cause and cause-specific mortality in 19,954 men with baseline serum urate measurement at enrollment in the 1988–1994 NHANES-III and 1999–2008 NHANES*

	Serum urate range, mg/dl					
	<4	4–5	5–6	6–7	7–8	>8
All-cause mortality						
Number of deaths	325	934	1,513	1,412	872	658
Mortality rate per 1,000 person-years	2.75 (2.46, 306)	1.83 (1.71, 1.95)	1.48 (1.41, 1.56)	1.53 (1.45, 1.61)	1.84 (1.72, 1.97)	2.75 (2.55, 2.97)
Age-race adjusted‡	1.33 (1.18, 1.50)†	1.20 (1.10, 1.30)†	1.00	1.00 (0.93, 1.08)	1.11 (1.02, 1.20)†	1.56 (1.43, 1.72)†
Multivariable§	1.28 (1.13, 1.45)†	1.15 (1.05, 1.25)†	1.00	1.03 (0.96, 1.11)	1.14 (1.05, 1.25)†	1.59 (1.44, 1.75)†
Extended multivariable¶	1.33 (1.17, 1.51)†	1.17 (1.07, 1.28)†	1.00	1.04 (0.96, 1.13)	1.13 (1.04, 1.24)†	1.52 (1.37, 1.69)†
Illness-related mortality						
Cardiovascular disease						
Number of deaths	75	257	408	377	270	194
Mortality rate per 1,000 person-years	0.63 (0.50, 0.80)	0.50 (0.44, 0.57)	0.40 (0.36, 0.44)	0.41 (0.37, 0.45)	0.57 (0.51, 0.64)	0.81 (0.70, 0.93)
Age-race adjusted‡	0.97 (0.76, 1.24)	1.12 (0.96, 1.31)	1.00	0.98 (0.86, 1.13)	1.24 (1.06, 1.44)†	1.44 (1.21, 1.72)†
Multivariable§	0.94 (0.73, 1.21)	1.08 (0.92, 1.27)	1.00	0.96 (0.84, 1.11)	1.21 (1.04, 1.42)†	1.39 (1.16, 1.67)†
Extended multivariable¶	0.97 (0.75, 1.27)	1.10 (0.93, 1.30)	1.00	0.93 (0.80, 1.08)	1.13 (0.96, 1.34)	1.22 (1.00, 1.49)
Malignancy-related						
Number of deaths	71	219	355	316	182	112
Mortality rate per 1,000 person-years	0.60 (0.47, 0.76)	0.43 (0.37, 0.49)	0.35 (0.31, 0.39)	0.34 (0.30, 0.38)	0.39 (0.33, 0.45)	0.47 (0.39, 0.56)
Age-race adjusted‡	1.12 (0.86, 1.44)	1.10 (0.93, 1.30)	1.00	0.95 (0.82, 1.10)	0.91 (0.76, 1.09)	0.85 (0.69, 1.06)
Multivariable§	1.05 (0.81, 1.37)	1.06 (0.90, 1.26)	1.00	0.97 (0.83, 1.13)	0.94 (0.78, 1.13)	0.88 (0.70, 1.09)
Extended multivariable¶	1.08 (0.82, 1.42)	1.12 (0.93, 1.34)	1.00	1.03 (0.87, 1.21)	1.04 (0.85, 1.26)	0.90 (0.71, 1.15)
Chronic lower respiratory disease						
Number of deaths	14	49	70	63	27	34
Mortality rate per 1,000 person-years	0.12 (0.06, 0.20)	0.10 (0.07, 0.13)	0.07 (0.05, 0.09)	0.07 (0.05, 0.09)	0.06 (0.04, 0.08)	0.14 (0.10, 0.20)
Age-race adjusted‡	1.09 (0.61, 1.94)	1.24 (0.86, 1.79)	1.00	0.96 (0.68, 1.35)	0.69 (0.45, 1.08)	1.42 (0.94, 2.14)
Multivariable§	0.97 (0.54, 1.73)	1.12 (0.77, 1.62)	1.00	1.05 (0.74, 1.50)	0.81 (0.52, 1.28)	1.70 (1.10, 2.61)†
Extended multivariable¶	0.92 (0.51, 1.68)	0.96 (0.64, 1.43)	1.00	1.01 (0.69, 1.47)	0.86 (0.53, 1.38)	1.91 (1.18, 3.10)†
Alzheimer's disease						
Number of deaths	<10	23	36	35	15	<10
Mortality rate per 1,000 person-years	0.07 (0.03, 0.13)	0.05 (0.03, 0.07)	0.04 (0.02, 0.05)	0.04 (0.03, 0.05)	0.03 (0.02, 0.05)	0.02 (0.00, 0.04)
Age-race adjusted‡	1.07 (0.49, 2.33)	1.11 (0.66, 1.87)	1.00	1.04 (0.65, 1.65)	0.73 (0.40, 1.33)	0.31 (0.11, 0.87)†
Multivariable§	1.05 (0.48, 2.30)	1.05 (0.61, 1.82)	1.00	1.10 (0.68, 1.78)	0.83 (0.45, 1.53)	0.29 (0.09, 0.93)†
Extended multivariable¶	1.13 (0.50, 2.55)	0.88 (0.48, 1.61)	1.00	1.14 (0.69, 1.91)	0.87 (0.45, 1.69)	0.23 (0.05, 0.99)†
Diabetes mellitus						
Number of deaths	18	38	37	29	19	22
Mortality rate per 1,000 person-years	0.15 (0.09, 0.24)	0.07 (0.05, 0.10)	0.04 (0.03, 0.05)	0.03 (0.02, 0.05)	0.04 (0.02, 0.06)	0.09 (0.06, 0.14)
Age-race adjusted‡	2.62 (1.47, 4.66)†	1.78 (1.13, 2.80)†	1.00	0.85 (0.52, 1.37)	0.98 (0.56, 1.71)	1.78 (1.04, 3.03)†
Multivariable§	2.89 (1.59, 5.23)†	1.80 (1.12, 2.91)†	1.00	0.90 (0.55, 1.46)	1.01 (0.57, 1.78)	1.77 (1.01, 3.10)†
Extended multivariable¶	3.39 (1.89, 6.09)†	1.81 (1.10, 3.00)†	1.00	0.86 (0.51, 1.44)	0.93 (0.51, 1.69)	1.60 (0.87, 2.95)

* Values are the hazard ratio (HR) (95% confidence interval [95% CI]) unless indicated otherwise. Cox proportional hazards models using age as a time scale were used to estimate HRs and 95% CIs. Counts below 10 were recorded as "<10" per the National Health and Nutrition Examination Survey (NHANES) analysis guidelines.
† $P < 0.05$.
‡ Race- and age-adjusted model was adjusted for age (time scale), race, NHANES cycle, and competing risk (for cause-specific mortality).
§ Multivariable adjusted model was further adjusted for body mass index, education (some high school or lower, high school, college, or graduate school or higher), smoking history (former, current, or never), alcohol consumption (drinks per month), and total cholesterol level.
¶ Extended multivariable model was further adjusted for presence of hypertension (yes/no) and estimated glomerular filtration rate.

at low levels of SU in men and no such effect among women (Supplementary Tables 1 and 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24476/abstract). A subgroup sensitivity analysis by race also showed a similar relationship between low SU level and higher all-cause mortality in White male subjects but not White female

Table 4. All-cause and cause-specific mortality in 21,853 women with baseline serum urate measurement at enrollment in the 1988–1994 NHANES-III and the 1999–2008 NHANES*

	Serum urate range, mg/dl					
	<3	3–4	4–5	5–6	6–7	>7
All-cause mortality						
Number of deaths	181	750	1,321	1,170	776	703
Mortality rate per 1,000 person-years	0.82 (0.70, 0.95)	0.75 (0.70, 0.81)	1.02 (0.97, 1.08)	1.47 (1.39, 1.56)	2.25 (2.09, 2.41)	3.94 (3.65, 4.24)
Age-race adjusted‡	1.13 (0.96, 1.32)	0.99 (0.90, 1.08)	0.96 (0.89, 1.04)	1.00	1.17 (1.07, 1.29)†	1.60 (1.46, 1.76)†
Multivariable§	1.09 (0.92, 1.28)	0.99 (0.90, 1.09)	0.98 (0.91, 1.07)	1.00	1.15 (1.05, 1.27)†	1.58 (1.43, 1.74)†
Extended multivariable¶	1.11 (0.93, 1.31)	1.03 (0.93, 1.14)	1.00 (0.92, 1.09)	1.00	1.11 (1.00, 1.22)	1.45 (1.31, 1.61)†
Illness-related mortality						
Cardiovascular disease						
Number of deaths	51	196	316	318	221	217
Mortality rate per 1,000 person-years	0.23 (0.17, 0.30)	0.20 (0.17, 0.23)	0.24 (0.22, 0.27)	0.40 (0.36, 0.45)	0.64 (0.56, 0.73)	1.22 (1.06, 1.39)
Age-race adjusted‡	1.20 (0.89, 1.63)	1.06 (0.89, 1.26)	0.90 (0.77, 1.05)	1.00	1.10 (0.93, 1.31)	1.41 (1.19, 1.68)†
Multivariable§	1.20 (0.88, 1.64)	1.07 (0.89, 1.29)	0.92 (0.79, 1.08)	1.00	1.10 (0.92, 1.31)	1.38 (1.15, 1.65)†
Extended multivariable¶	1.23 (0.88, 1.71)	1.11 (0.92, 1.34)	0.94 (0.80, 1.11)	1.00	1.06 (0.89, 1.28)	1.16 (0.95, 1.41)
Malignancy-related						
Number of deaths	31	163	289	229	122	112
Mortality rate per 1,000 person-years	0.14 (0.10, 0.20)	0.16 (0.14, 0.19)	0.22 (0.20, 0.25)	0.29 (0.25, 0.33)	0.35 (0.29, 0.42)	0.63 (0.52, 0.76)
Age-race adjusted‡	0.82 (0.56, 1.19)	0.95 (0.77, 1.16)	1.03 (0.87, 1.23)	1.00	0.97 (0.78, 1.21)	1.24 (0.99, 1.56)
Multivariable§	0.85 (0.58, 1.24)	0.98 (0.80, 1.21)	1.05 (0.88, 1.26)	1.00	0.95 (0.76, 1.19)	1.22 (0.97, 1.54)
Extended multivariable¶	0.75 (0.50, 1.12)	0.91 (0.73, 1.13)	1.01 (0.84, 1.22)	1.00	0.98 (0.78, 1.24)	1.26 (0.98, 1.61)
Chronic lower respiratory disease						
Number of deaths	<10	38	52	53	24	24
Mortality rate per 1,000 person-years	0.04 (0.02, 0.08)	0.04 (0.03, 0.05)	0.04 (0.03, 0.05)	0.07 (0.05, 0.09)	0.07 (0.04, 0.10)	0.13 (0.09, 0.20)
Age-race adjusted‡	1.32 (0.65, 2.66)	1.17 (0.77, 1.77)	0.86 (0.59, 1.26)	1.00	0.74 (0.46, 1.20)	0.95 (0.58, 1.55)
Multivariable§	1.18 (0.58, 2.39)	1.11 (0.73, 1.69)	0.88 (0.59, 1.29)	1.00	0.76 (0.47, 1.24)	0.95 (0.57, 1.57)
Extended multivariable¶	1.26 (0.62, 2.57)	1.11 (0.72, 1.72)	0.87 (0.58, 1.30)	1.00	0.66 (0.39, 1.12)	0.85 (0.49, 1.45)
Alzheimer's disease						
Number of deaths	<10	22	53	40	24	11
Mortality rate per 1,000 person-years	0.04 (0.02, 0.07)	0.02 (0.01, 0.03)	0.04 (0.03, 0.05)	0.05 (0.04, 0.07)	0.07 (0.04, 0.10)	0.06 (0.03, 0.11)
Age-race adjusted‡	1.82 (0.85, 3.92)	1.03 (0.62, 1.73)	1.26 (0.84, 1.90)	1.00	0.90 (0.54, 1.50)	0.51 (0.26, 1.00)
Multivariable§	1.46 (0.65, 3.26)	0.98 (0.59, 1.63)	1.17 (0.77, 1.77)	1.00	0.87 (0.51, 1.47)	0.50 (0.25, 1.02)
Extended multivariable¶	1.38 (0.57, 3.36)	0.97 (0.54, 1.73)	1.15 (0.73, 1.81)	1.00	0.79 (0.44, 1.41)	0.54 (0.25, 1.15)
Diabetes mellitus						
Number of deaths	<10	28	39	45	32	43
Mortality rate per 1,000 person-years	0.03 (0.01, 0.06)	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.06 (0.04, 0.08)	0.09 (0.06, 0.13)	0.24 (0.17, 0.32)
Age-race adjusted‡	0.95 (0.41, 2.21)	0.99 (0.62, 1.58)	0.77 (0.50, 1.18)	1.00	1.22 (0.78, 1.93)	2.14 (1.41, 3.25)†
Multivariable§	1.22 (0.52, 2.87)	1.23 (0.76, 2.01)	0.89 (0.57, 1.38)	1.00	1.14 (0.72, 1.82)	1.91 (1.23, 2.98)†
Extended multivariable¶	1.69 (0.71, 4.02)	1.50 (0.89, 2.53)	0.91 (0.56, 1.46)	1.00	1.11 (0.68, 1.82)	1.66 (1.02, 2.71)†

* Values are the hazard ratio (HR) (95% confidence interval [95% CI]) unless indicated otherwise. Cox proportional hazards models using age as a time scale were used to estimate HRs and 95% CIs. Counts below 10 were recorded as "<10" per the National Health and Nutrition Examination Survey (NHANES) analysis guidelines.
† $P < 0.05$.
‡ Age-race adjusted model was adjusted for age (time scale), race, NHANES cycle, and competing risk (for cause-specific mortality).
§ Multivariable adjusted model was further adjusted for body mass index, education (some high school or lower, high school, college, or graduate school or higher), smoking history (former, current, or never), alcohol consumption (drinks per month), and total cholesterol level.
¶ Extended multivariable model was further adjusted for presence of hypertension (yes/no) and estimated glomerular filtration rate.

subjects, although analyses were limited among Black subjects and subjects who belonged to other races due to small sample sizes available at the most upper and lower extremes of SU levels (Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24476/abstract).

Another analysis with follow-up time truncated at 10 years yielded similar results to the primary analysis (Supplementary Tables 4 and 5). An analysis of women limited to postmenopausal status also revealed similar results compared to the full cohort of women, with no significantly higher risk of all-cause or cause-specific mortality at the lowest SU range versus the referent range demonstrated (Supplementary Table 6). Lastly, after excluding patients who had diabetes mellitus, the risk of death in men who had SU levels in the lowest range was largely attenuated (multivariable HR 1.18 [95% CI 1.00–1.38] and extended multivariable HR 1.17 [95% CI 0.99–1.38]), and the risk of diabetes mellitus–related death was no longer significantly higher in men with SU levels in the lowest range compared to the referent SU level (multivariable HR 1.34 [95% CI 0.16–11.31] and extended multivariable HR 1.27 [95% CI 0.15–10.75]) (Supplementary Table 7, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24476/abstract).

DISCUSSION

In this US national survey follow-up cohort that collected data from multiple time periods, we found no long-term excess mortality risk among US women with SU levels as low as <3 mg/dl. Among men, we found an ~30% higher all-cause mortality risk among those with an SU level of <4 mg/dl, which was also associated with a nearly 3-fold higher risk of diabetes mellitus–related mortality. As hyperglycemia leads to uricosuria, and thus hypouricemia, in patients with diabetes mellitus, uncontrolled hyperglycemia in fatally severe diabetes mellitus could have led to extreme hypouricemia, which would be analogous to reverse causality (23). Overall, these findings appear to differ from data obtained from recent Asian study cohorts (2–6) and do not support a causal relationship between extreme hypouricemia and mortality. To that end, familial hypouricemia, a rare genetic disorder of urate handling in the renal tubules due to mutations in the *hURAT1* gene, is associated with chronic severe hypouricemia (generally <2 mg/dl), providing a natural model of extreme hypouricemia. Although the condition is associated with exercise-induced acute renal failure (24), it is not known to be associated with premature mortality (24,25), which is congruent with our findings.

Several previous studies from Asian countries including Japan, the Republic of Korea, and Taiwan have shown higher mortality among those with extreme hypouricemia (2,3,5,6). Earlier Japanese and Korean studies have independently demonstrated a higher mortality in hypouricemic men, but not women, which is similar to the findings of the present study (5,6). In these studies, the association with hypouricemia in Japanese men was driven by cardiovascular disease–related mortality (5), and the association with hypouricemia among Korean men was driven by cardiovascular disease– and malignancy-related mortality (6). However, neither study examined diabetes mellitus–specific mortality.

Another Korean cohort study showed higher rates of all-cause, cardiovascular disease–, and malignancy-related mortality in both hypouricemic men and women (2). Our study demonstrated no such associations with all-cause mortality or cardiovascular disease–related mortality among women or with malignancy-related mortality in either sex. A Taiwanese geriatric cohort study that analyzed data from participants ages 65 years or older concluded that a higher risk of mortality among hypouricemic men and women was explained by malnutrition (reflected by BMI and serum albumin level) (3), whereas our findings in the US general adult population, which was reflective of all age ranges, were not influenced by BMI or serum albumin levels. Last, a recent Japanese single center cohort study showed that women with SU levels of <2 mg/dl without cardiometabolic disease at baseline may be more likely to develop incident chronic kidney disease and hypertension (7), though mortality risk was not addressed in that investigation. In contrast, our study examined mortality risk in the US general population without excluding those with prevalent cardiometabolic comorbidities.

In the present study, a notable portion of the excess mortality risk in men with low SU levels was driven by presence of diabetes mellitus. Diabetes mellitus was recorded as the primary underlying cause of death in ~13% of decedents with diabetes mellitus in the National Death Index from January 1, 2000 through December 31, 2007 in the US (18). Over time, there has been a trend toward increased reporting of diabetes mellitus as the primary underlying cause of death, which correlates with decreased reporting of cardiovascular death as the underlying cause of death (18).

Furthermore, previous studies have shown a positive association between levels of blood glucose and levels of SU up to a serum glucose level of 180 mg/dl, after which SU level had a negative association with higher levels of glucose (a bell-shaped relationship) (23,26–29). An underlying biologic mechanism of this relationship is explained by the uricosuric effect of glycosuria, which occurs when the blood glucose level is >180 mg/dl (27), whereas the positive relationship before attaining that level is thought to be dominated by the physiologic effects of insulin resistance, which raises SU level (23,26–29). While prediabetes and obesity are associated with rising SU levels due to insulin resistance, chronic diabetes mellitus is associated with lower SU levels due to uricosuria, possibly due to impaired reabsorption of uric acid in the proximal tubules of the kidney in the setting of glycosuria (23). Interestingly, the relationship between hypouricemia and hyperglycemia has been shown to be stronger in men than in women (26,28,29). This is consistent with our sex-specific results, which showed higher diabetes mellitus–specific mortality at low SU levels in men, but not women. The mechanism underlying these sex-specific differences remains unclear, although the role of sex hormones in uric acid metabolism has been speculated (28,30).

Our study also found that high SU levels in men were associated with higher mortality due to chronic lower respiratory diseases.

As such, up to 50% of patients with sleep apnea have been found to have hyperuricemia (thought to be due to hypoxia-induced nucleotide turnover), which increases the risk of incident nocturnal gout attacks (31,32). Additionally, prior studies have demonstrated higher SU levels in patients with more severe chronic obstructive pulmonary disease (COPD), with an association between high SU level and higher risk of acute COPD exacerbation, hospitalization, and need for noninvasive ventilation (33,34). Furthermore, high SU levels have been associated with higher 30-day mortality in patients admitted with COPD exacerbations (34).

The present study had some strengths and limitations. Given that NHANES data are collected from community-based samples of men and women and weighted to be representative of the US population, our findings are likely generalizable. While evaluating chronic inherent risk factors such as SU level (as opposed to incident exposure) is always methodologically challenging, our stratification by sex, several levels of adjustments, and multiple sensitivity analyses have shown consistent results. Nevertheless, similar to other observational studies, our findings cannot rule out residual or unmeasured confounding. Causes of death recorded according to the National Death Index are subject to misclassification bias, similar to other studies using the same database. Some of the subgroups had a small number of deaths, especially at the extremes of SU levels, and further studies would be helpful to confirm our findings. As all covariates and SU measurements were performed at baseline, we cannot comment on the trajectory of SU level over time and its relationship to mortality risk. Although we were able to provide findings for women with SU levels of <3 mg/dl, analyses had to be performed at an SU level of <4 mg/dl in men due to the low number of male subjects with an SU level of <3 mg/dl. Last, due to the small number of patients with gout in the NHANES, we were unable to examine the relationship between SU levels and mortality risk in gout patients, and further studies are needed to investigate the relationship between SU levels and mortality in gout, especially among gout patients treated with urate-lowering therapy.

In conclusion, in a large cohort representative of the US general population, there was no significant long-term excess mortality observed in women with SU levels as low as <3 mg/dl, which does not support a causal link between hypouricemia and premature mortality. In men, higher mortality risk associated with hypouricemia was considerably driven by diabetes mellitus–related mortality, which may reflect the uricosuric effect of hyperglycemia rather than a deleterious causal effect of low SU itself. Overall, these findings challenge previously held concerns that prolonged extreme hypouricemia increases mortality risk in the general population.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. D'Silva had full access to all the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. D'Silva, Yokose, Zhang, Choi.
Acquisition of data. D'Silva, Lu, Choi.
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Comparison Between Clinical and Ultrasound Assessment of the Ankle Region in Children With Juvenile Idiopathic Arthritis

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Objective. To compare the frequency of joint and tendon disease on ultrasound (US) and clinical examination, and to investigate agreement between US and clinical evaluation in ankles with clinically active juvenile idiopathic arthritis (JIA).

Methods. US and clinical evaluation were performed independently in the joint and tendon compartments of 105 ankles. Gray-scale (GS) US and power Doppler (PD) US joint abnormalities were scored on a 4-point semiquantitative scale. A joint with a GS score ≥2 and/or a PD score ≥1 was defined as active on US. Agreement was tested using kappa statistics.

Results. A total of 163 joints in 89 ankles had active synovitis on US. The tibiotalar (TT) joint was the most commonly affected joint on US and on clinical evaluation. The intertarsal (IT) joint and the subtalar (ST) joint were the second in frequency on US and on clinical evaluation, respectively. Tenosynovitis was found more commonly on US than on clinical evaluation (70.5% and 32.4%, respectively), and was more frequent in the medial and lateral than in the anterior tendon compartment. Isolated tenosynovitis was detected on US in 12 of 105 ankles. Agreement between US and clinical evaluation for detection of active synovitis and tenosynovitis was less than acceptable ($\kappa < 0.4$). No correlation was found between any feature of active disease recorded on clinical evaluation (joint swelling, tenderness/pain on motion, and restricted motion) and active synovitis on US in the TT joint, ST joint, and IT joint.

Conclusion. Coupling clinical evaluation with US aids in correctly localizing pathology. US training of practitioners is recommended to manage ankle disease in JIA.

INTRODUCTION

Inflammatory involvement of the ankle region is common in juvenile idiopathic arthritis (JIA) (1–3). Chronic inflammation in the joints and tendons of this anatomical area may result in functional and structural damage. Furthermore, early occurrence of ankle arthritis has been correlated with unfavorable disease outcome (2,4). Ankle disease in JIA is frequently treated with the local injections of glucocorticoids, and systemic medications are often added in cases when the ankle remains inflamed or a multiplicity of its anatomical components are simultaneously affected (1,5,6). Precise identification of inflamed sites in the ankle is therefore crucial for a timely and effective treatment.

Clinical evaluation of the ankle is often challenging even for expert pediatric rheumatologists, especially in young patients, owing to the presence of numerous joints and tendons, and the physiologic abundant fat (7). These issues explain, at least in part, why signs and symptoms of disease, including pain, swelling, and impaired joint mobility may be related with difficulty to the involvement of a specific joint of the ankle region with clinical evaluation. Over the last few years, there has been an expanding application of ultrasound (US) in the management of JIA (8,9). The high acceptability by patients, the lack of exposure to ionizing radiation, the noninvasiveness, and the ability to allow real-time and multiplane imaging of joints and tendons make this imaging technique particularly suitable for the assessment of children with chronic inflammatory arthritis (9–11).

Studies of ankles in patients with JIA have shown the superiority of US over clinical evaluation in detecting joint and tendon inflammation (7,12–14). However, although these studies have

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SIGNIFICANCE & INNOVATIONS

- Clinical evaluation of the ankle region is often challenging even for expert pediatric rheumatologists.
- Definition of activity on ultrasound (US) does not improve the agreement between US and clinical evaluation.
- US aids clinical evaluation to identify precisely the inflamed sites of ankles with active juvenile idiopathic arthritis.

documented an overall disagreement between US and clinical evaluation in localizing the precise site of disease in the ankle region, all of these studies have considered the detection of any synovial abnormalities on US as a sign of synovitis. This choice may potentially lead to overestimate the disease burden in a joint, because low-level changes on US may merely represent residual findings of previous active disease in patients with JIA (8) and can be also seen in normal subjects (15,16). The discrimination between such changes and real signs of active synovitis by US may help to overcome this inaccuracy. Another limitation of previous studies is the lack of assessment of the levels of agreement between the clinical features of joint disease (i.e., pain, swelling, and impaired joint mobility) and the US detection of synovitis in each individual joint compartment of the ankle. Assuming US as a reference standard for documenting inflammation in JIA, the analysis of the correlation between active synovitis on US and the features of active disease recorded on clinical evaluation in the ankle region may help to improve the ability of clinical evaluation to detect involvement of specific joints. The results of this exercise may foster the application of US to improve the assessment of children with JIA by pediatric rheumatology centers in which US is not routine clinical practice (17,18). Against this background, the aim of the current study was 2-fold: to compare the frequency of active synovitis and of tenosynovitis in the joint and tendon compartments of the ankle region on US and clinical evaluation, and to investigate agreement between US and clinical evaluation in ankles with clinically active disease.

MATERIALS AND METHODS

Patient selection. The study included children with JIA, classified according to the International League of Associations for Rheumatology (ILAR) criteria (19), who had clinically active disease in the ankle region. Since the ILAR classification for JIA defines joint involvement based on the presence of active arthritis and does not take into account tenosynovitis, ankles of children with clinical evidence of isolated tenosynovitis without concomitant arthritis were not included in the study.

The patients were recruited from the pediatric rheumatology unit of the Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Maggiore Policlinico of Milan, Italy. Informed consent was obtained from all children, parents, or guardians, as appropriate. The study protocol was approved by the local institutional review board.

Clinical and laboratory assessment. At the study visit, the following data were recorded for each patient: sex, age at disease onset and at study entry, disease duration, ILAR category, antinuclear antibody (ANA) status, and ongoing medications. Clinical evaluation of the ankle region was performed by an experienced pediatric rheumatologist (GF). The joint compartments evaluated clinically were the tibiotalar (TT) joint, the subtalar (ST) joint, and the intertarsal (IT) joint (talonavicular and navicular–first cuneiform joints were assessed together). Clinically active disease was defined as the presence of swelling or, if no swelling was present, of tenderness/pain on motion and restricted motion in at least 1 of the joints of the ankle region (20). The presence of concomitant inflammation involving tendons of the anterior compartment (tibialis anterior, extensor hallucis longus, extensor digitorum longus), medial compartment (tibialis posterior, flexor digitorum longus, flexor hallucis longus), and lateral compartment (peroneus longus and brevis) of the ankle region was also assessed by clinical evaluation. Inflammation of a tendon compartment was defined as the presence of swelling in the related tendon area. No attempt was made to clinically identify the precise tendon/tendons inflamed for each tendon compartment. Clinical findings were recorded as present/absent.

US assessment. US assessment of the same joints and tendons of the ankle region as the clinical evaluation were performed immediately following the clinical evaluation, by a pediatric rheumatologist experienced in US assessment of patients with JIA (SL), who was blinded to clinical findings. Imaging was conducted using an Esaote MyLab Alpha machine, equipped with a multifrequency linear probe (3–13 MHz linear transducer). Images were collected using the power Doppler (PD) settings of pulse repetition frequency between 480 and 700 Hz, low wall filter, and color gain just below the level that did not display color noise in the underlying bone.

The joints and tendons were imaged according to published guidelines proposed for adults (21) and were investigated on gray-scale (GS) US and immediately thereafter on PDUS. For the assessment of the ST joint, a lateral scanning approach was used as described in JIA (7). US abnormalities were defined according to the Outcome Measures in Rheumatology Clinical Trials standardized definitions for US pathology (22). The PD signal was considered positive in the presence of vessel dots inside the synovial hypertrophy. Joint involvement on US was defined as the presence of both or either joint effusion and synovial hypertrophy, which could exhibit a PD signal. For the purpose of scoring, synovial hypertrophy and joint effusion were combined into an overall GSUS score, which was representative of the joint cavity widening. Overall GSUS and PDUS scores were graded on a

4-point semiquantitative scale based on previous studies (7,8,23–26). Joint cavity widening was graded as 0 = absent, 1 = mild, 2 = moderate, and 3 = marked. The PD signal was graded as 0 = absent, 1 = mild (presence of single-vessel dots), 2 = moderate (presence of confluent vessel dots in less than half of the synovial area), and 3 = marked (presence of confluent vessel dots in more than half of the synovial area). According to a study on adult rheumatology patients (27), a joint was defined as active on US in case of detection of a GS score ≥2 and/or a PD score ≥1. For the IT joint, activity on US was defined as the presence of activity on US in both or either the talonavicular joint and the navicular–first cuneiform joint.

Tenosynovitis was not graded on US and was recorded only as present/absent. The involvement on US of the anterior tendon compartment (ATC), medial tendon compartment (MTC), or lateral tendon compartment (LTC) was defined as the presence of tenosynovitis in at least 1 of the tendons of the tendon compartment.

Statistical analysis. Descriptive statistics were reported in terms of medians and interquartile ranges (IQRs) for continuous variables and as absolute frequencies and percentages for categorical variables. Agreement was estimated by computing the percentage of the exact agreement and through the unweighted Cohen's kappa statistics with 95% confidence intervals (28). The strength of kappa agreement was defined as κ ≤0.20 = poor, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = good, and >0.81 = excellent (29). The statistical package used was Stata, version 15.1.

RESULTS

Study population. A total of 78 patients, 53 girls (67.9%) and 25 boys (32.1%), n = 105 ankles with active disease on clinical evaluation, were included in the study. At study entry, the median disease duration was 1.8 years (IQR 0.3–6.4), and the median age was 8.1 years (IQR 4.9–11.3 years). Twenty-six patients (33.3%) had persistent oligoarthritis, 12 (15.4%) had extended oligoarthritis, 29 (37.2%) had polyarthritis (27 rheumatoid factor [RF]–negative and 2 RF-positive), 4 (5.1%) had systemic arthritis, 4 (5.1%) had enthesitis-related arthritis, 2 (2.6%) had psoriatic arthritis, and 1 (1.3%) had undifferentiated arthritis. ANAs were positive in 56 patients (71.8%). Forty-nine patients (62.8%) were on systemic medications: 18 (36.7%) and 10 (20.4%) were receiving methotrexate or a biologic agent alone, respectively, 7 (14.3%) methotrexate and a biologic agent in combination, 12 (24.5%) nonsteroidal antiinflammatory drugs as monotherapy, and 2 (4.1%) systemic glucocorticoids and methotrexate (1 together with a biologic agent).

Table 1. Frequency of inflammation by joint and tendon compartment on clinical evaluation and ultrasound in the 105 assessed ankles*

Area assessed	Clinical evaluation	Ultrasound
Synovitis	88 (83.8)	63 (60.0)
TT joint	70 (66.7)	45 (42.9)
ST joint	26 (24.8)	55 (52.4)
IT joint		
Tenosynovitis		
ATC	0 (0.0)	17 (16.2)
MTC	22 (21.0)	51 (48.6)
LTC	22 (21.0)	40 (38.1)

* Values are the number (%). Ultrasound synovitis: gray-scale score ≥2 and/or power Doppler score ≥1. ATC = anterior tendon compartment; IT = intertarsal; LTC = lateral tendon compartment; MTC = medial tendon compartment; ST = subtalar; TT = tibiotalar.

Table 2. Frequency of tenosynovitis on ultrasound for each individual tendon in the 105 assessed ankles*

Tendon assessed	Tenosynovitis
Tibialis anterior	8 (7.6)
Extensor hallucis longus	7 (6.7)
Extensor digitorum longus	13 (12.4)
Tibialis posterior	48 (45.7)
Flexor digitorum longus	26 (24.8)
Flexor hallucis longus	19 (18.1)
Peroneal tendons†	40 (38.1)

* Values are the number (%).
† Peroneal tendons were assessed together.

Clinical and US findings. The frequency of inflammation by joint and tendon compartment on clinical evaluation and US is shown in Table 1. Among the 105 ankles found to be affected clinically, active synovitis was detected by clinical evaluation in 184 joints: 88 TT joints, 70 ST joints, and 26 IT joints. A total of 163 joints in 89 ankles had active synovitis on US. The most frequently affected was the TT joint, followed by the IT joint. Tenosynovitis was detected by clinical evaluation in 34 of 105 ankles (32.4%) and by US in 74 of 105 ankles (70.5%). On clinical evaluation, tendons in the MTC and LTC were affected with equal frequency, whereas involvement of the ATC was never recorded. Tendons in the MTC were most commonly involved on US, followed by tendons in the LTC.

As shown in Table 2, the tibialis posterior was the most frequently affected tendon on US, followed by the peroneal tendons and the flexor digitorum longus tendon. Tenosynovitis alone was detected on US in 12 ankles of 10 patients. In particular, 9 ankles displayed isolated tenosynovitis of a single tendon compartment (the MTC in 7 cases, and the LTC and ATC in 1 case each); 3 ankles had isolated tenosynovitis affecting the LTC together with the ATC. Four of the 105 assessed ankles (3.8%) had no tenosynovitis and minimal synovial abnormalities in 1 joint compartment on US, but the definition of US activity was not met in any of them. Figures 1 and 2 show examples of synovitis and tenosynovitis on GSUS and PDUS in the ankle region.

Looking at articular signs/symptoms on clinical evaluation, 144 joints were swollen, 142 were tender/painful on motion, and 136 had restricted motion. The frequency of the specific signs/symptoms in each joint is reported in Table 3. Among the 184

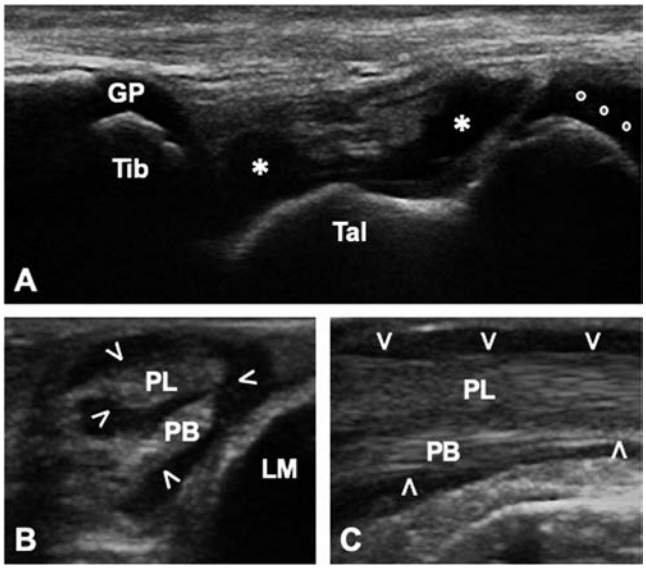

Figure 1. Gray-scale ultrasound scans of the tibiotalar joint (**A**), showing synovitis (asterisk) in a boy age 3 years with juvenile idiopathic arthritis (JIA) and of the transverse (**B**) and longitudinal (**C**) peroneal tendons in a boy age 9 years with JIA, showing tenosynovitis. GP = growth plate; LM = lateral malleolus; PB = peroneus brevis tendon; PL = peroneus longus tendon; Tal = talus; Tib = tibia; ° = cartilage; arrowheads = distension of the tendon sheath.

joints with clinically active synovitis, swelling was detected most commonly in the TT joint, whereas tenderness/pain on motion and restricted motion were recorded most frequently in the ST joint. The IT joint showed the lowest frequency of all 3 articular signs/symptoms.

Comparison between clinical and US findings. Concordance between clinical evaluation and US for the presence or absence of active disease was found in 56 (53.3%) and in 10 (9.5%) of 105 ankles, respectively, for the TT joint, in 36 (34.3%) and in 26 (24.7%) of 105 ankles, respectively, for the ST joint, and in 21 (20.0%) and in 45 (42.8%) of 105 ankles, respectively, for the IT joint. US disclosed active synovitis in 7 TT joints (6.7%), 9 ST joints (8.6%), and 34 IT joints (32.4%) that were considered as normal on clinical evaluation. Thirty-two TT joints (30.5%), 34 ST joints (32.4%), and 5 IT joints (4.8%) deemed to be affected clinically did not display activity on US.

Regarding tendon compartments, concordance between clinical evaluation and US for the presence of tenosynovitis was found in 16 ankles (15.2%) for the LTC and in 20 ankles (19.1%) for the MTC. Clinical evaluation and US were concordant in documenting the absence of tenosynovitis of the LTC in 59 ankles (56.2%), of the MTC in 52 ankles (49.5%), and of the ATC in 88 ankles (83.8%). Six LTCs (5.7%) and 2 MTCs (1.9%) were normal on US but were affected clinically. Twenty-four LTCs (22.9%), 31 MTCs (29.5%), and 17 ATCs (16.2%) showed tenosynovitis on US, but were unaffected clinically.

Agreement between clinical and US findings. The evaluation of agreement between clinical and US assessments is shown in Table 4. Considering the individual ankle joints, agreement for the presence/absence of active synovitis was poor for the TT joint ($\kappa = 0.14$) and fair for the ST joint and IT joint ($\kappa = 0.22$ and $\kappa = 0.27$, respectively). Concerning tendon compartments, the agreement for the presence/absence of tenosynovitis was fair for the MTC and LTC ($\kappa = 0.36$ and $\kappa = 0.34$, respectively). The absence of detection of tenosynovitis on clinical evaluation in the ATC did not allow calculation of agreement for that tendon compartment. Regarding specific clinical features, agreement was poor between active synovitis on US and all clinical findings for the TT joint. For the ST joint, the agreement ranged from poor to fair, being best between joint activity on US and tenderness/pain on motion on clinical evaluation ($\kappa = 0.24$). In the IT joint, tenderness/pain on motion and restricted motion showed the best agreement with active synovitis on US ($\kappa = 0.26$ and $\kappa = 0.22$, respectively), whereas agreement was poor for swelling ($\kappa = 0.19$).

DISCUSSION

The ankle is the second most frequently affected joint after the knee in children with JIA and is, together with the hip, the wrist, the cervical spine, and the temporomandibular joints, one of the most vulnerable sites of structural damage (1–3). Understanding the exact location of inflammation in the ankle compartments is crucial to optimize therapeutic decision-making and to pursue a successful local treatment with glucocorticoid injections (6). Achievement of complete control of inflammatory disease in the ankle helps to prevent the development of nonreversible joint damage and disability and may improve the disease outcome (4,30).

Over the last few years, the adoption of sensitive imaging modalities, in particular US and magnetic resonance imaging

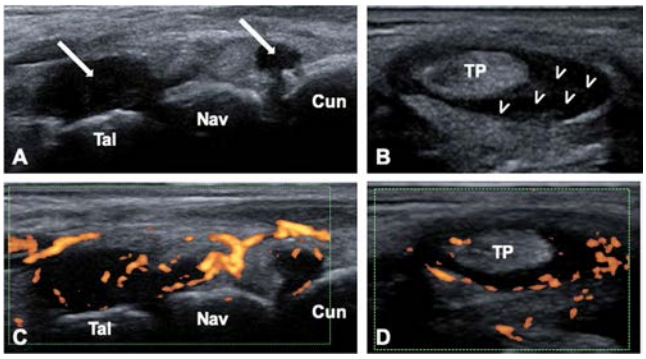

Figure 2. Longitudinal ultrasound scan of talonavicular and navicular–first cuneiform joints in a boy age 9 years with juvenile idiopathic arthritis (JIA), showing synovitis (arrows) on gray-scale ultrasound (GSUS) (**A**) and on power Doppler US (PDUS) (**C**). Transverse ultrasound scan of the tibialis posterior tendon in a girl age 8 years with JIA, showing tenosynovitis on GSUS (**B**) and on PDUS (**D**). Cun = first cuneiform; Nav = navicular; Tal = talus; TP = tibialis posterior tendon; arrowheads = distension of the tendon sheath.

Table 3. Frequency of the specific clinical signs/symptoms in each joint of the 105 assessed ankles*

Joint area	Swelling	Tenderness/ pain on motion	Restricted motion
TT joint	81 (77.1)	57 (54.3)	54 (51.4)
ST joint	44 (41.9)	62 (59.0)	63 (60.0)
IT joint	19 (18.1)	23 (21.9)	19 (18.1)

* Values are the number (%). IT = intertarsal; ST = subtalar; TT = tibiotalar.

(MRI), has improved the capability to assess the disease status in complex anatomical regions, such as the ankle joint, by enabling the precise visualization and topographic location of inflammatory changes in joints and tendons (9–11). The use of US is gaining increasing interest among pediatric rheumatologists because it can be applied directly in the clinic (9). However, its routine application in many centers is hampered by the small number of practitioners who possess the skills necessary to perform US in daily clinical practice (17,18).

In the current study, we compared the clinical evaluation and US assessment of the ankle in children with JIA who had clinically active disease in 1 or more of the 3 joint compartments that are part of the ankle region, the TT joint, the ST joint and the IT joint. The number of ankles evaluated in our study is larger than that of previous studies on ankles and US in JIA (6,7,12–14). Unlike previous studies (13,14), we set cutoff values on both GSUS and PDUS to minimize a bias in the interpretation of US findings. By establishing these criteria, we wanted to make sure that US discriminated reliably between minor synovial changes that may only represent residual findings of previous inflammation from synovial abnormalities clearly consistent with ongoing active disease. Despite the application of such criteria to define US findings, we found poor concordance between clinical evaluation and US for all joint compartments of the ankle region. Notably, in comparison to previous studies (13,14), we also included the IT joint in the analysis of agreement.

In a previous study (14), the level of agreement for clinical versus US features was evaluated and resulted in overall unsatisfactory findings for each clinical and US comparison. However, this analysis was conducted without examining separately the different articular recesses and by combining the data of all joints. In our study, we evaluated the correlations separately for each individual joint compartment of the ankle region. Despite this detailed evaluation, the agreement between the recorded clinical features of articular involvement and the location of active synovitis on US remained inadequate. Altogether, these findings underscore the challenges in making a reliable clinical assessment of the ankle region and the utility of coupling that assessment with a US examination that aids to identify precisely the inflamed sites.

Our results indicate that tendon involvement is frequent in JIA patients with ankle arthritis. A previous comparison of clinical and US assessment of the ankle region did not include the evaluation of the ATC in the data analysis (13). The same tendon compartment was not included in the US protocol of a more recent study comparing clinical and US findings of the foot (14). We included examination of the ATC in our US procedures and in our data analysis, but we found that tenosynovitis was less frequent in this compartment than in the MTC and LTC. This finding is in keeping with the notion that the use of US to guide tendon sheath injections in JIA is more common in the MTC and LTC of the ankle (31). The observation that the clinician did not report involvement of the ATC in any ankles in our patients may be explained, at least in part, by considering the fact that tenosynovitis affecting the ATC may easily mimic the presence of synovitis in the anterior joint structures of the ankle, particularly in the TT joint and IT joint, since this tendon compartment runs superficially above the anterior surface of the ankle region.

Importantly, despite the high rate of tendon involvement seen in the ankles examined, we found a lower prevalence of isolated tenosynovitis on US than in previous studies (12,13). This finding may be partially related to the fact that in these reports tendon

Table 4. Agreement between clinical and ultrasound (US) assessment in the studied ankles*

Description	Observed agreement, %	Kappa (95% CI)
TT joint clinical synovitis vs. US synovitis	63	0.14 (0.00–0.31)
ST joint clinical synovitis vs. US synovitis	59	0.22 (0.06–0.38)
IT joint clinical synovitis vs. US synovitis	63	0.27 (0.12–0.43)
ATC clinical tenosynovitis vs. US tenosynovitis	84	NA†
MTC clinical tenosynovitis vs. US tenosynovitis	69	0.36 (0.21–0.51)
LTC clinical tenosynovitis vs. US tenosynovitis	71	0.34 (0.16–0.52)
TT joint swelling vs. US synovitis	64	0.19 (0.01–0.37)
TT joint tenderness/pain on motion vs. US synovitis	56	0.11 (0.00–0.30)
TT joint restricted motion vs. US synovitis	55	0.10 (0.00–0.29)
ST joint swelling vs. US synovitis	61	0.20 (0.01–0.39)
ST joint tenderness/pain on motion vs. US synovitis	61	0.24 (0.06–0.41)
ST joint restricted motion vs. US synovitis	56	0.15 (0.00–0.33)
IT joint swelling vs. US synovitis	58	0.19 (0.05–0.33)
IT joint tenderness/pain on motion vs. US synovitis	62	0.26 (0.11–0.41)
IT joint restricted motion vs. US synovitis	60	0.22 (0.09–0.36)

* US synovitis: gray-scale score ≥2 and/or power Doppler score ≥1. ATC = anterior tendon compartment; IT = intertarsal; LTC = lateral tendon compartment; MTC = medial tendon compartment; ST = subtalar; TT = tibiotalar.
† NA = not assessable. The absence of positive cases for the clinical examination did not allow calculation of the kappa assessment.

involvement was considered isolated in the absence of TT joint disease on US, because the ST joint and IT joint were not included in the formal analysis. Furthermore, this disparity can be explained by our choice of excluding from the study the ankles in which the clinician detected isolated tenosynovitis without concomitant arthritis. Since the ILAR classification for JIA defines joint involvement based on the presence of active arthritis and does not take into account tenosynovitis, involvement of the ankle region is traditionally established only in the presence of active joint disease. Likewise, the current criteria for defining clinically inactive disease in JIA only consider joint synovitis and not tenosynovitis (32). There is the need of specific studies aimed to define the role of tenosynovitis in the definition of disease activity and remission in JIA.

Our findings should be interpreted in the light of some potential limitations. Due to the current lack of established cutoff values for GSUS and PDUS scores that discriminate between active and inactive disease in JIA, we used cutoff values published for adults. According to these cutoff values, active disease on US can also be identified by the presence of GSUS changes alone, without detection of PD signal on PDUS. However, this is not in contrast with the recently published preliminary definitions for US features of synovitis in children (33). Further studies are needed to understand whether the application of such cutoff values may lead to missing disease activity or, conversely, to overestimating the disease burden in a joint in JIA. We should also recognize that we did not validate the presence of joint and tendon abnormalities on US with other imaging modalities, particularly MRI. Notably, a study comparing these imaging techniques for the assessment of the hindfoot of patients with rheumatoid arthritis documented that both US and MRI may provide valuable information on disease activity (34). We finally acknowledge the shortcoming that US examination was performed by a single operator. Although we did not test the reliability of US in our cohort, the ultrasonographer who scanned all ankles showed acceptable intrareader and interreader reliability in previous studies (7,8).

In summary, despite the application of a score aimed to identify with greater accuracy the presence of active joint synovitis on US, we did not find satisfactory agreement between clinical and US assessment of the ankle region in our patients with JIA. Our observation suggests that clinical evaluation does not allow a proper evaluation of ankle disease activity, because it is not able to establish precisely the location of joint and tendon inflammation. Coupling clinical evaluation with US aids to correctly identify the inflamed sites in the ankle region, which enhances significantly the quality of the clinical assessment and may increase the effectiveness of local injection therapy. Training on US of practitioners who are involved in the care of children with JIA is recommended to increase the skills in the evaluation of ankle disease.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Lanni had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lanni, Civino, Alongi, Agostoni, Ravelli, Filocamo.

Acquisition of data. Lanni, Proverbio, Filocamo.

Analysis and interpretation of data. Lanni, Marafon, Ravelli, Filocamo.

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Consequences of Juvenile Idiopathic Arthritis on Single Leg Squat Performance in Youth

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Objective. Juvenile idiopathic arthritis (JIA) affects body structure and function outcomes that may increase the risk of acute joint injury. The purpose of this study was to examine single leg squat (SLS) biomechanics for youth with JIA and their healthy peers. The study design was a matched pair cohort study.

Methods. Sixty-five youth (JIA n = 30; control n = 35) participated in this ethics-approved study. Participants performed 3 sets of 5 consecutive SLS tasks. Disease activity and functional status were assessed using the Juvenile Arthritis Disease Activity Score and Child Health Assessment Questionnaire. Indexed (most-affected leg [JIA]; dominant leg [control]) and contralateral extremity biomechanics were obtained using a 12-camera system. Outcomes included hip flexion/extension (FE), adduction/abduction (AA), and internal/external (IE) rotation range of motion (ROM). Data were analyzed using a multivariate random coefficient model in R ($\alpha = 0.05$).

Results. A total of 29 matched pairs were analyzed. Youth with JIA had low disease activity and performed the SLS with a more internally rotated hip (indexed leg $P = 0.023$, $\beta = -1.9°$). Female participants displayed greater hip FE (indexed leg $P = 0.015$, $\beta = -4.3°$; contralateral leg $P = 0.005$, $\beta = -4.8°$) and IE ROM (indexed leg $P = 0.021$, $\beta = -2.1°$) than male participants. Associations were observed for body mass index and hip IE ROM (contralateral leg $P = 0.001$, $\beta = -0.4°$), knee flexion angle, and hip FE ROM (indexed leg $P = 0.001$, $\beta = 0.4°$; contralateral leg $P = 0.001$, $\beta = 0.5°$) and AA (indexed leg $P = 0.010$, $\beta = 0.1°$; contralateral leg $P = 0.002$, $\beta = 0.2°$).

Conclusion. This study identified functional alterations for an SLS in youth with JIA. These findings support the use of physical therapy as part of a multidisciplinary management approach, to restore normal hip posture and movement.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) describes a clinically heterogeneous group of arthritides of unknown cause, which begin before age 16 years (1). JIA affects approximately 0.1–4.0 per 1,000 children worldwide (2–4). Evidence from Canada indicates that contemporary management approaches enable an approximately 50% probability of achieving remission off medication within 5 years of diagnosis (5), with the exception of children with polyarthritis, who are at greater risk of continued arthritis into adulthood. In line with the increasing efficacy of clinical management approaches, a review of school sports participation in Germany indicates a continuous increase in participation by children and youth with JIA between the years 2000 and 2015 (6). This increase in participation in turn raises important questions regarding the secondary consequences of JIA, including limitations in body structure and function, activity, and participation outcomes. Continued limitations during periods of inactive disease could expose children and youth with JIA to a greater risk of incurring a sport-related joint injury and subsequent secondary joint pathology (7) when returning to physical activity and school sports.

A growing body of evidence indicates that the secondary consequences of JIA may include participation in less moderate-to-vigorous physical activity (8,9), impaired postural balance (10),

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SIGNIFICANCE & INNOVATIONS

- The findings of this study demonstrate that youth with juvenile idiopathic arthritis (JIA) performed the single leg squat with a more internally rotated hip posture.
- An internally rotated hip posture could indicate functional weakness of the gluteal muscles and altered movement control and may represent a potential risk factor for acute joint injury in sports participation.
- The research evidence provided by this study supports the inclusion of neuromuscular strengthening and proprioceptive training as part of needs-based physical therapy management to restore normal hip posture and movement in youth with JIA.

and decreased physical fitness (11), as well as bone and muscle structure (12) and strength deficits (13). Further, individuals with JIA appear to be more sensitive to mechanical and thermal stimuli, even in the absence of pain or active disease (14). Differences in joint biomechanics in individuals with JIA during walking and jumping (15–20) have been reported, providing evidence on body structure and function alterations, which are likely associated with underlying deficits in muscle strength and altered neuromuscular control. Differences in jump landing mechanics of youth with JIA (20) are particularly interesting because they indicate a stiff landing strategy, which has been suggested as a risk factor for lower-extremity injury in female youth athletes (21,22). With a view to the increasing participation in school sports by youth with JIA, knowledge of the presence of potential biomechanical injury risk factors becomes increasingly important to inform targets for physical therapy and to assess the efficacy of rehabilitation interventions to mediate risk factors in children and youth with JIA.

Within the clinical and injury prevention settings, the single leg squat (SLS) is often used to identify movement quality of the lower extremities (23) and to assess the risk of sustaining an acute lower-extremity injury (24). Crossley et al (25) suggest 5 visual rating criteria for the SLS task performance: 1) overall impression for 5 SLS trials, 2) posture of the trunk over the pelvis, 3) posture of the pelvis, 4) hip joint posture and movement, and 5) knee joint posture and movement. Stratification of individuals as good, fair, or poor performers enabled the identification of hip abductor muscle dysfunction and weakness of hip abductor and trunk flexor muscles by poor SLS performers (25). Further, Räisänen et al (24) showed that large frontal plane knee motion was associated with a 2.7-fold greater likelihood of sustaining a lower-extremity injury in young team sports athletes. Importantly, SLS performance may be reliably assessed by physical therapists and is a valid assessment task in the clinical and research setting (23,26). Therefore, the SLS may be ideally suited to provide clinically meaningful information on body structure and function consequences of JIA and to help identify potential injury risk factors for an increasingly active population of youth with JIA.

The objective of this study was to quantify differences in hip joint kinematics during an SLS task for youth with JIA compared to their age- and sex-matched healthy peers. This study focused on youth with JIA who have an involved knee joint and receive modern pharmacologic management as well as targeted physical therapy as needed. Research evidence on task-specific differences in body structure and function informs targets for clinical management to address functional deficits and support a safe return to physical activity participation and sports for youth with JIA.

SUBJECTS AND METHODS

Participants. This study employed a matched pair cohort study design, matching youth with JIA with their healthy peers (control group) based on the closest match in age (within 1.5 years) and sex. Recruitment details for this cohort have been previously reported by Kuntze et al (19). Participants with JIA were recruited sequentially as they presented to their acting physician and physical therapist at the Pediatric Rheumatology clinic at the Alberta Children's Hospital and the Richmond Road Diagnostic and Treatment Centre Rheumatology Clinic in Calgary. Control youth were recruited using the Healthy Infants and Children Clinical Research Program at the Alberta Children's Hospital, participant siblings and friends, and word-of-mouth recruitment. Ethics approval was granted by the University of Calgary Conjoint Health Research Ethics Board at the University of Calgary, Canada (REB15-3125) and Alberta Health Services. All participants provided signed consent/assent.

Youth with JIA were ages 10–20 years, had an ongoing diagnosis of JIA confirmed by a physician using International League of Associations for Rheumatology criteria (27), and involvement of at least 1 knee joint. Participants were not eligible if they had systemic symptoms, any change in medication for 3 weeks prior to testing, or active ankle joint involvement at the time of testing. Further, joints could be symptomatic (i.e., active disease) or in remission at the time of testing. Healthy control youth had no history of JIA or other rheumatic diseases. Exclusion criteria for all participants included contraindications according to the Physical Activity Readiness Questionnaire for Everyone, previous lower-extremity musculoskeletal injury (within 3 months prior to testing) resulting in time loss (work, school, or sport), diagnosis of any other arthritides, intraarticular steroid injection (within 3 months prior to testing), or any current medical problem that prevented study participation (e.g., neurologic conditions). All testing was conducted between July 2016 and January 2018.

Cohort characteristics. Details of disease activity, functional capacity, and cohort characteristics have been previously reported by Kuntze et al (19). Briefly, disease activity was recorded by the same study physician (SB) using the clinical Juvenile Arthritis

Disease Activity Score in 10 joints (cJADAS-10) guidelines. The clinical JADAS is a continuous score of disease activity developed for use among individuals with JIA (28) and consists of measures of active joint count (10 joints), physician global assessment of disease activity, and evaluation of the child's well-being. Further, the Child Heath Assessment Questionnaire (C-HAQ) (29) was used to quantify self-assessed physical disability across 8 domains. Each item of the C-HAQ is scored on a 4-point ordinal scale (0 = without any difficulty to 3 = unable to do) and the C-HAQ is complemented by 2 visual analog scales (VAS; 100-mm length) of disease-related pain and overall well-being, each scored on a scale of 0–3.

SLS assessment. Bilateral joint kinematics were recorded using a 12-camera optical motion capture system (Motion Analysis, 240 Hz) and 32 reflective spherical markers. Participants performed 3 sets of 5 consecutive SLS tasks for the right and left legs. Participants stood with 1 leg on a specified location on the floor marked with an X. Participants were then asked to bend their weight-bearing leg to 45° of knee flexion. This posture was confirmed using a handheld goniometer by a trained member of the study team. A string spanning 2 tripods was then adjusted to touch the front of the knee when bending to 45°. This end point was used as physical feedback to inform participants that they achieved the desired flexion angle and could return to the starting position. The SLS task was demonstrated to each participant by a member of the study team and emphasis was placed on performing the movement with good control rather than as quickly as possible. A supervised familiarization period was provided to allow participants to become accustomed to the SLS task. Adherence to the movement task criteria was visually confirmed during testing.

Data processing. Kinematics data were processed using EVaRT (Motion Analysis) and hip and knee joint angles were computed using Visual3D (C-Motion). Joint angle time series were normalized to 101 data points using Matlab software, version 2018b (MathWorks), starting at maximum knee extension and ending at maximum knee flexion, to investigate the descending phase of the SLS. Joint kinematics outcomes included bilateral hip flexion/extension (FE) range of motion (ROM; hip flexion positive); hip adduction/abduction (AA) ROM (adduction positive); and hip internal/external (IE) rotation ROM (external rotation positive). ROM refers to the difference in joint angles between the time of maximum knee extension (start) to maximum knee flexion (end); i.e., joint angle (end) – joint angle (start). A further measure of interest was the maximum knee flexion angle. While the SLS task was performed with a target knee joint angle of 45°, any differences in the actual knee flexion angle may influence the magnitude of the hip ROM outcomes. Consequently, the mean maximum knee flexion angle was computed for all participants and considered as a fixed effect in the statistical model. All joint angle outcomes were extracted using custom written Matlab code. Joint angles were analyzed with respect to the indexed leg (the affected leg of participants with JIA or dominant leg of control participants) and the contralateral leg (the unaffected or less affected leg of participants with JIA or the nondominant legs of control participants). In line with previous approaches (19), the indexed leg was identified by the study rheumatologist, and in cases of a bilateral knee involvement, the indexed leg was identified by the participant as the leg that they felt was generally affected worse. The dominant leg of control participants was identified by determining with which leg they preferred to kick a ball. This terminology will be used for the remainder of this article.

Statistical analysis. Data analysis was conducted using R software, version 3.5.0 (30). The effects of JIA on kinematics outcomes of the indexed leg and contralateral leg (i.e., JIA–control) were investigated using a multivariate random coefficient model (alpha 0.05) using the nlme package (30). Joint angle outcomes for each participant were analyzed as a single 3-dimensional DATA vector of correlated outcomes (30). Assumptions for normality of residuals were assessed using QQ plots of residuals and plots of residuals against the fitted values to assess for heteroscedasticity. In the multivariate random coefficient model, JIA and control joint angle data were considered as dependent multivariate samples with a random effect of pairing (i.e., matched pairs) to enable consideration of the within-pair variability. The effects of group (JIA and control) as well as the effects of potential confounders (e.g., age, sex, body mass index [BMI], and maximum knee flexion angle of the indexed leg and contralateral leg) were modeled as fixed effects. Differences in participant characteristics were explored using mean ± SDs, minimum and maximum data ranges, and medians and interquartile ranges.

RESULTS

Cohort characteristic results. Sixty-five youth participated in this study (JIA n = 30; control n = 35). One participant with JIA was excluded from the analysis due to missing data. Therefore, 29 youth with JIA and their age- and sex-matched control pairs were taken forward for analysis. Matched control youth were therefore a subgroup of 29 of 35 recruited participants. A high percentage of matched participants with JIA were female (69%), participants with JIA had a mean ± SD age of 14.9 ± 2.5 years, and presented with predominantly oligoarticular (44.8%) and polyarticular (48.3%) JIA subtypes, with 6.9% classified as enthesitis-related JIA (Table 1). The median disease duration was 6.4 years (range 0–14.4 years). The physician assessment was conducted for 25 of 29 youth with JIA who displayed low scores for physician global assessment of disease activity (0–10 range) (mean ± SD 0.5 ± 0.7), active joint count (mean ± SD 1.7 ± 4.9 joints), and joints with limited ROM (mean ± SD 1.8 ± 5.0 joints). Parent assessment of disease activity was completed for 19 of 29 participants (0–10 range, mean ± SD 1.1 ± 2.0) because not all participants were accompanied by their parents. The type of antirheumatic drug used was reported by 28 participants (71% disease-modifying

Table 1. Participant characteristics of youth with juvenile idiopathic arthritis (JIA) and typically developing healthy youth*

Characteristic	Control (n = 35)	Matched control (n = 29)	JIA (n = 29)
Age, years	15.0 ± 2.7	15.0 ± 2.7	14.9 ± 2.5
Height, meters	1.62 ± 0.11	1.62 ± 0.12	1.64 ± 0.13
Weight, kg	53.0 ± 13.1	53.4 ± 12.8	56.5 ± 14.4
Female, no. (%)	25 (71)	20 (69)	20 (69)
Disease course, no. (%)			
Oligoarticular	NA	NA	13 (44.8)
Polyarticular	NA	NA	14 (48.3)
Enthesitis-related	NA	NA	2 (6.9)
Time since diagnosis, median (range) years	NA	NA	6.4 (0.0–14.4)
PGA (0–10)	NA	NA	0.5 ± 0.7 (n = 25)
PtGA (0–10)	NA	NA	1.1 ± 2.0 (n = 19)
Active joint count	NA	NA	1.7 ± 4.9 (n = 25)
Joints with limited ROM	NA	NA	1.8 ± 5.0 (n = 25)
Drug management, no. (%)			
DMARDS	NA	NA	28 (71)
Biologics	NA	NA	28 (36)
Intraarticular steroid injections	NA	NA	28 (32)

* Values are the mean ± SD unless indicated otherwise. Data are shown for all recruited control youth and the subsection of control youth considered as matched pairs (matched control). DMARDS = disease-modifying antirheumatic drugs; NA = not applicable; PGA = physician global assessment of disease activity; PtGA = parent global assessment of disease activity; ROM = range of motion.

antirheumatic drugs, 36% biologics, 32% intraarticular steroid injections) (Table 1). All participants completed the C-HAQ pain and global evaluation VAS. Pair differences (JIA–control) indicated slightly elevated pain ratings (mean ± SD 0.2 ± 0.8, median 0.0 [interquartile range (IQR) –0.1, 0.6], range 0–3), reduced global evaluation scores (mean ± SD 0.5 ± 0.8, median 0.3 [IQR 0.0, 0.6], range 0–3) in youth with JIA, as well as elevated disability ratings for some individuals with JIA (mean ± SD 0.2 ± 0.3, median 0.0 [IQR 0.0, 0.4], range 0–3) (Table 2).

SLS biomechanics. Multivariate analysis revealed a significant effect of group (JIA–control) on maximum transverse plane hip angles of the indexed leg (P = 0.023, β = –1.9°) (Table 3). Here, participants with JIA displayed a smaller hip IE rotation ROM than control youth (JIA indexed leg mean ± SD 1.5 ± 2.6°; control indexed leg 3.7 ± 3.7°) (Table 4). No significant effect of group was observed for hip IE rotation ROM of the contralateral leg (P = 0.165, β = –1.1°), hip FE ROM (indexed leg P = 0.340, β = –1.6°; contralateral leg P = 0.293, β = –1.6°), or hip AA ROM (indexed leg P = 0.733, β = 0.3°; contralateral leg P = 0.943, β = 0.1°). A significant effect of sex (male-female) was observed for hip FE ROM (indexed leg P = 0.015, β = –4.3°; contralateral leg P = 0.005, β = –4.8°) and hip IE rotation ROM of the indexed leg only (P = 0.021, β = –2.1°), where females had a greater ROM for both hip FE and IE ROM than males. Further, a significant effect of BMI was observed for hip IE ROM for the contralateral leg (P = 0.001, β = –0.4°) with findings for the indexed leg close to the 0.05 cutoff (P = 0.064, β = –0.3°), where hip IE ROM

Table 2. Child Health Assessment Questionnaire outcomes for youth with juvenile idiopathic arthritis (JIA), their typically developing healthy peers, and pair differences*

Outcome	Control (n = 35)	JIA (n = 29)	Pair differences (JIA–control) (n = 29)
Pain (0–3)			
Mean ± SD	0.3 ± 0.6	0.4 ± 0.5	0.2 ± 0.8
Median (IQR)	0.0 (0.0, 0.2)	0.3 (0.0, 0.7)	0.0 (–0.1, 0.6)
Range: minimum, maximum	0.0, 2.0	0.0, 2.3	–2.0, 2.3
Global evaluation (0–3)			
Mean ± SD	0.1 ± 0.2	0.6 ± 0.8	0.5 ± 0.8
Median (IQR)	0.0 (0.0, 0.0)	0.3 (0.0, 0.7)	0.3 (0.0, 0.6)
Range: minimum, maximum	0.0, 0.7	0.0, 2.8	–0.7, 2.8
Disability index (0–3)			
Mean ± SD	0.0 ± 0.1	0.2 ± 0.3	0.2 ± 0.3
Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.4)	0.0 (0.0, 0.4)
Range: minimum, maximum	0.0, 0.3	0.0, 0.9	–0.3, 0.9

* IQR = interquartile range.

Table 3. Fixed effects outcomes of the multivariate model for the indexed leg*

Outcomes and fixed effect	β	SE	DF	*t*-value	*P*
Hip FE					
Group	−1.6	1.6	255	1.0	0.340
Age	0.2	0.4	255	0.6	0.543
Sex	−4.3	1.8	255	−2.5	0.015†
Body mass index	0.0	0.3	255	0.1	0.902
Maximum knee flexion	0.4	0.1	255	4.3	0.001†
Hip AA					
Group	0.3	0.8	255	−0.3	0.733
Age	0.1	0.2	255	0.5	0.585
Sex	0.4	0.8	255	0.5	0.621
Body mass index	0.0	0.1	255	−0.1	0.919
Maximum knee flexion	0.1	0.0	255	2.6	0.010†
Hip IE					
Group	−1.9	0.8	255	2.3	0.023†
Age	0.0	0.2	255	0.0	0.967
Sex	−2.1	0.9	255	−2.3	0.021†
Body mass index	−0.3	0.1	255	−1.9	0.064
Maximum knee flexion	0.0	0.1	255	0.8	0.430

* AA = adduction/abduction; DF = degrees of freedom; FE = flexion/extension; IE = internal/external rotation.
† Statistically significant.

decreased with participant BMI. The magnitude of maximum knee flexion during the SLS task had a significant effect on hip FE ROM (indexed leg $P = 0.001$, $\beta = 0.4°$; contralateral leg $P = 0.001$, $\beta = 0.5°$), and hip AA ROM (indexed leg $P = 0.010$, $\beta = 0.1°$; contralateral leg $P = 0.002$, $\beta = 0.2°$), where greater maximum knee flexion was associated with greater hip FE and AA ROM. Further, the effect of maximum knee flexion angle on hip IE ROM of the contralateral leg was close to the 0.05 cutoff ($P = 0.067$, $\beta = 0.1°$). No further fixed effects met the criteria for a significant effect. Assessment of the random effect (matched pairs) indicates that the variability explained by differences within pairs was low (0.12) compared to the variability across participants (6.0).

DISCUSSION

The findings of this investigation provide evidence for aberrant hip joint posture and movement of the more involved leg in youth with JIA who performed an SLS task. Despite low disease activity, youth with JIA performed the SLS with smaller hip IE rotation ROM than their healthy matched peers. These findings may indicate a possible strength deficit of the gluteal muscles of the indexed leg of youth with JIA and inform targets for physical therapy to mitigate potential injury risk factors associated with aberrant hip posture and movement control in sports participation.

Oligoarticular (44.8%) and polyarticular (48.3%) JIA were the main disease subtypes for youth with JIA in this cohort, with 6.9% of youth with JIA diagnosed with enthesitis-related JIA. Disease management (disease-modifying antirheumatic drugs [71%], biologics [36%], and intraarticular steroid injections [32%]) appeared to be effective, with participants reporting low scores for physician and parent outcomes of disease activity, active joint count, joints with limited ROM (Table 1), and C-HAQ outcomes (i.e., pain, global evaluation, and disability index subscores) (Table 2).

The focus of this research was on the posture and movement of the hip during the SLS due to the clinical and research use of the SLS as an assessment tool of possible muscle dysfunction and weakness (23,25,26). Despite low disease symptoms, youth with JIA appeared to perform the SLS task with a smaller range of hip IE rotation ($P = 0.023$, $\beta = -1.9°$) on their more involved leg compared to their age- and sex-matched control peers (Tables 3 and 4). While the magnitude of the difference was low, the difference in hip IE ROM represents a substantial deviation away from the range observed for healthy youth (indexed leg mean ± SD 3.7 ± 3.7°). Consequently, a lower hip IE ROM for youth with JIA indicates a preference for performing the SLS task with an internally rotated hip posture. A possible contributor to a more internally rotated hip is weakness of the gluteal muscles that control hip flexion, adduction, and internal rotation (31). However, because the contributions of the musculature were not assessed directly in this study, further work is needed to clarify the role of strength in youth with JIA. Notably, symptomatic joints of the hip and feet may affect hip joint motion in youth with JIA. However, active joint counts were generally low across participants with JIA in this study, with 1 individual reporting an active hip joint and 2 individuals reporting involvement of joints of the feet.

Internal hip rotation may also be associated with a greater frontal plane knee projection angle as a result of a more internally rotated femur with respect to the pelvis. A larger frontal plane projection angle in youth athletes has been associated with a 2.7-fold greater likelihood of sustaining an acute lower-extremity injury during sports (24). Given evidence of increasing school sports participation by youth with JIA (6), these findings highlight potential risk

Table 4. Joint angle outcomes for the indexed and contralateral legs of youth with juvenile idiopathic arthritis (JIA) and their healthy peers*

	Control		JIA	
Outcome, degrees	Indexed	Contralateral	Indexed	Contralateral
Hip FE ROM	20.2 ± 7.7	20.4 ± 7.9	17.7 ± 6.9	18.7 ± 6.3
Hip AA ROM	4.5 ± 2.7	4.7 ± 2.9	4.5 ± 3.3	4.7 ± 2.8
Hip IE rotation ROM	3.7 ± 3.7	4.6 ± 3.7	1.5 ± 2.6	3.1 ± 3.0
Maximum knee flexion	47.4 ± 6.7	46.0 ± 7.2	45.1 ± 9.1	46.0 ± 7.3

* Values are the mean ± SD. AA = adduction/abduction; FE = flexion/extension; IE = internal/external rotation; ROM = range of motion.

factors for injury in youth with JIA. Further research is needed to determine the risk of injury in youth with JIA and to ascertain the links between muscle strength and hip posture and movement during dynamic movement tasks. Given the current findings, a focus on hip strengthening and neuromuscular training in youth with JIA as part of a needs-based physical therapy management approach appears to be justified.

The results identified significant effects of sex, height, and SLS task performance effects on hip ROM outcomes (Tables 3 and 5). Specifically, female youth appeared to perform the SLS task with approximately 4.5° greater hip FE ROM than males. Such sex-specific differences are in line with previous observations for the same cohort of youth performing a vertical drop jump task (20), where females displayed greater maximum hip flexion during the jump landing. Further, females appeared to perform the SLS with approximately 2° greater hip IE ROM on the indexed leg than male youth (Table 3). While the specific reasons for these sex-related differences are difficult to ascertain, differences in gluteal muscle strength could have acted as a contributing factor. Notably, the findings on sex differences have to be treated with some caution because the cohort consisted of substantially more female (69%) than male participants (31%). However, such sample differences are in line with the expected sex distributions for a population of youth with JIA (1). BMI had an apparent effect on hip IE rotation ROM, where hip IE rotation ROM decreased with increasing BMI (Tables 3 and 5). These findings may indicate a combined effect of increasing height and weight, and likely muscle strength, in controlling hip posture and movement. As expected, the findings for fixed effects indicated that the magnitude of maximum knee flexion influenced hip ROM outcomes. Hip FE ROM increased by approximately 0.4° for every 1.0° increase in maximum knee flexion angle, while hip AA and IE ROM increased by approximately 0.1° for every 1.0° increase in maximum knee flexion angle. These findings are in line with the coupling of hip flexion, adduction, and internal rotation described by Powers (31), where the hip tends to adduct and internally rotate upon flexion. These findings illustrate the importance of considering the magnitude of knee flexion in the statistical analysis due to its effects on the kinematic chain of the lower extremities.

Table 5. Fixed effects outcomes of the multivariate model for the contralateral leg*

Outcomes and fixed effect	β	SE	DF	*t*-value	*P*
Hip FE					
Group	−1.6	1.6	255	1.1	0.293
Age	0.4	0.3	255	1.0	0.306
Sex	−4.8	1.7	255	−2.8	0.005†
Body mass index	0.0	0.3	255	−0.2	0.852
Maximum knee flexion	0.5	0.1	255	4.3	0.001†
Hip AA					
Group	0.1	0.7	255	−0.1	0.943
Age	0.1	0.2	255	0.9	0.387
Sex	−0.4	0.8	255	−0.5	0.648
Body mass index	−0.1	0.1	255	−0.6	0.577
Maximum knee flexion	0.2	0.0	255	3.1	0.002†
Hip IE					
Group	−1.1	0.8	255	1.4	0.165
Age	0.2	0.2	255	1.3	0.186
Sex	−0.8	0.9	255	−1.0	0.342
Body mass index	−0.4	0.1	255	−3.3	0.001†
Maximum knee flexion	0.1	0.1	255	1.8	0.067

* AA = adduction/abduction; DF = degrees of freedom; FE = flexion/extension; IE = internal/external rotation.
† Statistically significant.

The focus of this study was on a subset of youth with unilateral or bilateral knee involvement without active ankle involvement who attended the local pediatric and transition clinics. Therefore, the results cannot be generalized across individuals with JIA. Due to the inclusion of participants age >18 years, the results relating to the C-HAQ have to be viewed with caution. Given the small sample size and low disease activity scores, an assessment of the associations between SLS performance and disease activity is currently not feasible. Importantly, muscle weakness or inactivity may have been a contributing factor to difference in hip joint posture and movement. However, muscle strength was not assessed directly in this study. Further work is needed to clarify the role of strength and movement control in youth with JIA. Joint pain, including patellofemoral pain, may act as a confounder of dynamic joint mechanics. While patellofemoral pain was not specifically considered in this study, participants expressed only mild JIA-related pain, indicating that differences in SLS performance may be due to other factors associated with JIA (e.g., muscle weakness). Further, soft tissue movement artifact may influence biomechanics outcomes. However, because the SLS is not a high-impact movement task, the influence of such an error would probably be low in this specific application.

Youth with JIA adopted an internally rotated hip joint posture of the more involved leg during an SLS, which may indicate gluteal muscle weakness and dysfunction. Based on existing evidence for biomechanical risk factors of acute knee joint injury in youth sports, these findings support the implementation of physical therapy interventions to improve muscle strength and enhance movement quality of the lower extremities. This knowledge base informs future research on the risk of injury in youth with JIA and the efficacy of physical therapy to enable a safe return to physical activity, including school sports participation, for youth with JIA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Kuntze had full access to all of the data

in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Kuntze, Brooks, Esau, Nesbitt, Benseler.

Analysis and interpretation of data. Kuntze, Nettel-Aguirre, Emery.

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REVIEW

Exploring the Preferences of Women Regarding Sexual and Reproductive Health Care in the Context of Rheumatology: A Qualitative Study

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Objective. To explore the sexual and reproductive health (SRH) care and counseling needs of young women with rheumatic diseases in the context of their rheumatology care.

Methods. Semistructured qualitative telephone interviews were conducted with female patients with rheumatic diseases ages 18–45 years (n = 30). Women were recruited from outpatient rheumatology clinics in western Pennsylvania. Interviews were audiorecorded and transcribed verbatim. A codebook was inductively developed based on the interview transcripts, and the finalized coding was used to conduct a thematic analysis.

Results. Four themes emerged from interviews: 1) women want rheumatologists to initiate conversations about SRH and to revisit the conversation over time; 2) women desire clear and complete information regarding fetal, pregnancy, and infertility risks associated with their diseases and disease-modifying antirheumatic drugs (DMARDs); 3) women want to be treated holistically, with SRH addressed in the context of their life circumstances and personal values in addition to their rheumatic diseases; 4) women generally feel that they are intermediaries between their rheumatologists and obstetrician-gynecologists (OB/GYNs), but preferred for providers to communicate directly with one another about their SRH.

Conclusion. Patients strongly desired rheumatologists to play an active role in their SRH, by initiating family planning conversations, providing SRH education in the context of their diseases and DMARDs, and directly coordinating SRH care with OB/GYNs. To meet patients' SRH needs, further work is needed to clarify the specific role of rheumatologists in providing SRH care and to identify ways to better facilitate communication between rheumatologists and reproductive health care providers.

INTRODUCTION

Women with rheumatic diseases are at greater risk of adverse pregnancy and perinatal outcomes as compared to healthy women (e.g., preeclampsia, preterm birth, intrauterine growth restriction, and fetal loss across a broad spectrum of rheumatic diseases) (1–7). Therefore, sexual and reproductive health (SRH) care and counseling are essential components of the comprehensive health care of these women. By providing SRH care and counseling, the rheumatologist may be activated to provide preventive reproductive health care that could potentially enhance patients' SRH outcomes (8).

However, patients in several studies have reported that their rheumatologists rarely address pregnancy planning or prevention, and that their various health care providers give inconsistent SRH advice and counseling (9–12). Fewer studies have evaluated what SRH-related information patients feel that they need to make informed SRH decisions, and the extent to which

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SIGNIFICANCE & INNOVATIONS

- This is the first qualitative study to explore specific preferences of women with a diverse range of rheumatic diseases regarding their sexual and reproductive health (SRH) care.
- Some patients are uncomfortable initiating SRH-related conversations with their rheumatologists and prefer for their rheumatologists to initiate and continue these conversations over time.
- Patients desire clear and complete information from rheumatologists regarding pregnancy or infertility risks related to their diseases or disease-modifying antirheumatic drugs.
- Patients want their rheumatologists and obstetrician-gynecologists to collaborate about their SRH care, and do not wish to be intermediaries between these health care providers.

these needs are met in the rheumatology context. This qualitative study explored the attitudes and preferences of reproductive-age women with a broad range of rheumatic diseases regarding their SRH needs concerning their diseases, disease-modifying antirheumatic drugs (DMARDs), and health care interactions.

PATIENTS AND METHODS

Study participants. This study was approved by the University of Pittsburgh Institutional Review Board. Patients were recruited from 2 outpatient rheumatology clinics affiliated with a large academic medical institution in western Pennsylvania. Inclusion criteria included female sex, ages 18–45 years, prior establishment of care in 1 of the 2 rheumatology clinics, and at least 1 of the following rheumatic disease diagnoses: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), spondyloarthritis (e.g., psoriatic arthritis), undifferentiated connective tissue disease (UCTD), Sjögren's syndrome, systemic sclerosis, inflammatory myopathies (e.g., dermatomyositis), or vasculitis (e.g., Takayasu arteritis, Bechet's disease).

Research coordinators reviewed clinic schedules to identify potentially eligible patients, who were subsequently approached for recruitment during their clinic visits. Interested patients provided informed consent and scheduled an interview time with the research coordinator. Interviews were conducted via phone between January and April 2019. Participants were assured of anonymity and received a $45 honorarium.

Interviews. Semistructured qualitative interviews were conducted via telephone by individuals trained in qualitative interviewing (OMS and AC). The interviews broadly explored participants' reproductive histories, experiences with contraception and abortion, their perceptions of pregnancy and childbearing in the context of their rheumatic disease, and their expectations of their rheumatologists and other providers with respect to SRH. This article focuses on patients' information needs and reproductive health care experiences in the rheumatology context.

Data collection and analysis. Interviews were audiorecorded and transcribed verbatim. Interviews were conducted until the point at which no new themes were elicited, i.e., thematic saturation (13). The interviewers perceived that thematic saturation occurred after the 26th interview; 4 additional interviews were conducted to verify that thematic saturation had been reached. This process yielded a final sample size of 30 women.

The analytic framework for this study was based in grounded theory, an inductive methodology that seeks to uncover theory directly from the data (i.e., patient interviews) and therefore allows for the discovery of novel ideas and concepts (14). Our analysis used the editing method described by Crabtree and Miller (15). In this approach, the coder engages the data without a predefined codebook and relies on the interaction with the data and with the other coders to generate codes. To help to reduce potential bias in codebook development and analysis, we involved an independent qualitative analyst (TW) in the analytic process.

The analyst and a member of the research team (OMS) used the transcript content to make a preliminary codebook. This codebook was reviewed by the principal investigator (MBT) for comprehension and clarity and to facilitate investigator triangulation. The codebook was further modified as new themes emerged during the coding process. The coders applied the final codebook to all transcripts (i.e., double-coding) (16). To assess interrater reliability, a Cohen's kappa score was calculated based on 91 individual codes generated by the 2 coders. Each code was used an average of 15 times across the 30 interviews, and the rate of agreement and disagreement between the coders was calculated for each code. Cohen's kappa was calculated to $\kappa = 0.69$, indicating substantial agreement between coders (17). However, the coders subsequently adjudicated all coding differences to full agreement. Themes identified by the coders were discussed with the principal investigator as a means of investigator triangulation. Quotations from the interviews were selected to illustrate major themes and are presented in the text by women's ages and disease diagnoses; women who shared these basic demographic characteristics (with the same age) are distinguished as either patient 1 or patient 2.

RESULTS

Thirty-three women were invited to participate, and a total of thirty women completed interviews. Demographic characteristics are shown in Table 1. The average age of participants was 35.1 years (range 21–44 years); 13% were non-Hispanic Black, 74% were non-Hispanic White, 10% were Asian, and 3% were multiracial. RA, SLE, Sjögren's syndrome, and UCTD were the most prevalent diseases. A total of 47% of women did not have children, and 2 women were pregnant. Nineteen women were employed,

Table 1. Demographic characteristics (n = 30)*

Characteristic	Value
Age, mean ± SD years	35.1 ± 5.84
Race	
Black	4 (13)
White	22 (74)
Asian	3 (10)
Multiracial	1 (3)
Relationship status	
Single	11 (37)
Married	14 (47)
Divorced	2 (7)
Children	
0	14 (47)
1	7 (23)
2	5 (17)
≥3	4 (13)
Pregnant at interview	2 (7)
Diagnosis†	
RA	7 (23)
SLE	7 (23)
Sjögren's syndrome	5 (17)
UCTD	3 (10)
Spondyloarthritis	2 (7)
DMARD usage	28 (93)

* Values are the number (%) unless indicated otherwise. DMARD = disease-modifying antirheumatic drug; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; UCTD = undifferentiated connective tissue disease.
† The following diseases were each reported by 1 patient (3%): dermatomyositis, Behçet's disease, granulomatosis with polyangiitis, Takayasu arteritis, psoriasis, mixed connective tissue disease, psoriatic arthritis, autoimmune hepatitis.

7 were unemployed, 1 woman was an undergraduate student, and 3 women did not share current or past employment information. Four distinct themes emerged from the interviews, which are summarized below.

Theme 1: women want rheumatologists to initiate conversations about SRH and to revisit the topic over time. Women in the study expressed a strong preference for rheumatologists to initiate discussions about SRH, particularly at their first clinic visit, as described by 1 patient:

> "I think an initial conversation and opening the door to conversations about sexual and reproductive health on the initial visit is really helpful in building that relationship and that line of communication with the rheumatologist." (age 34 years, spondyloarthritis)

While some women felt confident initiating SRH conversations with their rheumatologists, nearly half of participants did not feel comfortable introducing these topics, as described by 1 patient:

> "I would just say [the rheumatologist] should bring it up. I know with my [rheumatologist], they didn't bring it up, I brought it up. It made it even more uncomfortable when I brought it up because of my age. I was still kind of shy, I guess, and it was hard for me to bring it up. I think if they would bring it up once in a while it would make it more open, you know?" (age 29 years, SLE, patient 1)

Participants also expressed that as their pregnancy plans and desires were likely to change over time, they preferred for SRH counseling to be addressed longitudinally by their rheumatologists. One patient, who indicated that her family planning goals had changed since establishing care with her rheumatologist, mentioned a misconception about the safety of azathioprine in the context of pregnancy:

> "[My rheumatologist] was relieved that I told her that I wasn't planning on getting pregnant. But the fact that I've been married for 5 years now and my husband wants his own kids… I'd like the option [for pregnancy] in the future. My friend told me that it takes 8 months to get off the [azathioprine] to get pregnant, but my rheumatologist and I haven't talked in detail or anything. I see [my rheumatologist] every 4 months. I'm not satisfied with the response that I get from her because [my reproductive goals] have changed… and I'd like to know if I could actually conceive someday… But I don't bring it up [with my rheumatologist]. I haven't for a year." (age 35 years, SLE, patient 1)

Women generally preferred for SRH conversations to occur at least several times a year, with approximately half of patients expressing that they preferred for SRH to be discussed at every rheumatology visit:

> "I would just say always keep that conversation on the table. Like, I think it is good to at least check in on the subject every visit with rheumatologists. I really think that, as a female at my age, I would expect that my PCP [primary care provider], my gynecologist, and my rheumatologist are all going to check in on that subject because, you know, that's pertinent to my real life right now and my real health situation, and it's, like, a big deal, it's a really big deal." (age 29 years, SLE, patient 2)

While many women used websites, blogs, or chat groups to gain information about SRH, they preferred for SRH information to be delivered by rheumatologists and other health care providers:

> "I googled and it was saying how a baby can develop lupus in utero and you hear about lupus and all these bad things about it, so it kind of freaked my boyfriend out about that, but you still have to sit down and talk to your doctor and see what they say." (age 31 years, Sjögren's syndrome)

Theme 2: women desire clear and complete information from rheumatologists regarding fetal risks, pregnancy risks, medication risks, and risk of infertility associated with their diseases. Along with a regular assessment of pregnancy goals and plans, women wanted

rheumatologists to provide individualized and accurate information regarding risks of pregnancy in the context of their rheumatic diseases and overall health. Women preferred for rheumatologists to be "black and white" about the possible risks related to pregnancy and to "not sugarcoat" the possible complications of pregnancy (age 31 years, UCTD). Rather than being protected from information "because they don't want me to worry about something" (age 25 years, Sjögren's syndrome), patients desired transparency about potential outcomes prior to making the decision to conceive. As described by 1 woman,

> "Really, I just expect honest answers, like I really appreciate how knowledgeable he [my rheumatologist] is on it and how honest he is with me about… with the reality of it. You know, lupus is not a good disease; it's a really brutal, ugly disease that manifests in a lot of ways, this being one of them, and I want to be prepared for the future. So I appreciate that he is able to tell me what this is really going to look like, and what's going to help me have the smoothest pregnancy." (age 29 years, SLE, patient 1)

Other women also expressed that they wanted their rheumatologists to address whether they had an increased risk for infertility related to their rheumatic diseases and DMARDs, and that they would be interested in learning about assisted reproductive technologies.

> "I mean, I would hope they wouldn't be afraid to have that discussion [about fertility] early because I do know women who've been able to have children. I know that's difficult for some, but if you had that discussion early before you start taking all those harsh medications, I think your doctors could take that into consideration that that's something you really want in your life and can adjust their plan to fit what it is that you want. I just think they need to be vocal about it right away." (age 35 years, SLE, patient 1)

All women expressed concerns about the safety of their DMARDs during pregnancy, primarily citing concerns about the potential effects on the health and development of their children. As one woman explained, "I wouldn't want to do anything to jeopardize the pregnancy, I wouldn't want to do anything to jeopardize the health of the child" (age 43 years, UCTD). Most women were generally aware of which of their DMARDs were potentially teratogenic, either due to physician counseling or their own research. Some women expressed that they would be "terrified to take [my] medications" (age 39 years, Takayasu arteritis) in the event of pregnancy. Women felt that rheumatologists should educate patients about DMARD safety in the context of SRH care and counseling.

> "I think that's a big thing, just being aware of medications that you're going to go on or if you want to plan on having a child, what you need to do in order to do that because you want to obviously not have any of those things in your system for so long if you're going to try to have one because then that could be bad too." (age 38 years, RA)

Several women also indicated that while they were reluctant to use DMARDs during pregnancy, they would generally follow their physician's recommendations regarding medication use during pregnancy. This response emerged primarily from patients who had reported that their rheumatologist regularly provided education on medication safety in the context of SRH care.

> "[My rheumatologist] is always asking if I'm using some sort of birth control and reminding me about the complications that the medication and things that could happen if I were to get pregnant. He always iterates that I need to be using some type of birth control." (age 43 years, spondyloarthritis)

Other women received less support from their rheumatologists in terms of DMARD management regarding pregnancy or fertility. As one woman described, "When he [my rheumatologist] prescribed medication [methotrexate] for me, I don't think he asked me if I would want kids" (age 35 years, Sjögren's syndrome). Another woman, who was pregnant at the time of interview, was unsure of the effects of her medications when she initially learned she was pregnant but decided to manage her own regimen: "I kind of self-discontinued my medication and I didn't know if that was OK to do or if I'd be hurting myself or my baby." (age 34 years old, spondyloarthritis)

Theme 3: women want to be treated holistically, with SRH addressed in the context of their life circumstances and personal values as well as their rheumatic disease. Though women acknowledged that their rheumatic diseases were important to consider with respect to pregnancy, they also underscored the importance of stable partnerships, financial stability, completion of education, reaching an appropriate age, and/or feeling it would be "the right time for our family" (age 31 years, UCTD). Women wanted their rheumatologists to acknowledge that factors beyond their rheumatic disease were integral in pregnancy planning.

> "I think people when they get so focused on their specialty, sometimes they're not thinking about how that can affect other aspects of someone's life… Thinking holistically about their approach to an individual's care, they need to consider other parts of their life, mental, physical, and what your plans are, what your life is about." (age 34 years, RA)

Another woman described how her disease management did not reflect recent changes in her reproductive goals and plans:

> "Rheumatologists don't really make [SRH] a priority. They care more about how you're feeling day-to-day… When I first started to see my rheumatologist, I was in law school… I would have liked to have foreseen that maybe 5 years from

then I would have been engaged and getting married… I would have liked her [rheumatologist] to talk with me about this before ever starting the chemo drugs. I would have liked her to say, OK, before we start, do you want to freeze any eggs? I would have liked to have known that 10 years ago. I would have frozen my eggs." (age 35 years, SLE, patient 2)

Theme 4: women generally feel that they are intermediaries between their rheumatologists and obstetrician-gynecologists (OB/GYNs). Most women expressed frustration that they were required to relay information between their rheumatologists and OB/GYNs and felt that communication between specialties is the responsibility of health care providers. These patients expressed that they would prefer rheumatologists to consult with their OB/GYNs in advance of and during pregnancy.

"I think providers in a sense should be able to collaborate amongst themselves. So if I'm needing my gynecologist to communicate with my rheumatologist, I shouldn't be a middle person for that, so they should be able to connect and discuss my plan of care. But right now, how it's set up, I am the mediator for that plan of care." (age 34 years, RA)

The preference for care coordination was underscored by the experiences of several women, who believed their OB/GYNs were not sufficiently knowledgeable about the rheumatic diseases, or whose advice conflicted with their rheumatologists':

"Before we were thinking about trying [to conceive], we were referred to maternal fetal medicine because I'm high-risk pregnancy… my rheumatologist seemed really supportive of me wanting to get pregnant… my [maternal fetal medicine physician] said, 'Are you sure you want to do this? You know, a million horrible things could happen.' Like, I know, that's why I'm coming to you, so they don't." (age 29 years, SLE, patient 2)

Some women were not sure which of their providers was responsible for managing their SRH. As expressed by 1 patient:

"I'd probably [talk to] my OB because I don't know how much my rheumatoid arthritis doctor knows. You know what I mean? Because she's female, I'd probably go to my OB, I wouldn't know who else to go to." (age 39 years, RA)

Besides updating other providers on changes in patient management, most women expected their rheumatologists to guide their OB/GYNs on disease-specific issues that may arise during pregnancy or pregnancy planning:

"I expect [my rheumatologist] to advise my OB/GYN when it comes time. To tell them what I have and what to watch out for. For instance, to watch out for lupus in the infant or in the womb… Not all OB/GYNs I've seen know about that." (age 35 years, SLE, patient 2).

DISCUSSION

A patient-centered approach to SRH care in the rheumatology context is required to better meet the information needs and priorities of patients with rheumatic diseases. However, few studies to date have explored what patients need from their rheumatologists regarding their SRH care. Our qualitative study indicates that women strongly desire for rheumatologists to assume a prominent and sustained role in SRH care and counseling.

Patients wanted rheumatologists to provide SRH care and conversations beginning at their first clinic visit, and to continue to address SRH at subsequent visits. Many patients felt uncomfortable initiating SRH conversations with rheumatologists. However, our prior qualitative study involving a national sample of rheumatologists found that rheumatologists prefer for patients to initiate conversations regarding SRH (12). This preference discrepancy may explain why various studies report that SRH conversations rarely occur between rheumatologists and female patients of reproductive age. For example, 1 patient survey reported that 59% of women with SLE who were at risk of unintended pregnancy did not receive any contraceptive counseling within the prior year (9). A separate patient survey found that only 32% of young women with autoimmune diseases, including SLE and RA, had received family planning care from rheumatologists or other health care providers (10). An important message to rheumatologists is that even if reproductive-age female patients do not initiate questions about their SRH, it should not be assumed that they do not have SRH-related questions or concerns that are within the purview of the rheumatologist. Future quality initiatives are needed to explore how SRH can be better operationalized in the rheumatology clinical context. For example, prompts could be built into the routine office workflow via either the electronic medical record or intake forms to remind rheumatologists to address relevant SRH care with patients (18,19).

Patients also had strong preferences regarding the information they wished to be conveyed in SRH conversations with rheumatologists. Patients overwhelmingly desired clarity about their specific pregnancy-associated risk factors, effects of their diseases and DMARDs on their fertility, and safety and compatibility of their DMARDs in the context of pregnancy planning. These findings suggest that patients need their rheumatologists to address medication safety and side effects specifically in the context of SRH. Because participants were hesitant to use DMARDs during pregnancy, rheumatologists may need to underscore that many DMARDs are pregnancy-compatible. Patients may also need to learn that discontinuation of treatment may lead to undertreated, uncontrolled disease that will increase a patient's risk of maternal and fetal morbidity and mortality (20–22). This understanding is particularly important, because previous studies have found that 31% to 67% of women with rheumatic diseases self-discontinue even safe DMARDs during pregnancy (23–25). Resources about DMARD safety in pregnancy include the American College of

Rheumatology Reproductive Guideline (26), European Alliance of Associations for Rheumatology consensus guidelines (27,28), the patient-oriented MotherToBaby website by the Office of Teratology Information Specialists (29), and the provider-oriented Healthy Outcomes in Pregnancy with SLE through Education of Providers website (HOP-STEP, www.lupuspregnancy.org).

Another key finding of our study was that patients desired greater collaboration between their rheumatologists and OB/GYNs regarding their SRH care, without relying on the patients to serve as intermediaries for communication. Studies suggest that multidisciplinary collaboration may help women to gain better access to reproductive health care; for example, women who received care from both a rheumatologist and gynecologist in several studies have been more likely to receive contraception and highly effective contraception methods than women who received care from a rheumatologist alone (9,30). Referral to an OB/GYN may be a good first step for rheumatologists to facilitate SRH care for patients. A future challenge is to find ways to better coordinate care between rheumatologists and OB/GYNs or other reproductive health providers, particularly among providers practicing in different medical systems. Furthermore, rheumatologists must also not assume that patients have an OB/GYN who will provide SRH care; our prior work indicated that only one-third of young women with rheumatic diseases had visited an OB/GYN over a multiyear period, even though they saw rheumatologists more regularly (30).

This study has several limitations. Although we achieved thematic saturation, and patients saw different rheumatologists across the health care system, we did recruit from a single health care system. Thus, sampling bias could affect the generalizability of our findings. However, our questions were designed to elicit patients' general preferences for SRH care in the rheumatology context. Outcomes of our study may have further been affected by selection bias, because patients who entered the study may have had greater interest in reproductive planning than those who chose not to participate. However, 91% of women who were approached for the study ultimately chose to participate, which may suggest that SRH is a major concern for many female patients. We chose to prioritize women's privacy and confidentiality by limiting the number of demographic characteristics that we collected, but in retrospect, assessing women's educational attainment could have helped us to better contextualize their information needs as described in Theme 2. Finally, our findings may be affected by social acceptability bias, in that participants might have answered questions based on social acceptability rather than expressing their real perspectives or experiences. We tried to mitigate this bias by ensuring that the interviewers were not rheumatologists or involved in the health care of the participants.

To summarize, this study found that patients are deeply invested in their reproductive health and that they desire for their rheumatologists to provide continual SRH care and counseling and address specific SRH concerns related to their diseases and DMARDs. Future work is needed to clarify the specific role of rheumatologists with respect to meeting these specific SRH needs, streamlining communication between rheumatologists and other reproductive health providers, and better coordinating the SRH needs of reproductive-age women with rheumatic diseases.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Birru Talabi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Chodoff, Birru Talabi.

Acquisition of data. Stransky, Chodoff, Birru Talabi.

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Factors Associated With Time to Pregnancy in Women With Axial Spondyloarthritis: A Registry-Based Multicenter Study

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Objective. The present study was undertaken to study time to pregnancy (TTP) and factors associated with TTP in women with axial spondyloarthritis (SpA) compared to women with rheumatoid arthritis (RA).

Methods. We included 274 women with axial SpA and 317 women with RA from the Norwegian nationwide registry RevNatus. For all the women, we had retrospectively collected data on TTP, and a subgroup also had prospectively collected data. We compared TTP in women with axial SpA to women with RA using Kaplan-Meier plots and a log rank test. To identify factors associated with TTP, we used Cox proportional hazards regression.

Results. TTP exceeded 12 months in 21% of women with axial SpA. In the subgroup followed prospectively, 32% had TTP that exceeded 12 months. Longer TTP was associated with older age, nulliparity, and longer disease duration, with hazard ratios of 0.97 (95% confidence interval [95% CI] 0.94–1.00), 0.66 (95% CI 0.50–0.88), and 0.94 (95% CI 0.91–0.98), respectively. Disease activity, medication, and self-reported health-related quality of life were not associated with TTP. We found no statistically significant differences between axial SpA and RA in regard to TTP.

Conclusion. In women with axial SpA, longer TTP was associated with older age, nulliparity, and longer disease duration.

INTRODUCTION

Motherhood is important for many women regardless of whether or not they have a chronic disease. Studies have shown that women with chronic arthritis have lower fertility rates and more often are childless compared to healthy peers (1,2).

Fertility is a person's capacity to achieve pregnancy (3). Time from the start of actively trying to conceive to achieved pregnancy exceeding 12 months is often defined as subfertility (3). The prevalence of subfertility in the general population is estimated to be 9% (4). A study from 2015 demonstrated that 42% of women with rheumatoid arthritis (RA) were subfertile according to the above definition and that longer time to pregnancy (TTP) was associated with older age, nulliparity, disease activity, and use of prednisolone or nonsteroidal antiinflammatory drugs (NSAIDs) (5). Previous studies have found higher occurrence of subfertility in women with RA compared to healthy controls and women with systemic lupus erythematosus (6,7).

Axial spondyloarthritis (SpA) is a chronic inflammatory rheumatic disease affecting the spine, as well as entheses and joints, with common onset in childbearing age (8). Ankylosing spondylitis (AS), now also called radiographic axial SpA because the diagnosis requires established sacroiliitis on radiographs, was traditionally seen as a disease affecting men. After the recognition of nonradiographic axial SpA, which is axial SpA without characteristic findings on radiographs, more women are diagnosed with axial SpA. Including nonradiographic axial SpA, the male:female ratio is 2–3:1 (9). A Norwegian study found that fertility rate and occurrence of childlessness were similar in women with SpA or unspecified arthritis compared to those with RA (2). To our knowledge, there are no studies on TTP in women with axial SpA.

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SIGNIFICANCE & INNOVATIONS

- In this study on time to pregnancy in women with axial spondyloarthritis, more than one-fifth of women were subfertile.
- Longer time to pregnancy was associated with longer disease duration, older age, and nulliparity.
- Findings suggest that young women with stable axial spondyloarthritis should be encouraged not to postpone pregnancy for too long.

Our aim was to study TTP and factors associated with TTP in women with axial SpA. Also, we wanted to compare women who conceived within 12 months to subfertile women with regard to preconception disease activity, health-related quality of life (HRQoL), medication, and factors that are known to affect fertility in the general population. Hypothesizing that fertility in axial SpA is similar to that in RA, we compared women with axial SpA to women with RA.

PATIENTS AND METHODS

RevNatus registry. RevNatus is a Norwegian nationwide registry designed for prospective follow-up of women with inflammatory rheumatic diseases from the time of planning a pregnancy until 1 year postpartum (10). The registry was established in 2006 by the Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases. Enrollment in RevNatus is carried out by rheumatologists and nurses at the collaborating rheumatology units.

Women enrolled in RevNatus ideally have 7 visits at their local rheumatology unit: when planning pregnancy, in each trimester, and at 6 weeks, 6 months, and 12 months postpartum. RevNatus has a prospective design and provides data on disease activity, medication, HRQoL, TTP, and pregnancy outcomes. Although we aim to enroll women in RevNatus when they plan a pregnancy, a minority of women with axial SpA or RA were actually enrolled preconception.

Patient population. This study comprises women with axial SpA or RA enrolled in RevNatus between January 2006 and October 2018. Before 2016, RevNatus did not differentiate between radiographic axial SpA and nonradiographic axial SpA. For the present study, we included women with information on whether they had tried to get pregnant for >12 months or not, and preferably those who had information on the number of months they had tried to conceive. Women were allowed to participate more than once.

Study design and outcome variables. This study has the combination of both a prospective and retrospective design. We studied time trying to conceive in 1) the total study population, where a large proportion was already pregnant at enrollment, and 2) a subgroup of women who enrolled prior to conception. These 2 approaches yield complementary results.

The 2 main outcome variables were subfertility defined as TTP >12 months (yes/no) and TTP (months). The variable TTP >12 months (yes/no) was introduced in RevNatus in 2009, while self-reported TTP (months) was introduced in 2014. We defined TTP as months trying to conceive either resulting in pregnancy or in censoring. For women who enrolled preconception, we collected TTP prospectively either when they became pregnant or at censoring. For women who were already pregnant at the time of enrollment, self-reported data were collected retrospectively. Data were collected from hospital records for women enrolled before 2009. Other outcome variables were achieved pregnancy during the study period, live birth, and receiving fertility treatment.

The variable planned pregnancy (yes/no) was not available in RevNatus before 2016. In the analyses of the total study population, TTP = 0 months means either conceiving within the first menstrual cycle of attempting pregnancy or unplanned pregnancy.

Covariates. A rheumatology health care professional recorded information on disease characteristics, medication history, and prior pregnancies at enrollment in RevNatus. Information on disease activity, current medication, and self-reported HRQoL was recorded at each visit.

Disease activity of axial SpA was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The BASDAI gives scores between 0 and 10 (10 = maximal disease activity) based on 6 patient-reported items (11). The 3-variable Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) was used to measure disease activity in RA. The score is composed of a 28-joint count for swelling and tenderness combined with the level of CRP (12). Where available, we used preconception disease activity as a covariate. For women who were pregnant at enrollment, we used first trimester disease activity.

Self-reported HRQoL was assessed using the RAND Short Form 36 (SF-36) health survey. The SF-36 is composed of 36 questions in 8 health-related dimensions, resulting in 1 score in each dimension with value 0–100 (100 = best possible health) (13). We studied 4 dimensions that theoretically could affect sexual function preconception and the ability to conceive: mental health, vitality, bodily pain, and physical functioning. In analyses, we only used preconception SF-36 scores.

Other covariates were age, parity, smoking, body mass index (BMI), and disease duration. In addition, medication used within 1 year prior to conceiving constituted 4 dichotomous covariates (yes/no): prednisolone, NSAIDs, methotrexate (MTX), and tumor necrosis factor inhibitor (TNFi).

Statistical analysis. We compared women with axial SpA to women with RA with regard to achieving pregnancy, subfertility, TTP, fertility treatment, and giving birth to a live child. Within the axial SpA group, we also compared women who conceived within

12 months to subfertile women with regard to the covariates listed above. We used an independent samples *t*-test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables.

We compared TTP between groups using Kaplan-Meier plots and a log rank test. Furthermore, we used Cox proportional hazards regression models to explore associations between TTP and the covariates listed above in each diagnostic group. In analyses of the associations between TTP and disease duration and parity, we adjusted for age. We use the term "pregnancy ratio" for hazard ratio in Cox regression.

Two-sided *P* values less than 0.05 were considered significant. We compared Cox regression assuming independent times with Cox

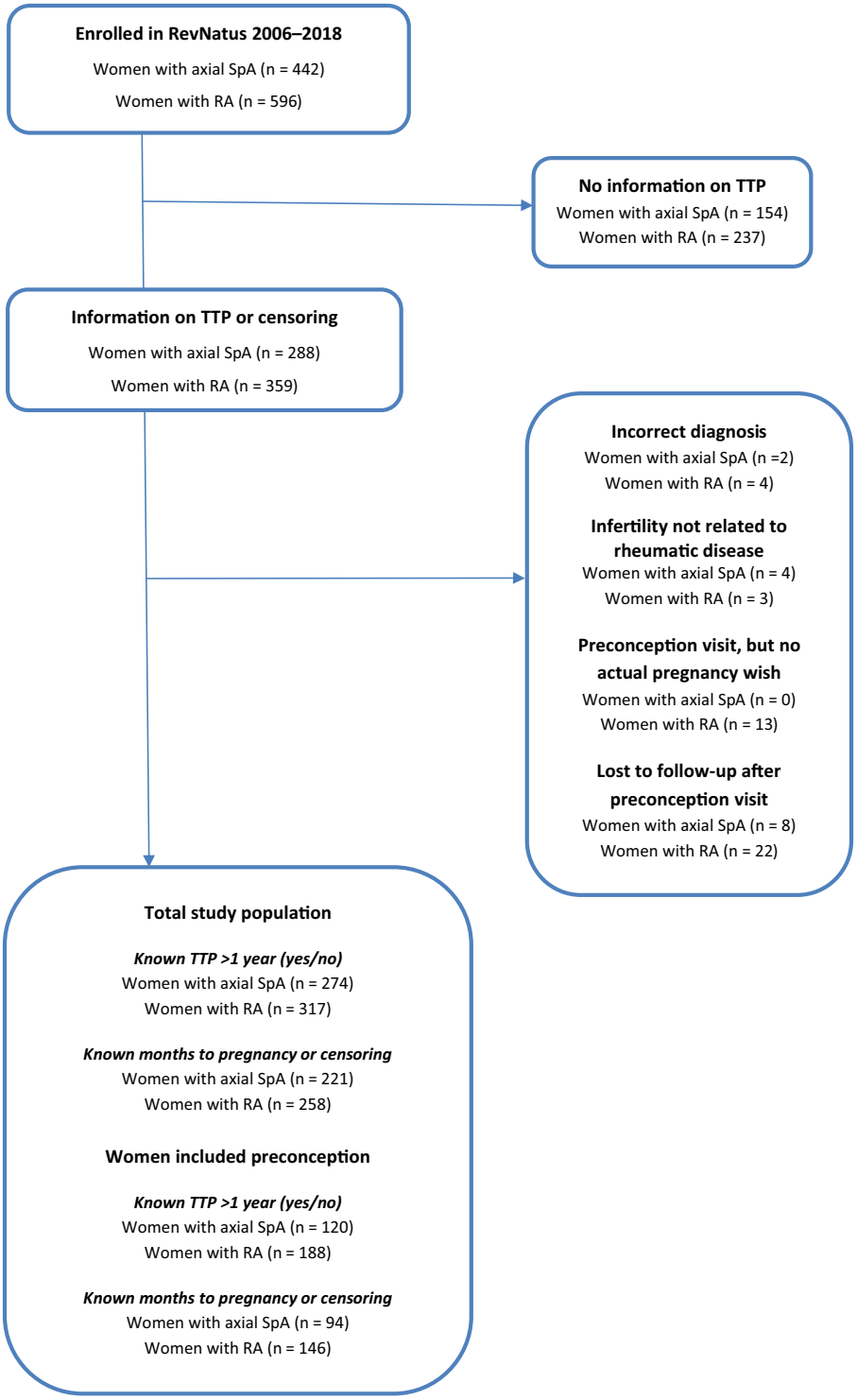

Figure 1. Flow chart showing inclusion data and data available for analyses. RA = rheumatoid arthritis; SpA = spondyloarthritis; TTP = time to pregnancy.

regression with gamma shared frailty, the latter taking into account the possible dependence between TTP in the same woman, using Stata, version 14.0. Other analyses were carried out in SPSS, version 25.0.

Ethics. The regional committee for medical and health research ethics approved this study in 2013 (REK 2013/649). Women enrolled in RevNatus gave written informed consent that data from the registry can be used for research purposes. The study is in compliance with the Declaration of Helsinki.

RESULTS

Patient inclusion data. RevNatus included 442 women with axial SpA and 596 women with RA between January 2006 and November 2018. Of these, we excluded 154 women with axial SpA and 237 women with RA with no information on TTP. Most of the excluded women were enrolled before information on TTP was routinely recorded in RevNatus. In addition, we excluded women with an incorrect diagnosis, no actual wish for pregnancy, or known infertility not related to their rheumatic disease.

As shown in Figure 1, this study comprised 274 women with axial SpA and 317 women with RA, all with data on TTP >12 months (yes/no). Of these, 154 women with axial SpA (56.2%) and 129 women with RA (40.7%) were pregnant at enrollment. Information on TTP was self-reported in 188 (68.6%) of women with axial SpA and 187 (59.0%) of women with RA. The remaining women had information on TTP that was retrieved from hospital records.

Women with information on months trying to conceive were included in the survival analyses. We included 221 women with axial SpA, of whom 94 (42.5%) were enrolled when planning pregnancy, and 258 women with RA, of whom 146 (56.6%) were enrolled when planning pregnancy. Fourteen women with axial SpA and 20 women with RA had not conceived by the end of the study period and hence were censored. Three women with axial SpA and 9 women with RA, who moved or changed their mind about pregnancy, were also censored. After confirming that Cox regression with gamma shared frailty gave the same results as Cox regression assuming independent TTP, we carried out analyses assuming all TTP to be independent.

Demographic and disease characteristics. Women with axial SpA had a median age of 31 years (range 21–46 years) and a median disease duration of 4 years (range 0–26 years). Women with RA had a median age of 32 years (range 19–44 years) and a median disease duration of 5 years (range 0–22 years). More than one-half of the women had previously given birth to a live child. In the axial SpA group, polycystic ovary syndrome was reported in 11 women (4.0%), while endometriosis was reported in 4 women (1.5%).

The majority of the study population fulfilled the Assessment of SpondyloArthritis international Society (ASAS) criteria for axial SpA and the 1987 revised criteria of the American College of Rheumatology for RA, respectively (11,14). Table 1 shows demographics and disease characteristics recorded at enrollment.

Table 1. Characteristics of the study population at baseline*

Basic characteristics	Axial SpA (n = 274)	RA (n = 317)
Age, mean ± SD years	30.7 ± 4.9	31.7 ± 4.7
BMI, mean ± SD kg/m^2	25.1 ± 4.6	25.0 ± 5.0
Smoking		
Yes	264/17 (6.4)	306/12 (3.9)
Parity		
0	272/129 (47.4)	313/155 (49.5)
1	99 (36.4)	117 (37.4)
2+	44 (16.2)	41 (13.1)
Prior pregnancy loss		
Yes	270/69 (25.6)	310/70 (22.6)
Educational level†		
Low	261/11 (4.2)	304/4 (1.3)
Intermediate	69 (26.4)	63 (20.7)
High	181 (69.4)	237 (78.0)
Disease-related characteristics		
Disease duration, years	5.2 (4.6)	6.0 (4.8)
Classification criteria fulfilled‡		
Yes	270/264 (97.8)	310/300 (96.8)
Rheumatoid factor positive		
Yes	NA	275/172 (62.5)
Anti-CCP positive		
Yes	NA	286/186 (65.0)
HLA–B27 positive		
Yes	166/125 (75.3)	NA
Psoriasis	9 (3.3)	NA
IBD§	26 (9.5)	NA
Uveitis	24 (8.9)	NA

* Values are the total no./no. (%) unless indicated otherwise. Anti-CCP = anti–cyclic citrullinated peptide; BMI = body mass index; IBD = inflammatory bowel disease; NA = not available; RA = rheumatoid arthritis; SpA = spondyloarthritis.
† Low: ≤10 years, intermediate: 10–13 years, high: >13 years.
‡ American College of Rheumatology criteria or Assessment of SpondyloArthritis international Society criteria (refs. 11 and 14).
§ Ulcerative colitis: n = 6, morbus Crohn's disease: n = 7, nonspecified IBD: n = 13.

Fertility outcomes in women with axial SpA. In the total axial SpA population, 257 women (93.8%) became pregnant, and 154 (46.2%) were already pregnant at enrollment (Table 2). Median TTP was 2 months, and 58 women (21.2%) had TTP >12 months. Twenty-one women with axial SpA (7.7%) had fertility treatment.

Among the 120 women with axial SpA followed from planning pregnancy, a smaller proportion became pregnant (103 women, 85.8%), and a more substantial proportion was subfertile (38 women, 31.7%). The median TTP was 4 months. Among the 93 women with axial SpA enrolled preconception and followed until after delivery, 75 women (80.6%) had a live birth.

Differences between fertile and subfertile women. Subfertile women with axial SpA were significantly older and had a significantly longer disease duration than women with axial SpA who conceived within 12 months (Table 3). They were also significantly more likely to be nulliparous and have been smokers prior to conception. There were no differences with regard to disease activity or medication.

Table 2. Fertility-related outcomes*

Outcomes	Axial SpA	RA	*P*
Total study population			
Achieved pregnancy	274/257 (93.8)	317/288 (90.9)	0.18†
Months to pregnancy, no.	204	229	
Mean ± SD	5.8 ± 12.1	6.9 ± 15.4	0.41‡
Months to pregnancy or censoring, no.	221	258	
Median (range)	2 (0–126)	3 (0–137)	0.12§
Time to pregnancy >1 year¶	58 (21.2)	75 (23.7)	0.47†
Fertility treatment[1]			
Yes	253/21 (8.3)	290/38 (13.1)	0.07†
Included preconception			
Achieved pregnancy	120/103 (85.8)	188/159 (84.6)	0.76†
Live birth#			
Yes	93/75 (80.6)	147/124 (84.4)	0.45†
Months to pregnancy or censoring, no.	94	146	
Median (range)	4 (0–113)	3 (0–137)	0.62§
Time to pregnancy >1 year, no. (%)¶	38 (31.7)	56 (29.8)	0.72†

* Values are the total no./no. (%) unless indicated otherwise. RA = rheumatoid arthritis; SpA = spondyloarthritis.
† By Pearson's chi-square test.
‡ By Independent samples *t*-test.
§ By log rank test.
¶ Including women not achieving pregnancy.
# Among women achieving pregnancy having gone through the entire pregnancy.

Women with axial SpA reported considerable pain and low vitality preconception, with a mean SF-36 bodily pain score of 55.1 and a mean SF-36 vitality score of 46.3. However, we found no significant differences in self-reported HRQoL between subfertile and fertile women with axial SpA. Subfertile women with RA were also older and more often nulliparous; otherwise, there were no differences compared to fertile women with RA (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24233/abstract).

Table 3. Differences between subfertile and fertile women with axial spondyloarthritis*

Variable	Subfertility†		
	Yes (n = 58)	No (n = 216)	*P*
Age, years (n = 274)	32.2 ± 5.6	30.3 ± 4.6	0.022‡
Nulliparity, % (n = 272)	38 (65.5)	91 (42.5)	0.002§
Smoking, % (n = 264)	9 (15.8)	8 (3.8)	0.003§
Duration, years (n = 236)	7.3 ± 5.3	4.6 ± 4.1	0.001‡
BMI, kg/m^2 (n = 261)	25.1 ± 4.9	25.1 ± 4.5	0.96‡
BASDAI score (n = 188)	2.9 ± 1.8	3.4 ± 2.3	0.22‡
Mental health (n = 101)	72.8 ± 14.4	75.5 ± 15.1	0.40‡
Vitality (n = 100)	48.3 ± 19.9	45.2 ± 23.3	0.51‡
Bodily pain (n = 102)	54.4 ± 25.3	55.5 ± 23.5	0.83‡
Physical function (n = 101)	80.9 ± 19.3	79.6 ± 18.5	0.75‡
NSAIDs, % (n = 129)	10 (26.3)	28 (30.8)	0.61§
Prednisolone, % (n = 127)	1 (2.6)	4 (4.5)	1.00¶
Methotrexate, % (n = 271)	4 (7.0)	12 (5.6)	0.75¶
TNFi, % (n = 271)	32 (56.1)	101 (47.2)	0.23§

* Values are the mean ± SD unless indicated otherwise. BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BMI = body mass index; NSAIDs = nonsteroidal antiinflammatory drugs; TNFi = tumor necrosis factor inhibitor.
† Time to pregnancy >12 months.
‡ By Independent samples *t*-test.
§ By Pearson's chi-square test.
¶ By Fisher's exact test.

Variables associated with TTP. Cox regression analyses showed that older age, longer disease duration, and nulliparity were associated with longer TTP in the total axial SpA population (Table 4). Longer disease duration and nulliparity were still associated with longer TTP after adjusting for age, with pregnancy ratios of 0.95 (95% confidence interval [95% CI] 0.92–0.99) and 0.62 (95% CI 0.47–0.82), respectively. Women who smoked had a pregnancy ratio of 0.77, but the association was not statistically significant. Scores of the BASDAI or HRQoL were not significantly associated with TTP. Preconception use of NSAIDs, prednisolone, MTX, or TNFi were not significantly associated with TTP.

In the total RA population, younger age, multiparity, and MTX use preconception were associated with shorter TTP (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24233/abstract). Cox regression analyses including only women enrolled preconception did not show a significant association between nulliparity and longer TTP. Apart from this, results were substantially the same (see Supplementary Tables 3 and 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24233/abstract). Fertility outcomes in axial SpA were comparable to those in RA.

Fertility outcomes in axial SpA compared to RA. As shown in Table 2, subfertility was more common in women with RA when including the total study population while more common in axial SpA when considering only the women who were enrolled

Table 4. Cox regression analyses for occurrence of pregnancy in women with axial spondyloarthritis 1 covariate at a time*

Variable	Pregnancy ratio	95% CI	*P*
Age, per year (n = 221)	0.97	0.94–1.00	0.030
Nulliparity (n = 219)	0.66	0.50–0.88	0.004
Smoking (n = 221)	0.77	0.54–1.11	0.16
BMI, per unit (n = 196)	1.01	0.99–1.04	0.37
Duration, per year (n = 221)	0.94	0.91–0.98	0.001
BASDAI score, per point (n = 152)	1.08	0.99–1.18	0.072
Mental health (n = 78)	1.00	0.99–1.02	0.93
Vitality (n = 77)	0.99	0.98–1.00	0.14
Bodily pain (n = 79)	1.00	0.99–1.01	0.29
Physical function (n =78)	0.99	0.98–1.01	0.31
NSAIDs (n = 101)	1.28	0.80–2.04	0.31
Prednisolone (n = 99)	1.91	0.77–4.74	0.17
Methotrexate (n = 220)	0.99	0.55–1.77	0.96
TNFi (n = 220)	0.88	0.67–1.16	0.38

* 95% CI = 95% confidence interval; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BMI = body mass index; NSAIDs = nonsteroidal antiinflammatory drugs; TNFi = tumor necrosis factor inhibitor.

prior to conception. However, differences between diagnostic groups were small and not statistically significant. The Kaplan-Meier plot in Figure 2 shows that median TTP in women with axial SpA was 2 months (95% CI 1.3–2.7) compared to 3 months (95% CI 2.3–3.7) in women with RA, but the difference was not statistically significant (log rank test $P = 0.112$).

DISCUSSION

In this large registry-based study on fertility in axial SpA, we found a median TTP of 4 months in the subgroup of women enrolled when planning a pregnancy. Of these women, 32% were subfertile, defined as attempting to conceive longer than 12 months. In the total study population, where approximately one-half were already pregnant at enrollment, the median TTP was 2 months, and 21% were subfertile. Longer TTP was related to older age, nulliparity, and longer disease duration. There were no significant differences between women with axial SpA and women with RA in fertility-related outcomes.

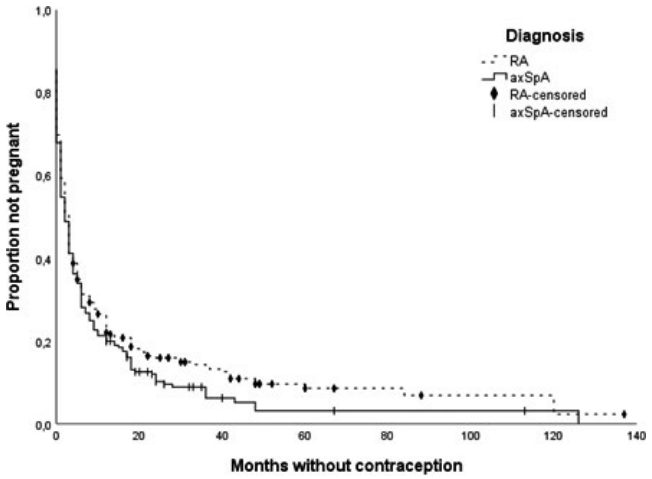

Figure 2. Kaplan-Meier plot for time to pregnancy in women with axial spondyloarthritis (axSpA) compared to women with rheumatoid arthritis (RA).

To our knowledge, this is the first study on TTP in women with axial SpA. A Norwegian study demonstrated a lower fertility rate in women with RA and in a group of women with SpA or unspecified arthritis compared to healthy peers (2).

A study from 1999 showed a prevalence of subfertility of 16% in a general Western European population and a median TTP of 3 months (15). A later study based on population surveys from 25 countries found a mean prevalence of subfertility of 9% (4). In this setting, subfertility appears to be more common in women with axial SpA despite a median TTP similar to that of the general population. However, for direct comparison to the general population, we should have included a healthy control group.

The associations between subfertility and the factors older age, nulliparity, and smoking are well known (16–18). Lack of statistical power may explain why we did not find a significant association between nulliparity and longer TTP in the subgroup that was enrolled preconception. We have no reason to believe that the association between parity and fertility is different in women with axial SpA planning their pregnancy than in healthy women. Mean age and frequency of smoking in the study population were similar to mean maternal age at time of childbirth and the frequency of smoking in early pregnancy in the general Norwegian population (19). Thus, these factors do not seem to explain why subfertility is more common in women with axial SpA. Contrary to what is reported for the general population (20), we did not find an association between a high BMI and longer TTP. It is possible that some women struggling to conceive intentionally lose weight in order to improve fertility, diluting a negative association between a high BMI and fertility.

In the current study, the only disease-related factor associated with longer TTP was disease duration. This association has not been demonstrated in RA or systemic lupus erythematosus (5,7). Studies have shown reduced levels of anti–müllerian hormone (an indicator of ovarian reserves) in women with AS and RA compared to healthy controls (21,22). One study showed that HLA–B27 positivity was associated with lower anti–müllerian hormone (21). Whether some aspect of the pathophysiology of axial SpA over time affects fertility via reduced ovarian reserves or other biologic mechanisms is not known.

The current study confirmed previous findings of poor self-reported HRQoL with regard to vitality and pain in women with axial SpA and RA (7,23). Studies have shown an association between HRQoL and sexuality in women with axial SpA (24,25). We found no association between HRQoL and TTP that could explain an increased prevalence of subfertility.

In the current study, ~19% of women with axial SpA experienced pregnancy loss, compared to ~15% reported in the general

population (26,27). However, in order to study the risk of pregnancy loss in axial SpA, we need population-based case–control studies.

Regarding RA, we found that TTP exceeded 12 months in 24% of the total study population and 30% of the women enrolled preconception. In accordance with our study, a retrospective TTP study by Jawaheer et al found subfertility in 25% of women with RA (6). This study included a healthy control group and was able to demonstrate significantly longer TTP in women with RA. In the Dutch PARA cohort, Brouwer et al found a higher occurrence of subfertility; 42% of 245 women with RA had TTP exceeding 12 months (5). Brouwer et al demonstrated that TTP was associated with age, nulliparity, disease activity, and preconception use of NSAIDs or prednisolone. Similar to the current study, the PARA study had the combination of a prospective and retrospective design; 25% of women were pregnant at inclusion. There are several possible reasons for different findings regarding subfertility. The PARA study was conducted before 2008, while we included women until 2018. Only 15% of the women in the PARA cohort had ever used a biologic disease-modifying antirheumatic drug, while in our study 44% used TNFi in the last year before pregnancy. Additionally, our population had lower disease activity, with a mean DAS28-CRP score of 2.6 versus 3.6 in the PARA cohort.

The low disease activity in our study population, both in RA and axial SpA, may also explain why we found no association between disease activity and TTP. Our previous study of women with axial SpA in RevNatus revealed no significant difference between preconception BASDAI score and first trimester BASDAI score (28). Thus, we do not think that using the first trimester BASDAI score where the preconception score was missing relevantly affected our results.

One reason why we did not find associations between TTP and the use of NSAIDs or prednisolone may be that few women in our study population used prednisolone or NSAIDs continuously. Also, women struggling to conceive might have discontinued NSAIDs in order to facilitate pregnancy, diluting a possible adverse effect of NSAIDs on fertility. Reassuringly, we found no association between preconception TNFi and TTP.

Surprisingly, we found that MTX preconception was associated with shorter TTP in women with RA. Animal studies have suggested a harmful effect of MTX on ovarian reserve (29). In the PARA cohort, there was no association between MTX and TTP (30). We found no known variables explaining why women with RA using MTX preconception had shorter TTP in our study; age, disease duration, and disease activity did not differ significantly compared to those of women not using MTX. We can only speculate about reasons for the association. Women on MTX could have had stable disease activity for a longer period of time before deciding to get pregnant, which may have improved fertility. It is also possible that women who discontinue MTX because they desire to become pregnant have more concrete pregnancy plans and are therefore more aware of the importance of frequency and timing of intercourse.

Fertility is a complex biologic process involving gametogenesis, sperm transport, tubal patency, hormonal preparation of the endometrium, implantation, and the viability of the embryo. In addition, there are several psychosocial and cultural factors involved. Although they only tell part of the story, studies on TTP have proved useful in identifying factors with adverse effects on fertility (31,32).

Retrospectively studying TTP in a group of women who have achieved pregnancy does not yield the same data as prospectively studying TTP in a group of women trying to conceive. In the former group, the sampling unit is the pregnancy, while in the latter the sampling unit is the attempt to become pregnant. In the current study, we used a combination of prospective and retrospective approaches. The main strength of the prospective approach is that it also includes infertile women. In addition, in prospective studies of TTP, it is possible to address underlying biologic processes. However, since RevNatus was not originally designed for studying fertility, we did not have information on ovulation, factors associated with male fertility, or frequency and timing of intercourse.

TTP studies that only include women who are already pregnant may be affected by right truncation bias so that women with longer TTP tend not to be included. Although excluding infertile women and underrepresenting subfertile women, the retrospective approach offers complimentary knowledge. This approach may include unplanned pregnancies not represented in a prospective study. Although telling less about fertility in a strictly biologic sense, studying the total population of women with axial SpA enrolled in RevNatus gives us useful knowledge on how long it takes for women with axial SpA to achieve pregnancy in a real-life setting. Generally, populations in retrospective TTP studies are considered more representative of the target population (32).

Despite being retrospective, recall bias is minimal in TTP studies where the study population is comprised of pregnant women (32). However, this design may cause other types of bias (32). We already mentioned 2 examples of possible behavior change bias: losing weight and discontinuing NSAIDs in order to achieve pregnancy in women struggling to conceive. It is not possible to examine whether our study was affected by planning bias because information on the planning of pregnancy was not recorded in RevNatus before 2016. In the current study, we included all women with TTP of 0 months regardless of pregnancy being planned or unplanned. We do not suspect pregnancy recognition bias. We included miscarriages, but the timing of recognition of pregnancy did not differ according to diagnoses or other relevant variables.

We do not suspect medical intervention bias. Fertility treatment was more common in women with RA than in women with axial SpA, but TTP in women referred to fertility treatment was comparable between diagnoses, showing no tendency for earlier referral of women with RA. When censoring TTP at 14 months in women receiving fertility treatment, as recommended by Joffe et al (32), the median TTP in both diagnoses was the same as in the original analyses. Left truncation bias, resulting in women with relatively shorter TTP not being included, is of particular importance

when studying time trends. We do not suspect left truncation bias in the current study.

The main strength of this study is the large study population, where the majority fulfilled the ASAS criteria. In Norway, the majority of pregnant women with inflammatory rheumatic diseases are followed in the public specialist health care system and enrolled in RevNatus, which makes the registry representative of the population at large. However, there are limitations to generalizability. We cannot exclude that the healthiest women with axial SpA are followed in general practice and thus less likely to be enrolled in RevNatus. On the other hand, some women with axial SpA with high disease activity may never feel healthy enough for pregnancy and will therefore never be enrolled in RevNatus.

Our study would have been strengthened by considering the possible effects of SpA comorbidities. While little is known about fertility and psoriasis, subfertility has been related to disease activity in inflammatory bowel disease (33). However, in the current study, the subpopulations with psoriasis or inflammatory bowel disease were too small for analyses with sufficient statistical power.

In conclusion, women with axial SpA had an occurrence of subfertility surpassing the occurrence demonstrated in the general population. Longer TTP was associated with older age, nulliparity, and longer disease duration. Our findings suggest that women with stable axial SpA should be encouraged not to postpone pregnancy.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Drs. Ursin and Wallenius had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ursin, Skomsvoll, Salvesen, S. S. Koksvik, Jakobsen, Wallenius.

Acquisition of data. Ursin, S. S. Koksvik, Jakobsen, Wallenius.

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Illness Experiences of Chilean Women With Sjögren's Syndrome: The Patient Perspective

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Objective. Sjögren's syndrome (SS) challenges everyday functioning and well-being. The aim of this study was to structure and summarize the life experiences of Chilean women with SS in an integrated model.

Methods. Interviews from a previous study yielded 75 experiences of living with SS. A sample of 30 women with SS sorted these experiences by content and rated their level of agreement with each experience. A hierarchical cluster analysis was used to structure the experiences of the participants with SS in a comprehensive overview. A team-based consensus analysis was used to define the number of clusters. The level of agreement was examined with Wilcoxon's signed rank test.

Results. Ten clusters were identified and grouped into 6 main categories: symptoms (clusters: mucosal dryness and related symptoms), social environment, emotion management (clusters: fears and sadness), information (clusters: uncertainty and lack of knowledge), coping strategy (clusters: resilience and self-care), and health staff relationship. The clusters that describe the more common experiences among patients were resilience, self-care, uncertainty, lack of knowledge, health staff relationship, and mucosal dryness.

Conclusion. This study provided an integrated and structured overview of disease experiences comprising both biomedical and psychosocial aspects as being of vital importance for the health of patients with SS. The overview can be used to get a quick impression of disease experiences that are important for an individual patient, in a therapeutic goal setting, and in the construction and evaluation of medical and nonmedical interventions or education.

INTRODUCTION

Sjögren's syndrome (SS) is a chronic systemic autoimmune disease that mainly affects the exocrine (salivary and lacrimal) glands in the form of a lymphocytic infiltrate (1). Key symptoms are dry eyes and dry mouth (2), and this dryness, along with systemic features, pain, and fatigue can progressively affect daily life (3). People with SS encounter a series of transformations in their daily activities, and considering these aspects is important to develop a clinical approach focused on patients' welfare. This study examined illness experiences that are conceptualized as the means and ways in which individuals and social groups perceive, conceive, and respond to a specific episode of disease (4). The concept of experience is defined according to a phenomenologic approach: the interpretation or meaning that each participant attributes to a life event influences the cognitive, emotional, and behavioral aspects in relation to that event (5). For the purpose of this study, illness experience is defined as a cognitive-emotional and behavioral response as a result of the interpretation of illness phenomena. Examples are feelings of loneliness as a consequence of perceived social rejection when living with stigmatized disease, or changes in family roles as a consequence of symptoms of the disease.

Illness experiences have commonly been investigated under the label health-related quality of life (HRQoL), which refers to limitations faced in different areas (biologic, psychological, and social) resulting from pathology or an accident (6) such as reductions in well-being and functioning (7,8). Assessments of HRQoL are used to evaluate the results of health interventions and treatments, understand the burden of a particular disease, identify health inequities, distribute health care resources, and support epidemiologic studies (9). Patients with SS have lower HRQoL than the general or healthy population; specifically, physical and mental functioning components of HRQoL are reduced (10,11), and the prevalence

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SIGNIFICANCE & INNOVATIONS

- Concept mapping provided a comprehensive and structured overview of illness experiences of women with Sjögren's syndrome.
- Most participants agreed with having experiences relating to resilience, self-care, uncertainty, lack of knowledge, health staff relationship, and mucosal dryness.
- The overview serves as an input guiding interviews supporting communication and the quality of the doctor-patient relationship.

of mood disorders is higher, which is associated with symptom burden and disability (12).

These findings using generic HRQoL measures highlight the importance of evaluating and knowing how patients with SS live their illness, make sense of it, and respond to the adversities of their disease. Illness experiences of SS include more facets than measured with generic HRQoL instruments. Illness experiences specific for SS have been indicated in qualitative and quantitative studies. Patients with SS apparently have little understanding of their disease, which could be due to the large variety of symptoms in this disease (11). When assessing their health condition, patients consider somatic experiences that are unique for SS, such as dryness and related psychological, functional, and social consequences, which probably influence the overall interpretation of the disease that they experience. The psychological response to SS is related to loss of health but also to a lack of knowledge of the disease and problems within social interaction (13). In interviews, patients reported experiencing feelings of sadness, abandonment, and powerlessness and difficulties in maintaining social relationships, while social support is fundamental to maintaining activities and sustaining social networks (13). Results from these interviews are considered a basis for the comprehensive description that the current study aims to provide.

The first aim of the current study was to structure and summarize the individual life experiences of Chilean women with SS in an integrated model using a concept mapping method. Based on previous research, the expectation was that multiple life domains would be influenced by SS, especially illness experiences, psychological responses, and social interaction (13), and that efforts to manage the disease would be part of the life experiences of patients (14). Moreover, we aimed to determine the degree of agreement with the experiences of illness among patients with SS by using a checklist including all identified experiences.

MATERIALS AND METHODS

Ethics approval and participants. The ethics committee of the Faculty of Dentistry at the University of Chile approved the research proposal (May 2017). All participants provided written informed consent. Participants were recruited through the treating doctors at the University of Chile Clinical Hospital and through a Facebook message by the national association of patients with SS. Interested participants could send an email to register. This process resulted in 30 women with SS who wanted to participate. The inclusion criteria were women age 18 to 70 years with a medically confirmed diagnosis of SS by a rheumatologist of the University of Chile Clinical Hospital and based on American–European Consensus Group criteria (15). Exclusion criteria were pregnancy, untreated other chronic conditions, being an inpatient, mental disorders, and having an acute phase of SS. The sample was heterogeneous in terms of disease characteristics and consisted of 30 women with SS without distinguishing between primary and secondary SS. The women experienced different symptoms and glandular or systemic signs of the disease. The sociodemographic characteristics of the participants are shown in Table 1.

Procedure. This study employed a concept mapping design (16) to structure qualitative content obtained from semistructured interviews in a previous study that examined experiences about the disease in 19 women with SS, medically confirmed by a rheumatologist (13). From an original set of 129 experiences derived from the interviews, a representative set of 75 experiences was selected by a group comprising researchers, clinicians, and a patient representative. The experiences were selected to represent an encompassing variety of experiences. Similar experiences were combined, and a statement involving multiple experiences was split into single experiences, with a decision that the experience should neither be ambiguous or abstract nor too specific. The research group discussed until consensus was reached about selected experiences.

The concept mapping technique consisted of 3 steps. First, in a session at the Faculty of Dentistry, participants individually sorted 75 cards with experiences about SS (card-sorting task) by categorizing them into piles using similarity of content as a criterion. The participants gave each pile a label that could be used by the researchers to interpret the sorting. One member of the research team was present during the task with each participant. Second,

Table 1. Characteristics of the sample (n = 30)*

Characteristic	Value
Age, years	52.23 ± 10.6 (29–74)
Diagnosis duration, years	6.9 ± 6.0 (<1–30)
Symptom duration, years	10.9 ± 6.6 (1–31)
Symptom duration before diagnosis, years	3.4 (3.0)
Marital status, no. (%)	
Married or cohabiting	17 (56.7)
Divorced	6 (20.0)
Widowed	1 (3.3)
Single	6 (20.0)
Highest level of education, no. (%)	
Primary	1 (3.3)
Incomplete secondary	1 (3.3)
Complete secondary	10 (33.3)
Technical-professional	10 (33.3)
Incomplete university	1 (3.3)
Complete university	4 (13.3)
Postgraduate	3 (10.0)

* Values are the mean ± SD (range) unless indicated otherwise.

to classify and structure the experiences that were sorted by the participants, a hierarchical cluster analysis was performed using a statistical software program (SPSS). Finally, a team-based consensus analysis consisting of 1 patient, 2 psychologists, 2 dentists, and 1 dentistry student examined and discussed the hierarchical cluster analysis results and decided on the number of clusters.

Using a checklist of 75 experiences with SS, the participants in this study indicated their level of agreement related to each experience included in the card-sorting task on a 4-point Likert rating (agree, mildly agree, mildly disagree, and disagree). In addition to the card-sorting and the level of agreement tasks, the participating women completed demographic questions.

Statistical analysis. IBM SPSS software, version 22 for Windows, was used for all analyses. Descriptive statistics were obtained to describe the sociodemographic variables (age, diagnosis, symptom duration, marital status, and education level). Hierarchical cluster analysis (Ward's method, squared Euclidian distances) was used to analyze the experiences that were individually sorted by the participants during the card-sorting task according to the similarity of meaning. In cluster analysis, the cells of the input matrix of experiences comprised the number of times that 2 experiences were not sorted in the same pile. The number of clusters was set, guided by the dendrogram and agglomeration schedule produced by the statistical software, showing which experiences were being combined at each stage of the hierarchical clustering process. The main criterion to decide on the number of clusters was that the clusters should reflect distinct components of experiences.

To analyze the level of agreement, a nonparametric statistical test for 1 sample (Wilcoxon's signed rank test) was used to compare the response of the participants with the median (2.5) response possibility. A P value less than 0.05 was considered to indicate statistical significance. Statistical significance of an item indicates that there was agreement among patients reflecting a common or uncommon experience. Based on the number of significant items in each cluster, the agreement percentage of each cluster was calculated. The median was derived to describe the agreement of the participants with the items.

RESULTS

Concept analysis. Figure 1 shows a schematic overview of the outcome of hierarchical cluster analysis, grouping the 75 experiences of having SS. The experiences included in the clusters

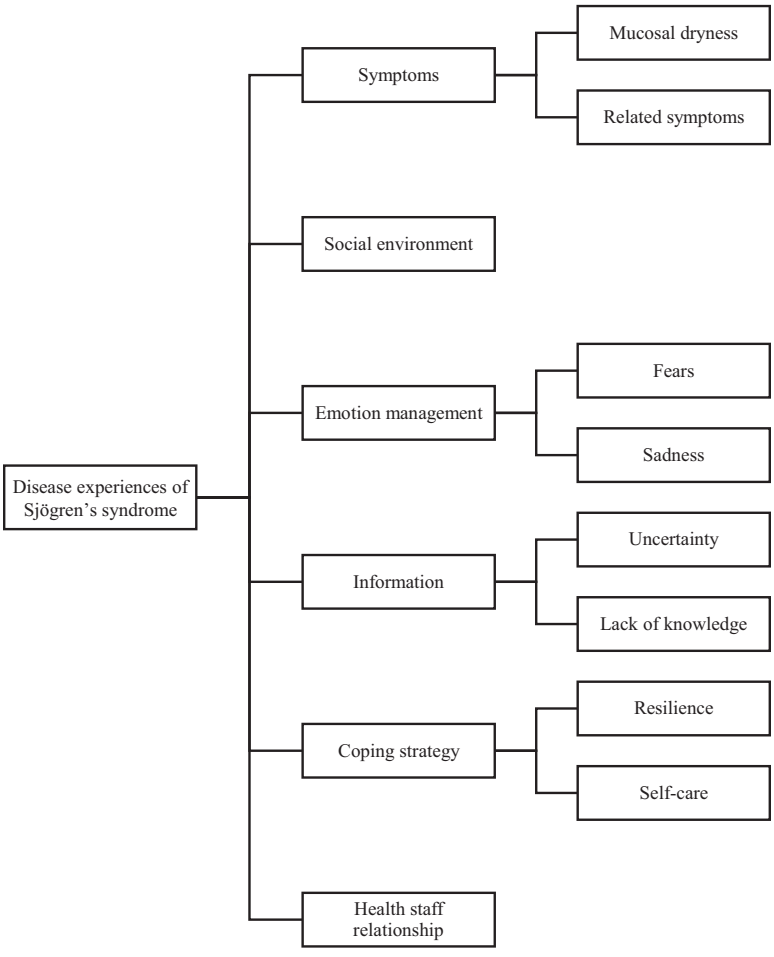

Figure 1. Schematic overview of the outcome of hierarchical cluster analysis grouping 75 experiences of having Sjögren's syndrome.

Table 2. Level of agreement with experiences, organized into 10 clusters, of patients with Sjögren's syndrome (SS)*

Cluster (% agreement) and experiences	Median	*P*
Mucosal dryness (73%)		
5. There is tooth loss or tooth damage by the dry mouth.	2	0.0788
7. The oral mucosa and the lips stick and become irritated.	1	0.0007
9. I feel a sensation of burning or sensitive oral mucosa.	1.5	0.0206
16. Eyes become red and sore by lack of tears.	1	0.0000
72. You cannot eat without drinking.	1	0.0007
53. Patients do not recognize dry mouth as a symptom of a disease.	1	0.0003
58. We do not recognize dry eyes as a symptom of a disease.	1	0.0009
49. It is difficult to talk clearly and for a long time.	1	0.0114
57. It is difficult to have a job that involves talking.	2	0.0009
26. The sense of taste is lost or decreased.	1	0.5774
75. The sense of smell is lost or decreased.	3	0.6728
Related symptoms (67%)		
4. There is deterioration of the physical appearance.	2	0.1419
36. There is weakness, tiredness, and permanent apathy. The energy does not last long.	1	0.0000
59. Avoid doing everyday tasks such as housework or shopping.	2	0.5012
17. The quality of sleep is poor.	1	0.0000
24. The disease gets worse because of daily stress.	1	0.0020
8. My mood changes according to my symptoms.	1	0.0009
Social environment (44%)		
23. Relationship break-up due to physical problems.	2.5	0.6310
28. The understanding of the partner is essential to maintain the relationship.	1	0.0000
32. Sexual intercourse is avoided because of the vaginal dryness, body ache, or dry mouth.	2	0.4840
12. The SS disease draws attention of the family and causes concern in the family.	2	0.1240
38. The family minimizes the illness of the patient.	2	0.0462
40. Social roles (mother, housewife, wife) are affected.	2	0.9913
43. The social environment is unwelcoming for SS sufferers and does not consider the limitations of the disease.	1.5	0.0475
70. The social environment does not either know or understand the disease.	1	0.0000
52. Physical difficulties (pain, fatigue, dry mouth) cause a withdrawal from social network.	3	0.4614
Fear (50%)		
62. I feel embarrassed for the state of my mouth.	2	0.8020
68. I am afraid of losing teeth because of dry mouth.	1	0.0004
11. I am afraid of possible blindness because of SS.	2	0.1438
27. I am afraid that the drugs can cause other diseases.	1	0.0001
Sadness (50%)		
34. The inability to cry with tears can lead to a nervous breakdown or depression.	3.5	0.0319
45. I prefer to avoid speaking about sad issues to avoid crying.	4	0.0062
31. I feel sadness, but I cannot cry with tears.	3	0.1783
2. An intense muscle contraction (neck, face, shoulders) happens when you cannot cry.	3	0.0896
33. Emotions like sadness, blame, rage, and resentment may be the cause of SS.	2	0.6867
39. I feel sadness for having an irreversible and complex disease.	2.5	0.7453
Uncertainty (80%)		
29. Before arriving at the diagnosis of SS, one visits a lot of doctors.	1	0.0003
48. The patient is able to actively participate in the diagnosis and treatment.	1	0.0000
37. The SS diagnosis is uncertain and provisional.	2	0.1641
60. The SS diagnosis can be a relief, as it ends the uncertainty of not having a diagnosis.	1	0.0002
61. There is uncertainty in the face of future events (complications).	1	0.0000
Lack of knowledge (78%)		
35. SS is a hereditary disease; it is part of our body.	3	0.5178
50. Past sad or traumatic experiences may initiate SS.	2.5	0.4193
3. SS is a disease whose name is hard to read, write, and pronounce.	1	0.0001
18. I had never heard about SS.	1	0.0259
65. I do not understand what the disease is about.	3.5	0.0376
54. The symptoms of SS are common with other diseases.	1.5	0.0053
56. The symptoms of SS appear many years before the diagnosis.	1	0.0000
73. Confusion when facing unexpected symptoms.	1	0.0001
30. It is necessary to search for additional information, either on the internet or in books.	1	0.0000
Resilience (83%)		
19. It is better to accept that you have to live with SS because there are worse diseases.	1	0.1214
66. It is better not to think about what could happen. Whatever has to happen, let it happen.	1	0.0012
47. The faith in God helps to face the disease.	1	0.0000
51. The disease is an opportunity for personal growth.	1	0.0218

(Continued)

Table 2. *(Cont'd)*

Cluster (% agreement) and experiences	Median	*P*
46. I try to maintain a normal life despite the symptoms.	1	0.0000
67. Being calm and in a good mood helps for a better health status.	1	0.0000
Self-care (83%)		
13. Herbs and natural foods are part of the self-care.	1	0.0000
64. Alternative medicine (Reiki, acupuncture, apitherapy, and so on) helps to control the symptoms.	1	0.0028
15. Taking self-care measures (diet, relaxation, following medical advice) is very helpful.	1	0.0000
14. I abandon the treatment when it causes unpleasant symptoms.	2	0.7878
25. If the medicine puts my health at risk, I stop taking it.	2	0.0152
21. The symptoms are the same, with or without treatment.	3	0.0443
Health staff relationship (77%)		
10. This disease implies spending a lot of money.	1	0.0016
41. It is exhausting to go to the doctor again and again, to complete health checks, and to face bureaucratic procedures.	1	0.0004
1. The doctors have little time to spend with patients.	1	0.0016
22. It is extremely difficult to get an appointment with the doctor when it is required.	1	0.0019
6. You must fully trust in the decisions and instructions of the rheumatologist.	1	0.0084
63. It is comforting for the patient that the doctor considers the human side of the patient.	1	0.0000
74. I drop out of treatment because it is impossible to get an appointment for medical check-up.	3.5	0.0376
44. Even the physicians from other medical specialties do not know much about SS.	1	0.0001
55. Doctors do not provide sufficient and clear information to guide the patient.	1	0.0081
42. I fear being admonished by the physician for not following the instructions.	2	0.5808
69. Physicians do not consider expectations, fears, and preferences of patients.	1.5	0.0595
71. Some limitations of the medical care are the responsibility of the institution and not of the doctors.	1	0.0010
20. The doctors think that other diseases are more important than SS.	2	0.0607

* Shown are the cluster name, the percentage of subjects agreeing with a cluster, the experiences (numbered 1–75), the median agreement (lower scores reflect higher agreement), and whether the agreement or disagreement significantly deviates from neutral. Scores of 1 to 4 reflect agree, mildly agree, mildly disagree, and disagree, respectively.

are shown in Table 2. Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24256/abstract, shows the dendrogram of the grouped experiences.

The team-based consensus analysis determined that the number of clusters was set to 10. Increasing the number of clusters from 10 to 11 divided the cluster self-care into 2 clusters: deciding for oneself about abandoning pharmacologic treatment (items 14, 25, and 21) and deciding for oneself about complementary therapies (items 13, 64, and 15). Although the division was evident, both clusters contained items clearly reflecting the fact that the patients wanted to manage care related to SS themselves; therefore, there was no need to further divide these clusters. Increasing the number of clusters to 12 also divided the cluster health staff relationship into 2 different clusters: not directly related to physician care (items 10 and 41) and directly related to physician care (items 1 to 20). Because both clusters had the same items concerning health staff, this cluster was not split.

Decreasing the number of clusters from 10 to 6 indicated a solution combining 4 pairs of clusters into overarching categories (Figure 1). The items included in the clusters are shown in Table 2. The clusters mucosal dryness and related symptoms both involved symptoms. Mucosal dryness is a primary symptom of SS, and its management is different from other, more generic symptoms, such as fatigue or sleep disturbance. Also the pairs of clusters fear and sadness, uncertainty and lack of knowledge, and resilience and self-care. could be combined into overarching categories (Figure 1). We decided to maintain these separate clusters. Although both fear and sadness are emotions, they are distinct emotions. Sadness is an important issue in patients with SS because of the difficulty and the pain of crying without tears. Both uncertainty and lack of knowledge are related to information about SS; nevertheless, uncertainty is a feeling, while lack of knowledge is a cognition that could cause someone to feel uncertain. While both resilience and self-care are means to cope with the consequences of the disease, resilience concerns the cognitive and positive reappraisal of the disease, and self-care involves behavioral management of SS. Thus, the experiences of having SS comprise on the highest-order level 6 domains, of which 4 include 2 lower-order clusters each.

Level of agreement with experiences. Patients indicated their level of agreement with the 75 experiences associated with the illness. The median of the patients' responses (agree, mildly agree, mildly disagree, and disagree) to the 75 illness experiences and the agreement percentage of each cluster are shown in Table 2. These experiences are arranged according to membership in one of the higher-order dimensions obtained and shown in Figure 1. Significance (*P* value), obtained through statistical analysis with Wilcoxon's signed rank test, established whether the pattern in the answer options indicated agreement (is significantly lower than 2.5)

or disagreement (is significantly higher than 2.5) with the experience. The score distributions of the level of agreement with the 75 experiences at the 10 clusters are shown in Table 2. For 52 experiences of illness, the agreement or disagreement of the participants deviated from neutral, which corresponds to 69.3% of the total of illness experiences analyzed. Clusters that describe the more common experiences among patients are resilience, self-care, uncertainty, lack of knowledge, health staff relationship, mucosal dryness (Figure 2). Other clusters, especially sadness, are less common. A large range of scores indicating individual differences in the level of agreement with experiences were especially observed for lack of knowledge and self-care and, to a lesser extent, for mucosal dryness, related symptoms, and resilience.

Experiences related to oral mucosa (items 7, 9) are common, while experiences related to teeth (item 5), sense of smell (item 75), and taste (item 26) are particular to each patient. Many of the experiences on coping with SS are common, except the idea that other diseases are worse (item 19). Similar to options to care about oneself, most experiences related to being active on self-care are common. Patients agree that the diagnosis process generates uncertainty, but they disagree on whether a diagnosis is uncertain and provisional. Most of the participants agree on a lack of knowledge related to SS, both on social and medical environment, while there is no agreement on the origin or cause of SS. There is an agreement on how the functioning of the health care center influences the adherence to treatment. About the patient–health provider relationship, there is agreement on the importance of considering the human side of the patient and the need to trust in medical decisions.

DISCUSSION

The main aim of the current study was to structure and summarize the life experiences of Chilean women with SS in an integrated model. Ten clusters were identified that were arranged in 6 main categories: symptoms, social environment, emotion management, information, coping strategy, and health staff relationship. Some clusters of experiences were more common to the broad group of patients than others.

The participants in this study recognized many illness experiences, and several clinical characteristics of the disease and its psychological and social repercussions appear to constitute a relatively homogeneous experience. Interviewees shared the experience that they do not recognize, at an initial stage, the symptoms of dryness as part of a disease. Evidently, dry mouth may be interpreted as an irrelevant or transient symptom that could be explained by a variety of circumstances, such as anxiety or aging instead of an autoimmune disease. The lack of consideration of oral dryness as a disease symptom may mean that medical professionals are not consulted. This delay is relevant, because symptoms of dryness are a core symptom of the disease (15–19). The fear of losing teeth, another illness experience with high concordance, is related to objective aspects, such as the decrease in salivary flow that occurs in SS (20–24); however, for interviewees, this fear does not necessarily come

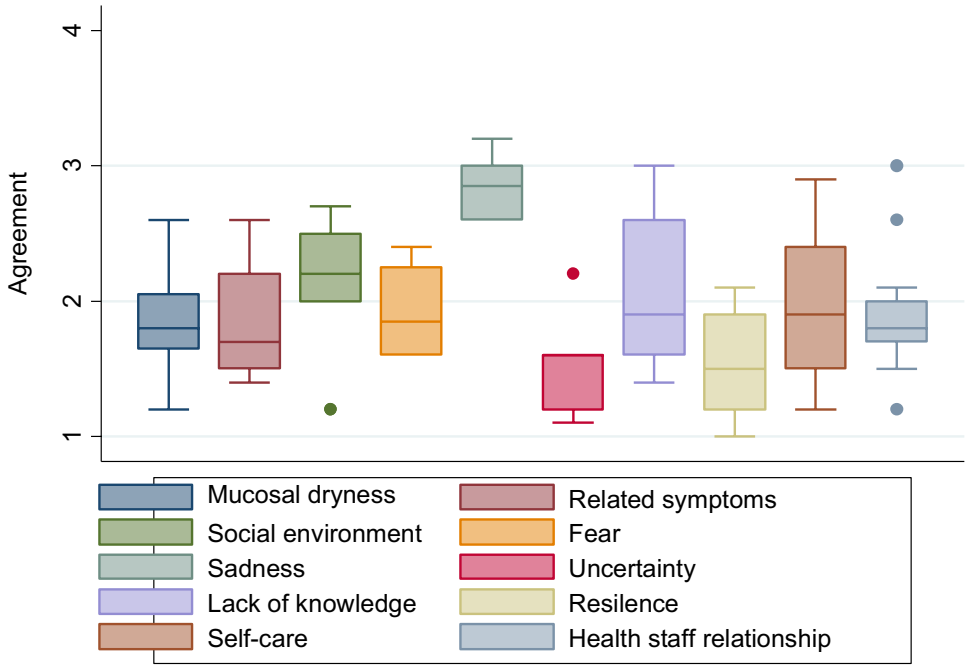

Figure 2. Box-and-whisker plot showing the level of agreement related to each experience of illness. The lowest possible score is 1 (agree) and the highest possible score is 4 (disagree). A wider range (indicated by the whiskers) indicates greater variability in agreement levels. Outliers are represented by dots.

from direct experience with professionals but rather from information they receive through the internet (13).

Chronic fatigue and poor sleep quality are other highly shared experiences that are widely supported by the literature (25,26) and that affect HRQoL (10,26). Both experiences are linked to the perception of a lack of understanding and devaluation of experience by others, a phenomenon described as invalidation (27). It is related to reduced physical health (28) and to low social support, which also constitutes a risk factor that affects HRQoL (23,24,29,30).

Difficulty in managing sadness due to lack of tears affects few women, although it is perceived as relevant. Difficulty in crying does not involve physical or psychological problems; our findings contradicts literature, which observes that the lack of tears hampers the recognition and expression of emotions (31).

A particular finding of this study was the lack of information represented by the experiences of uncertainty and lack of awareness regarding SS. The limited recognition of the disease by the community could contribute to patients not knowing what to expect or how to react. Also the difficulty in pronouncing the Swedish name "Sjögren" by Spanish speakers may contribute to the lack of information. In addition, the nonspecific symptomatology of the clinical picture may lead to a delay in disease diagnosis, which may have implications for health. The time course before diagnosis is generally long (3.4 years on average), which is consistent with the findings reported in the literature for this disease (32). Uncertainty and lack of awareness are characteristics of SS. This finding is consistent with a previous study showing that the uncertainty and strangeness experienced by patients with SS are phenomena that impact daily life (13).

Patients accept and try to give positive value to their disease, trusting their faith in God and mixing feelings of acceptance and resignation. In general, patients give great value to self-care strategies that are not part of conventional medical treatment, such as relaxation, alternative medicine, or the use of herbs. Psychological interventions, such as stress management or relaxation therapies, have been reported as being effective as complementary therapies in other chronic rheumatic diseases, improving clinical indicators, such as pain and functional disability (33).

One of the experiences about which patients agreed relates to their relationship with doctors and other professionals (dentists, nurses, kinesiologists, etc.), with a demand for attention that emphasizes the relational rather than the technical. A collaborative relationship between the patient and health providers, which includes effective communication and patient satisfaction, is relevant for patient adherence to treatment (34,35). The emergence of this domain in the current study and the observation of some negative experiences with the health care system, shows that there is room for improvement and emphasizes the need to incorporate the relationship with the health system as a relevant variable in the pursuit of well-being for patients. Such demand is frequent, as reported by several studies (36,37); therefore, it should be a priority consideration in the clinical field.

To the extent that the clusters of symptoms, information, and health staff relationship can be classified under illness experiences, emotion management under psychological responses, social environment under social interaction, and coping strategy under efforts to manage the disease, our findings are close to previously found categorizations of experiences with SS (13,14). Illness experiences related to symptoms and social environment are to a certain extent reflected in the dimensions of some scales of HRQoL, such as the Short Form 36 health questionnaire (38,39), and emotion management and coping strategy are reflected in generic coping measures. However, the current overview yields experiences that are more specific for SS. Moreover, other domains, such as information and health staff relationship, that emerged in this study have not been identified in prior HRQoL studies, although they are important areas of illness experiences that may influence disease management and general life satisfaction (32).

The biopsychosocial model of illness highlights the patient's subjective experience as an essential contribution to accurate diagnosis, health outcomes, and in general, the care of people (40). The findings of this study show that there is diversity in experiences that is fundamental to understanding the behaviors involved in facing a disease, as well as the possibility of having a satisfactory life, which includes the acceptance and proper management of SS. The identification of the most and least common domains with their respective illness experiences is in line with the biopsychosocial approach and provides elements that strengthen this perspective and are useful for the clinical approach to treating patients with SS. As the results show, the disease involves a series of phenomena not only involving the somatic experience or the psychological response, but actually is the combination of different levels of human experience, confirming the ongoing relevance of Engel's biopsychosocial model of illness (40).

A strength of our study is that the perspective of patients was consistently applied. This design allowed a description beyond the subjective interpretation of researchers, because patients instead of researchers categorized the experiences in meaningful constructs. A distinguishing feature of our study was also that not only outcomes of the disease per se but also mediator variables that influence outcomes were included in the set of illness experiences.

A limitation of this study relates to the generalizability of findings. First, only women participated. Some findings about illness experience may be related to the female sex. Second, more unique experiences, such as those associated with specific systemic manifestations, were not represented in this study. They can, however, severely reduce the quality of life and require attention in clinical practice. Third, how much the findings generalize beyond patients from a Latin American country is unclear. A larger sample size is needed to increase the external validity by including the more unique experiences of patients with SS. From a statistical point of view, a sample size of 10–20 people has been suggested to be a workable number for a card-sorting task (16) and as few as 25–30 participants will likely yield results similar to those of several

hundred, provided these participants are representative of actual users and are familiar with the domain being considered (41).

Notably, this study used as a starting point the uniqueness of patients instead of generic components of the disease. Therefore, this study provides a valuable description of the disease for the purposes of the clinical care of patients with SS, since the findings can be used as input to guide interviews and help improve both communication and the quality of the doctor-patient relationship. There is a great need for education of health care professionals and the public about this disease. We hope this research will increase awareness of SS and enhance personalized assessment and treatment. Future research should examine intercultural aspects of the findings and investigate which SS experiences are more specific for a culture and which are more general. The current structured overview of illness experiences can be used in research, assessment, therapeutic goal setting, the construction of interventions aimed to improve quality of life, and the evaluation of medical and nonmedical interventions or education.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Rojas-Alcayaga had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Herrera, Espinoza, Geenen, Rojas-Alcayaga.

Acquisition of data. Sánchez, Wurmann, Bustos, Rojas-Alcayaga.

Analysis and interpretation of data. Herrera, Espinoza, Wurmann, Leiva, Geenen, Rojas-Alcayaga.

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BRIEF REPORT

Hydroxychloroquine and Mortality Among Patients With Systemic Lupus Erythematosus in the General Population

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Objective. Hydroxychloroquine (HCQ) has been associated with improved survival among patients with systemic lupus erythematosus (SLE) from tertiary referral centers. We aimed to determine the potential impact of HCQ use on the risk of mortality among SLE patients in the general population.

Methods. We conducted a nested case–control study within an incident SLE cohort from the entire population of British Columbia, Canada. Deceased patients were matched with up to 3 living controls by age, sex, and SLE disease duration. HCQ exposure was categorized by the time between the last HCQ prescription date covered (i.e., end of supply) and the index date (i.e., death date) as current (<30 days), recent (30–365 days), remote (>365 days), or never used. We used conditional logistic regression to assess the risk of all-cause mortality associated with current or recent HCQ exposure compared with remote HCQ users.

Results. Among 6,241 patients with incident SLE, we identified 290 deceased patients and 502 matched SLE controls. Adjusted odd ratios for all-cause mortality were 0.50 (95% confidence interval [95% CI] 0.30–0.82) for current users and 2.47 (95% CI 1.21–5.05) for recent users compared with remote users. Associations were similar in subgroups according to SLE duration (≤5 years versus >5 years).

Conclusion. Our general population data support a substantial survival benefit associated with current HCQ use. Increased mortality among patients who had discontinued HCQ recently could be due to a sick stopper effect or the loss of actual HCQ benefits.

INTRODUCTION

Hydroxychloroquine (HCQ) is nearly universally recommended for patients with systemic lupus erythematosus (SLE). Its use has been associated with multiple benefits including reduced disease activity and damage, a lower risk of lupus nephritis, and lower risks of several comorbidities including hyperglycemia, hyperlipidemia, venous thromboembolism, and pregnancy complications (1). HCQ has also been associated with a substantial overall survival benefit among SLE patients. Three prior cohort studies from tertiary referral/lupus expert centers compared HCQ users and nonusers among individuals with SLE and demonstrated a 38–85% reduction in overall mortality associated with HCQ use (2–4). However, this benefit has not been previously demonstrated in the context of the general population. Furthermore, patients who are never prescribed HCQ may have systematic differences from active users of this medication. We aimed to investigate the potential survival impact of HCQ use at the general population level in a cohort of patients with incident SLE using remote users as the comparison group to reduce potential confounding by indication (5,6).

All inferences, opinions, and conclusions drawn herein are those of the authors and do not reflect the opinions or policies of the data steward(s).

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SIGNIFICANCE & INNOVATIONS

- We investigated the potential survival benefit associated with hydroxychloroquine (HCQ) use at the general population level.
- To reduce potential confounding by indication, we chose remote users as the comparison group rather than patients who had never used HCQ.
- We found a substantial survival benefit associated with current HCQ use and increased mortality associated with recent HCQ discontinuation.

PATIENTS AND METHODS

Data source, study population, and study design. We conducted a nested case–control study within an incident SLE cohort. The source population was identified using linked administrative health databases from Population Data BC, which cover the entire population of the province of British Columbia, Canada (7). These databases capture demographics, vital statistics, and health care utilization data since 1990, including all provincially funded outpatient medical visits and hospital admissions and discharges. They also capture medications through the comprehensive prescription database PharmaNet, which includes all outpatient-dispensed medications for all residents of British Columbia since 1996. Each PharmaNet record contains information on the medication and dose dispensed (via the Drug Information Number), dispensing date, and quantity and days' supply dispensed. These databases have been used previously to conduct population-based assessments of mortality in other inflammatory rheumatic conditions (8).

An inception cohort of SLE patients has been previously described (9). This cohort included 6,241 patients at least 18 years of age with SLE diagnosed between 1997 and 2015. Subjects were classified as having SLE if they met the following criteria: ≥1 International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision, Clinical Modification (ICD-10-CM) code for SLE by a rheumatologist or from a hospital encounter (710.0 or ICD-10 M32.1, M32.8, and M32.9) or at least 2 ICD-9 codes for SLE (710.0) at least 2 months apart within 2 years by a nonrheumatologist physician. We excluded individuals with diagnoses of other inflammatory rheumatic diseases (i.e., rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis) occurring in at least 2 physician visits at least 2 months apart after the first SLE diagnosis. To ensure incident cases, all individuals were required to have no SLE diagnosis recorded for at least 7 years prior to the index date (i.e., from January 1990, the earliest data available) (9). From this incident SLE cohort, we conducted a nested case–control study by identifying patients who died and up to 3 living controls selected from risk set samples by age, sex, and SLE disease duration at the index date (e.g., death date).

Assessment of exposure. The exposure of interest was HCQ use status relative to the index date (death date). Using the PharmaNet dispensing database, we determined the final prescription date covered by the last HCQ prescription to determine the end of the medication supply and categorized HCQ use as current, recent, remote, or never. For current users, their HCQ supply ended within 30 days prior to the index date or they had an active supply of HCQ spanning the index date. For recent users, their HCQ supply ended between 30 and 365 days prior to the index date, whereas for remote users, their HCQ supply ended >365 days prior to the index date. Never users had no HCQ prescriptions dispensed during the study period. This classification was designed to minimize exposure misclassification due to delayed prescription refills.

Assessment of covariates. Covariates were assessed during the year prior to the underlying inception cohort entry and included chronic kidney disease (CKD), the Charlson comorbidity index (10), glucocorticoid use, cardiovascular medication use (including statins, antihypertensives, cardiac glycosides, diuretics, antiarrhythmics, nitrates, and anticoagulants), other immunosuppressive drug use (including azathioprine, methotrexate, mycophenolate, leflunomide, cyclosporine, cyclophosphamide), financial assistance for public health insurance as a surrogate for socioeconomic status, and health care utilization (including hospitalizations and outpatient visits).

Statistical analysis. We used conditional logistic regression to calculate the odds ratios (ORs) for all-cause mortality associated with current or recent HCQ use compared with remote HCQ users. Remote users were chosen as the reference group over nonusers to minimize confounding by indication, as in previous studies (5,6). To evaluate the potential impact of SLE duration and other patient characteristics on our findings, we conducted a subgroup analysis by the disease duration (≤5 years versus >5 years), age (>60 years or ≤60 years), female sex, and CKD. Statistical analyses were performed using SAS, version 9.3. All *P* values were 2-sided ($\alpha = 0.05$).

All procedures were conducted in compliance with British Columbia's Freedom of Information and Privacy Protection Act. Ethics approval was obtained from the University of British Columbia's Behavioral Research Ethics Board.

RESULTS

Among 6,241 patients with incident SLE between 1997 and 2015, we identified 290 deceased patients and 502 matched living controls. Both deceased patients and controls were predominately female (88% and 91% of deceased patients and controls, respectively), with a mean age of 60 and 59 years, respectively. The mean SLE disease duration on the index date (matching time

point) was 5.3 years. As expected, the deceased patients had a higher mean Charlson comorbidity index score and higher rates of cardiovascular medication usage than controls at cohort entry. They also had higher rates of immunosuppressive drug and glucocorticoid usage. Deceased patients had more frequent hospitalizations and outpatient visits than the controls and were more likely to have financial assistance for public health insurance (Table 1).

Current HCQ use was associated with an unadjusted OR of 0.55 (95% confidence interval [95% CI] 0.36–0.85) for all-cause mortality compared with remote users (Table 2). The fully adjusted OR was 0.50 (95% CI 0.30–0.82) for current users. Recent HCQ use was associated with an unadjusted OR of 2.00 (95% CI 1.08–3.69) and a fully adjusted OR of 2.32 (95% CI 1.13–4.77) compared with remote users. HCQ nonusers had similar risk of death as remote users (unadjusted OR 0.80 [95% CI 0.53–1.20]).

Among the subgroups according to SLE disease duration (≤5 years versus >5 years), female sex, age, and patients without CKD, the ORs associated with current HCQ use remained very similar (Table 2). Current HCQ users with CKD also had numerically lower odds of death relative to remote users.

DISCUSSION

In this study nested in a general population-based incident SLE cohort, we found a substantial survival benefit associated with current HCQ use compared with past use. These findings were similar among patients with shorter disease duration and those with longstanding SLE as well as younger and older patients alike. These findings support the generalizability of previous study findings generated from tertiary or lupus specialist centers (2–4). Furthermore, by using the remote HCQ users as the reference unlike previous studies (2–4), our study population consisted of those who were started on the medication, helping to minimize confounding by indication.

We also found a 2-fold increased risk of death associated with recent HCQ discontinuation compared with remote discontinuation. We speculate that patients may have been less likely to adhere to taking or to be prescribed this chronic medication near the end of life due to potentially unrelated illness (11). Although numbers were too small to conduct a meaningful cause of death analysis, we did note a higher number of cancer deaths among recent users than in the other HCQ exposure categories (8 cancer deaths among recent users, 6 among current users, and 6 among remote users, with an unadjusted cancer-specific mortality OR of 5.04 [95% CI 0.91–27.78] compared with remote users and 0.53 [95% CI 0.15–1.88] for current users). An alternative possibility is that this observed increase in mortality could be partially explained by a true biologic protective effect of HCQ that is lost and even reversed in the short term following discontinuation, such as its impact on endothelial function (12,13) and/or platelet aggregation (14). However, further studies are needed to understand the short-term impact of HCQ discontinuation on mortality, cardiovascular disease, and other important SLE-related outcomes.

This study has several strengths and limitations worth noting. The main limitations are those inherent with the use of administrative data. The SLE diagnoses were not clinically confirmed, but patients were identified using a strict case definition that employed ICD codes and additional exclusion criteria. This SLE definition has been previously validated with 98% sensitivity and 72% specificity (15). We did not have data on SLE disease activity. However, we adjusted for several indicators of illness including

Table 1. Characteristics of deceased patients (cases) and living controls with systemic lupus erythematosus (SLE)*

Variable	Cases (n = 290)	Controls (n = 502)	*P*
Age, mean ± SD years	60 ± 13	59 ± 13	0.31
Sex, female	88	91	0.11
SLE disease duration, mean ± SD years†	5.3 ± 3.9	5.3 ± 3.9	0.85
Chronic kidney disease	37	21	<0.001
Charlson comorbidity index, mean ± SD	2.12 ± 2.03	1.32 ± 1.06	<0.001
Medications			
Glucocorticoids	60	41	<0.001
Cardiovascular medications‡	57	41	<0.0001
Immunosuppressive medications§	22	16	0.038
Financial assistance	47.2	30.7	<0.001
Health care utilization, mean ± SD			
No. of hospitalizations	3.0 ± 2.5	0.5 ± 1.1	<0.001
No. of outpatient visits	63.2 ± 39.8	27.4 ± 23.2	<0.001

* Values are the % unless indicated otherwise. Characteristics are at the cohort entry date unless indicated otherwise.
† At the index date.
‡ Cardiovascular medications include antihypertensives, cardiac glycosides, diuretics, antiarrhythmics, nitrates, and anticoagulants.
§ Immunosuppressive medications include azathioprine, methotrexate, mycophenolate, leflunomide, cyclosporine, and cyclophosphamide.

Table 2. All-cause mortality according to hydroxychloroquine (HCQ) exposure*

All-cause mortality	No. of cases	No. of controls	Crude OR (95% CI)	Adjusted OR (95% CI)†
All patients				
Remote HCQ users	72	106	1.0 (ref.)	1.0 (ref.)
Recent HCQ users	37	27	2.00 (1.08–3.69)	2.47 (1.21–5.05)
Current HCQ users	60	163	0.55 (0.36–0.85)	0.50 (0.30–0.82)
HCQ nonusers	121	206	0.80 (0.53–1.20)	0.80 (0.50–1.27)
Age >60 years				
Remote HCQ users	45	68	1.0 (ref.)	1.0 (ref.)
Recent HCQ users	26	19	2.33 (1.11–4.92)	2.56 (1.08–6.05)
Current HCQ users	32	97	0.51 (0.29–0.88)	0.45 (0.24–0.85)
HCQ nonusers	92	141	0.94 (0.58–1.53)	0.86 (0.51–1.47)
Age ≤60 years				
Remote HCQ users	27	38	1.0 (ref.)	1.0 (ref.)
Recent HCQ users	11	8	1.80 (0.65–4.95)	3.10 (0.69–13.94)
Current HCQ users	28	66	0.62 (0.32–1.19)	0.52 (0.18–1.48)
HCQ nonusers	29	65	0.62 (0.30–1.24)	0.61 (0.21–1.78)
Female patients				
Remote HCQ users	65	102	1.0 (ref.)	1.0 (ref.)
Recent HCQ users	32	23	2.36 (1.25–4.46)	2.75 (1.30–5.84)
Current HCQ users	56	150	0.59 (0.38–0.91)	0.53 (0.32–0.90)
HCQ nonusers	102	184	0.87 (0.57–1.31)	0.86 (0.53–1.39)
SLE duration ≤5 yrs				
Remote HCQ users	31	42	1.0 (ref.)	1.0 (ref.)
Recent HCQ users	22	19	1.68 (0.76–3.73)	2.05 (0.76–5.52)
Current HCQ users	36	96	0.51 (0.28–0.92)	0.45 (0.21–0.97)
HCQ nonusers	64	105	0.80 (0.43–1.47)	0.69 (0.32–1.51)
SLE duration >5 yrs				
Remote HCQ users	41	64	1.0 (ref.)	1.0 (ref.)
Recent HCQ users	15	8	2.91 (1.10–7.72)	2.60 (0.83–8.15)
Current HCQ users	24	67	0.57 (0.30–1.09)	0.45 (0.20–1.01)
HCQ nonusers	57	101	0.89 (0.52–1.52)	0.83 (0.44–1.54)
CKD				
Remote HCQ Users	23	24	1.0 (ref.)	1.0 (ref.)
Recent HCQ users	12	<6	NA‡	NA‡
Current HCQ users	24	39	0.71 (0.21–2.45)	0.88 (0.10–8.12)
HCQ nonusers	48	39	1.10 (0.29–4.14)	0.61 (0.07–5.07)
No CKD				
Remote HCQ users	49	82	1.0 (ref.)	1.0 (ref.)
Recent HCQ users	25	26	2.24 (1.04–4.83)	2.23 (0.87–5.69)
Current HCQ users	36	124	0.66 (0.38–1.16)	0.52 (0.26–1.07)
HCQ nonusers	73	167	0.78 (0.46–1.34)	0.85 (0.46–1.58)

* 95% CI = 95% confidence interval; CKD = chronic kidney disease; NA = not applicable; ref. = reference; SLE = systemic lupus erythematosus.
† Adjusted for Charlson comorbidity index, glucocorticoid use, disease-modifying antirheumatic drug use, cardiovascular medication use, health care utilization, and financial assistance.
‡ Odds ratio (OR) not available due to small numbers.

comorbidities, medication use, and health resource use. A major strength of our study is the use of a comprehensive prescription drug database, which captures all dispensed outpatient medications and the timing of refills regardless of age or funding. Our ascertainment of HCQ exposure status by actual prescription refills was less susceptible to misclassification of nonadherent patients as HCQ users than could occur with reliance on prescribing data alone. Furthermore, our population-based data source adds to the generalizability of our findings. Additionally, as mentioned, our remote user design, which has been employed in prior pharmacoepidemiology studies (5), reduced the potential for confounding by indication for HCQ use. Although we demonstrated a survival benefit among patients with >5 years' disease duration, future studies could further evaluate the impact of HCQ on late mortality in patients with SLE.

In conclusion, our findings confirm the survival benefit of ongoing HCQ use among patients with SLE in the context of the general population. Future studies should further explore the potential link between HCQ discontinuation and increased mortality as well as its impact on other SLE-related outcomes.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Aviña-Zubieta had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Jorge, McCormick, Lu, Zheng, Choi, Aviña-Zubieta.

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