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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AMERICAN COLLEGE OF RHEUMATOLOGY
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EDITORIAL

A Fresh New Look, and a Fresh New Journal

Marian T. Hannan[1] and Richard J. Bucala[2]

The founding of *Arthritis & Rheumatism* (*A&R*) in 1958 by the American Rheumatism Association (now the American College of Rheumatology [ACR]) occurred at the advent of knowledge of immunologic abnormalities in patients with rheumatoid arthritis, systemic lupus erythematosus, and related disorders. Over its ensuing 60-year history, *A&R* (renamed *Arthritis & Rheumatology* in 2014) developed into a preeminent publication for disseminating research findings and advancing the field scientifically. Landmark papers addressed the role of autoantibodies and lymphocytes in rheumatic diseases and, in recent years, the clinical translation of cell- and cytokine-based paradigms of disease. Publication was expanded in 1988 with *Arthritis Care & Research* (*AC&R*), which increased the coverage of clinical research and included reports of studies analyzing economic, educational, and policy issues. Both journals have become international in scope yet remain first and foremost anchored to the academic and educational mission of the ACR.

This month introduces two initiatives by the ACR to better attend to the information and educational needs of our community, which includes not only investigators but practicing physicians and health professionals. First, *Arthritis Care & Research* and *Arthritis & Rheumatology* introduce a new article presentation format to enhance readers' experience with online and print publication. Second, the inaugural issue of *ACR Open Rheumatology*, a fully open access and online publication, debuts as the ACR's third venue for original research reports and scholarly articles.

The global expansion of research activities and scope of clinical medicine, together with the accessibility and speed of the internet, have led to an unprecedented expansion of new information and spawned alternative and innovative means of disseminating research findings. "Living" digital documents offer instantaneous links to graphical, video, and complex data files that promote discussion and continued analysis of published findings. The new formatting of the ACR's journals will facilitate these operations and improve readers' ability to access and make use of published content. It will include a clearer presentation of figures and tables, and a new font to enhance online and print reading.

Both *Arthritis Care & Research* and *Arthritis & Rheumatology* have thrived, with annual submissions numbering in the thousands, and they have become distinguished for publishing research to advance scientific rheumatology and improve clinical practice. Both journals have enjoyed great success but also are now weighted with so many submissions that they are not able to publish as much content as desired and must turn away many interesting reports and leave topical areas underserved. *ACR Open Rheumatology* will expand the ACR's portfolio of publications, which also includes *The Rheumatologist*, to better fulfill its mission to disseminate the highest-quality original research and information for rheumatologists. *ACR Open Rheumatology* will provide online access to full content to anyone, with no login or membership required. In addition, articles in *ACR Open Rheumatology* will be published under a Creative Commons Attribution-Noncommercial license, which means they can be used, reproduced, and distributed openly, with only a requisite for proper citation and noncommercial use. *ACR Open Rheumatology* will offer an added opportunity for authors to publish under the aegis of the ACR. Authors will be able to take advantage of internal resubmission from *AC&R* and *A&R* directly to *ACR Open Rheumatology*, and with expedited review (i.e., the review from *AC&R* or *A&R* could be utilized by *ACR Open Rheumatology*). Authors also may submit articles directly to *ACR Open Rheumatology*, without having submitted previously to *AC&R* or *A&R*.

In current circumstances, where the impact of biomedical research on clinical practice has never been greater, the need for thoughtful and expert peer review, professional editing, and high standards for data reporting is essential. The operating philosophy of our journals, now augmented with *ACR Open Rheumatology*, is unchanged: to offer the best publications in rheumatology for a diverse audience of researchers and health care professionals. We are excited by these new initiatives, which will better advance scientific discourse and improve clinical practice.

This editorial is published simultaneously in *Arthritis & Rheumatology*.

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SPECIAL ARTICLE

2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis

Jasvinder A. Singh,[1] Gordon Guyatt,[2] Alexis Ogdie,[3] Dafna D. Gladman,[4] Chad Deal,[5] Atul Deodhar,[6] Maureen Dubreuil,[7] Jonathan Dunham,[3] M. Elaine Husni,[5] Sarah Kenny,[8] Jennifer Kwan-Morley,[9] Janice Lin,[10] Paula Marchetta,[11] Philip J. Mease,[12] Joseph F. Merola,[13] Julie Miner,[14] Christopher T. Ritchlin,[15] Bernadette Siaton,[16] Benjamin J. Smith,[17] Abby S. Van Voorhees,[18] Anna Helena Jonsson,[13] Amit Aakash Shah,[19] Nancy Sullivan,[20] Marat Turgunbaev,[19] Laura C. Coates,[21] Alice Gottlieb,[22] Marina Magrey,[23] W. Benjamin Nowell,[24] Ana-Maria Orbai,[25] Soumya M. Reddy,[26] Jose U. Scher,[26] Evan Siegel,[27] Michael Siegel,[28] Jessica A. Walsh,[29] Amy S. Turner,[19] and James Reston[20]

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 health care provider 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. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

The American College of Rheumatology is an independent, professional, medical and scientific society that does not guarantee, warrant, or endorse any commercial product or service.

Objective. To develop an evidence-based guideline for the pharmacologic and nonpharmacologic treatment of psoriatic arthritis (PsA), as a collaboration between the American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF).

Methods. We identified critical outcomes in PsA and clinically relevant PICO (population/intervention/comparator/outcomes) questions. A Literature Review Team performed a systematic literature review to summarize evidence supporting the benefits and harms of available pharmacologic and nonpharmacologic therapies for PsA. GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was used to rate the quality of the evidence. A voting panel, including rheumatologists, dermatologists, other health professionals, and patients, achieved consensus on the direction and the strength of the recommendations.

Results. The guideline covers the management of active PsA in patients who are treatment-naive and those who continue to have active PsA despite treatment, and addresses the use of oral small molecules, tumor necrosis factor inhibitors, interleukin-12/23 inhibitors (IL-12/23i), IL-17 inhibitors, CTLA4-Ig (abatacept), and a JAK inhibitor (tofacitinib). We also developed recommendations for psoriatic spondylitis, predominant enthesitis, and treatment in the presence of concomitant inflammatory bowel disease, diabetes, or serious infections. We formulated recommendations for a treat-to-target strategy, vaccinations, and nonpharmacologic therapies. Six percent of the recommendations were strong and 94% conditional, indicating the importance of active discussion between the health care provider and the patient to choose the optimal treatment.

Conclusion. The 2018 ACR/NPF PsA guideline serves as a tool for health care providers and patients in the selection of appropriate therapy in common clinical scenarios. Best treatment decisions consider each individual patient situation. The guideline is not meant to be proscriptive and should not be used to limit treatment options for patients with PsA.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease associated with psoriasis, manifesting most commonly with peripheral arthritis, dactylitis, enthesitis, and spondylitis. Nail lesions, including pitting and onycholysis, occur in ~80–90% of patients with PsA. The incidence of PsA is ~6 per 100,000 per year, and the prevalence is ~1–2 per 1,000 in the general population (1). The annual incidence of PsA in patients with psoriasis is 2.7% (2), and the reported prevalence of PsA among patients with psoriasis has varied between 6% and 41% (1). In the majority of patients the skin symptoms develop first, followed by the arthritis; however, in some patients the skin and joint symptoms present at the same time, and in 10–15% the arthritis presents first (2).

PsA affects men and women equally. The distribution of the peripheral arthritis varies from asymmetric oligoarthritis (involving ≤4 joints) to symmetric polyarthritis (involving ≥5 joints). Distal interphalangeal joints are commonly affected and, in some patients, are the only affected joints. Axial disease, when present, usually occurs together with peripheral arthritis. Some patients present with rapidly progressive and destructive PsA–arthritis mutilans. PsA is associated with an adverse impact on health-related quality of life (3–5) and high health care costs and utilization (6,7). Greater disease activity is associated with progressive joint damage and higher mortality (8–11). Early identification of PsA and early initiation of therapy are important for improving long-term outcomes (12).

Both nonpharmacologic and pharmacologic treatment can ameliorate PsA symptoms and can occasionally result in disease

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remission (Figure 1). Clinicians and patients can now choose from a wide variety of pharmacologic therapies, including symptomatic treatments such as nonsteroidal antiinflammatory drugs (NSAIDs) and intraarticular injections, as well as immunomodulatory therapies.

The presentation of PsA is heterogeneous, and health care providers frequently face challenges when considering the various treatment options. Our objective was to develop evidence-based treatment recommendations for the management of active PsA in adults, using pharmacologic and nonpharmacologic therapies. These PsA treatment recommendations can help guide both clinicians and patients to arrive at optimal management decisions.

METHODS

Methodology overview. This guideline followed the American College of Rheumatology (ACR) guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines). This process includes using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology (13–15) (www.gradeworkinggroup.org) to rate the quality of the available evidence and to develop the recommendations. ACR policy guided disclosures and the management of conflicts of interest. The full methods are presented in detail in Supplementary Appendix 1, on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23789/abstract.

This work involved 4 teams selected by the ACR Quality of Care Committee after reviewing individual and group volunteer applications in response to an open request for proposals announcement: 1) a Core Leadership Team, which supervised and coordinated the project and drafted the clinical questions and manuscript; 2) a Literature Review Team, which completed the literature search and abstraction; 3) an Expert Panel, composed of patients, patient advocates, rheumatologists, dermatologists, 1 dermatologist-rheumatologist, and 1 rheumatology nurse practitioner, which developed the clinical questions (PICO [population/intervention/comparator/outcomes] questions) and decided on the scope of the guideline project; and 4) a Voting Panel, which included rheumatologists, 1 dermatologist, 1 dermatologist-rheumatologist, 1 rheumatology physician assistant, and 2 patients (1 of whom was also a physical therapist), who provided input from the patient perspective and voted on the recommendations. Additionally, a Patient Panel consisting of 9 adults with PsA reviewed the evidence and provided input on their values and preferences, which was reviewed before discussion of each section of PsA management (e.g., treatment-naive, treated, comorbidities), and was incorporated into discussions and formulation of recommendations. Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/acr.23789/abstract) presents rosters of the team and panel members. In accordance with ACR policy, the principal investigator and the leader of the literature review team were free of conflicts, and within each team, >50% of the members were free of conflicts.

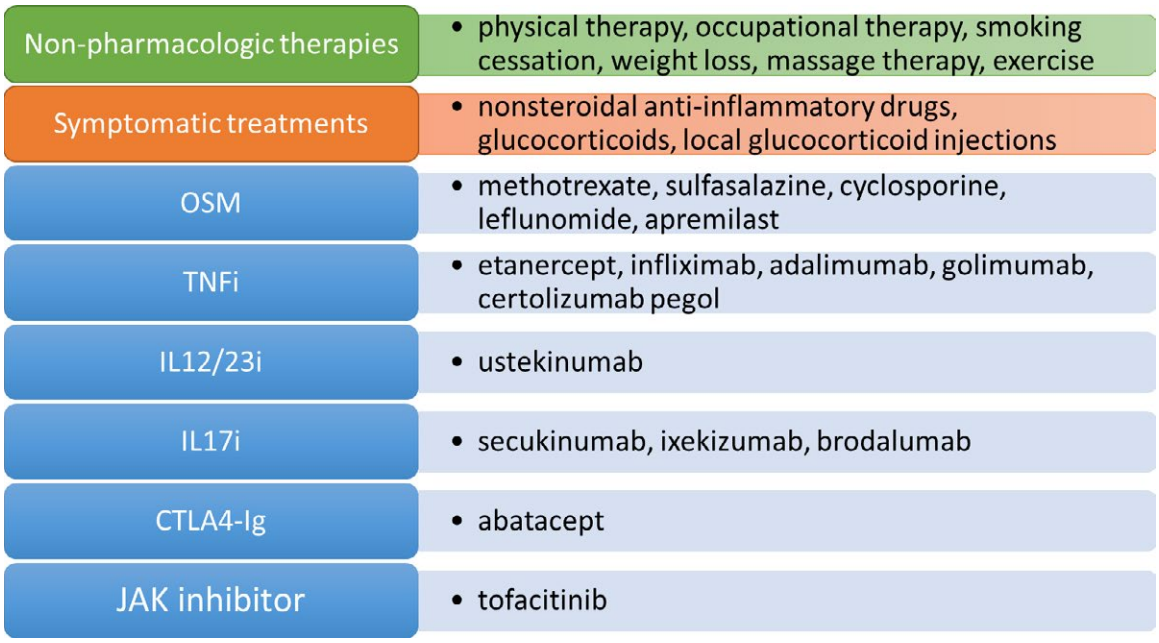

Figure 1. Pharmacologic, nonpharmacologic, and symptomatic therapies for psoriatic arthritis. Pharmacologic therapies are displayed in the blue boxes and include oral small molecules (OSMs), tumor necrosis factor inhibitor (TNFi) biologics, interleukin-17 inhibitor (IL-17i) biologics, an IL-12/23i biologic, CTLA4-immunoglobulin, and a JAK inhibitor. While there are numerous nonpharmacologic therapies available, 6 of these are addressed in this guideline. Symptomatic therapies include nonsteroidal antiinflammatory drugs, systemic glucocorticoids, and local glucocorticoid injections. Systemic glucocorticoids or local injections are not addressed in this guideline.

Framework for the PsA guideline development and scope of the guideline. Because there are numerous topics within PsA that could be addressed, at the beginning of the process the guideline panels made several decisions regarding the focus of this guideline and how to define aspects of the disease (e.g., active disease). At an initial scoping meeting, the Voting Panel and Expert Panel agreed that the project would include the management of patients with *active* PsA, defined as symptoms at an unacceptably bothersome level as reported by the patient and judged by the examining health care provider to be due to PsA based on the presence of at least 1 of the following: actively inflamed joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and/or extraarticular manifestations such as uveitis or inflammatory bowel disease (IBD). The health care provider may, in deciding if symptoms are due to active PsA, consider information beyond the core information from the history and physical examination, such as inflammation markers (C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]) and imaging results. At the scoping meeting, the panels decided that the guideline would address both pharmacologic and nonpharmacologic therapies for the treatment of PsA. We examined evidence regarding vaccinations, treatment in the presence of common comorbidities, and implementing a treat-to-target strategy.

In addressing pharmacologic therapies, we focused on immunomodulatory agents for long-term management rather than addressing acute symptom management (i.e., through intraarticular injections and the use of systemic glucocorticoids). Tofacitinib and ixekizumab were submitted for review and potential approval by the US Food and Drug Administration (FDA) at the time of formulation of this guideline (16,17) and for this reason, these drugs were addressed in the guideline. Both drugs have been approved for PsA since then (18,19). Tofacitinib is not included within the oral small molecules (OSM) category since its benefit/risk profile differs from that of the rest of the OSMs, especially with regard to risks (20–22), and consistent with its being considered separately in other treatment guidelines (23,24). Additionally, the panel addressed alternatives in patient subpopulations (e.g., patients with predominant enthesitis, axial disease, dactylitis, comorbidities), and greater versus lesser disease severity.

There are currently no widely agreed-upon definitions of disease severity in PsA or psoriasis. Thus, health care providers and patients should judge PsA and psoriasis severity on a case-by-case basis. For the purpose of these recommendations, severity includes not only the level of disease activity at a given time point, but also the presence or absence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of 1 or more of the following: a poor prognostic factor (erosive disease, dactylitis, elevated levels of inflammation markers such as ESR and CRP attributable to PsA), long-term damage that interferes with function (e.g., joint deformities), highly active disease that causes a major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease (Figure 2). In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) (25) score of ≥12 and a body surface area score of ≥10. However, because it is cumbersome, physicians seldom use the PASI in clinical practice. Examples of definitions of severe PsA and severe psoriasis are shown in Figure 2. Finally, because the National Psoriasis Foundation (NPF) and American Academy of Dermatology are concurrently developing psoriasis treatment guidelines, the treatment of skin psoriasis separately from the inflammatory arthritis was not included in the current ACR/NPF PsA guideline.

Systematic synthesis of the literature. Systematic searches of the published English-language literature included Ovid Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Health Technology Assessments) from the beginning of each database through November 15, 2016 (Supplementary Appendix 3, on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23789/abstract); we conducted updated searches on May 2, 2017 and again on March 8, 2018. DistillerSR software (https://distillercer.com/products/distillersr-systematic-reviewsoftware/) (Supplementary Appendix 4; http://onlinelibrary.wiley.com/doi/10.1002/acr.23789/abstract) was used to facilitate duplicate screening of literature search results. Reviewers entered extracted data into RevMan software (http://tech.cochrane.org/revman), and evaluated the risk of bias in primary studies using the Cochrane risk of bias tool (http://handbook.cochrane.org/). We exported RevMan files into GRADEpro software to formulate a GRADE summary of findings table (Supplementary Appendix 5; http://onlinelibrary.wiley.com/doi/10.1002/acr.23789/abstract) for each PICO question (26). Additionally, a network meta-analysis was performed when sufficient studies were available. GRADE criteria provided the framework for judging the overall quality of evidence (13).

The panels chose the critical outcomes for all comparisons at the initial scoping; these included the American College of Rheumatology 20% response criteria (ACR20) (the primary outcome for most PsA clinical trials), the Health Assessment Questionnaire disability index (a measure of physical function), the PASI 75% response criteria (PASI75) (a measure of skin psoriasis improvement), and serious infections. Both the ACR20 and the PASI75 are accepted outcome measures specified by regulatory agencies, including the US FDA, for the approval of treatments for PsA (27). Serious infections are among the issues of greatest concern for patients and physi-

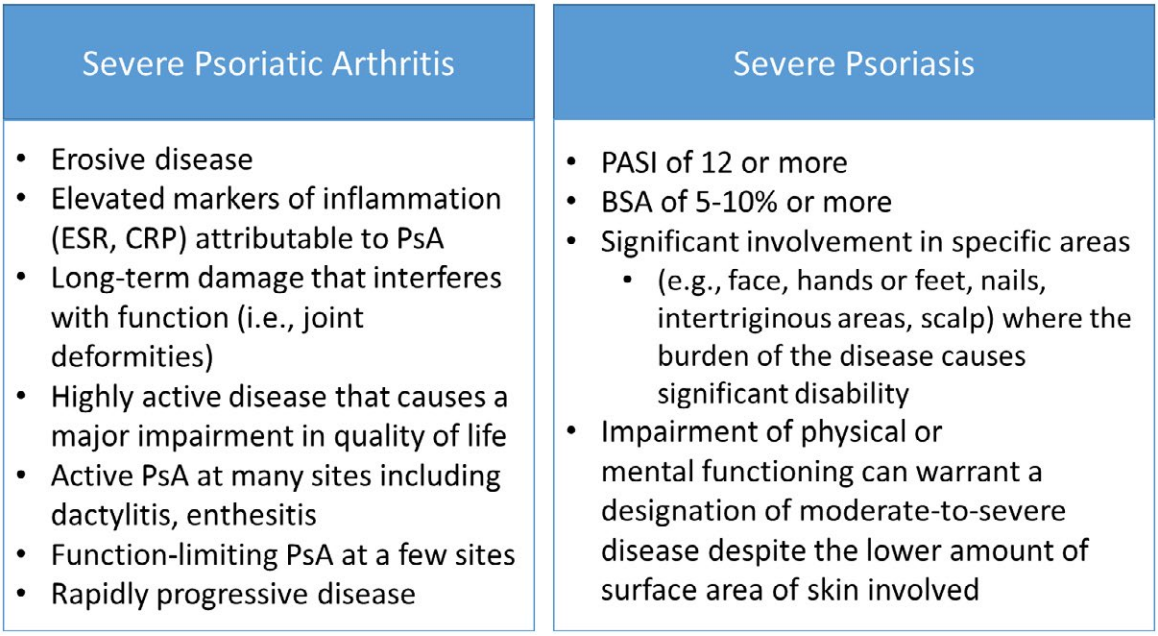

Figure 2. Examples of "severe" psoriatic arthritis (PsA) and psoriasis. The guideline development group defined severe PsA and psoriasis as the presence of 1 or more of the items listed. This is not a formal definition. There have been many definitions of severe psoriasis used over time—the items here are adapted from the 2007 National Psoriasis Foundation expert consensus statement for moderate-to-severe psoriasis (68). In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score of ≥12 and a body surface area (BSA) score of ≥10 (25). ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

cians when selecting among therapies. Other specific harms (e.g., liver toxicity with methotrexate [MTX]) were included as critical outcomes for individual comparisons. We included other outcomes, such as total infections (regardless of severity), when appropriate.

Moving from evidence to recommendations. GRADE methodology specifies that panels make recommendations based on the balance of benefits and harms, the quality of the evidence (i.e., confidence in effect estimates), and patients' values and preferences. Deciding on the balance between desirable and undesirable outcomes requires estimating the relative value patients place on those outcomes. When the literature provided very limited guidance, the experience of the Voting Panel members (including physicians, a rheumatology physician assistant, and the 2 patients present) in managing the relevant cases and issues became an important source of evidence. Values and preferences, crucial to all recommendations, derived from input from the members of the Patient Panel were particularly salient in such situations. GRADE methodology allows the panels the possibility of not coming to a decision, and a summary of the discussion is noted in such cases. However, during the development of this guideline, the Voting Panel came to a conclusion in each case scenario, and such a situation did not arise.

Consensus building. The Voting Panel voted on the direction and strength of the recommendation related to each PICO question. Recommendations required a 70% level of agreement, as used previously in other similar processes (28) and in the previous ACR guidelines (23,29,30); if 70% agreement was not achieved during an initial vote, the panel members held additional discussions before revoting. For all conditional recommendations, a written explanation is provided, describing the reasons for the decision and conditions under which the alternative choice may be preferable.

Moving from recommendations to practice. These recommendations are designed to help health care providers work with patients in selecting therapies. The presence or absence of concomitantly occurring conditions, such as IBD, uveitis, diabetes, and serious infections, and the knowledge of previous therapies, influence decisions regarding optimal management. In the context of PsA, the physical examination, which is also required for selecting therapy, includes assessment of the peripheral joints (including for dactylitis), the entheses, the spine, the skin, and the nails. Health care providers and patients must take into consideration all active disease domains, comorbidities, and the patient's functional status in choosing the optimal therapy for an individual at a given point in time.

RESULTS/RECOMMENDATIONS

How to interpret the recommendations

1. A *strong recommendation* means that the panel was *confident* that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion of clinicians/patients not wanting to follow the recommendation. We use the phrase "*should use*" or "*should be used*" for strong recommendations.
2. A *conditional recommendation* means that the panel believed the desirable effects of following the recommendation *probably* outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but a small proportion of clinicians/patients may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. We use the phrase "*is recommended over*" or "*is/would be recommended*" for conditional recommendations. We specify conditions under which the less preferred drug may be used by using the phrase "*may be used*" or "*may consider*" or "*Y (less preferred drug) may be used instead of X (preferred drug)" or "may consider Y instead of X (preferred drug)"* for conditional recommendations.
3. Conditional recommendations were usually based on low- to very-low-quality evidence (in rare instances, moderate-quality evidence). Strong recommendations were typically based on moderate- or high-quality evidence.
4. For each recommendation, Supplementary Appendix 5 (on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23789/abstract) provides details regarding the PICO questions and the GRADE evidence tables.
5. In each case, the Voting Panel's recommendation was based on a judgment of the most likely net benefit, i.e.,1) more benefit with the medication conditionally recommended with no difference in harms between the medications being compared (e.g., choosing a TNFi over OSMs in treatment-naive patients) or 2) less harm with the medication conditionally recommended and no difference in benefit (e.g., choosing abatacept over a TNFi in patients at risk of or with a history of previous infections, or preferring a different OSM over MTX in patients with PsA and diabetes due to an increased risk of liver toxicity in this subpopulation).
6. This is an evidence-based guideline, in that we explicitly use the best evidence available and present that in a transparent manner for the clinician reader/user (31,32). In some instances, this includes a randomized trial directly comparing the interventions under consideration. In other cases, in the absence of any published evidence, the best evidence comes from the collective experience of the Voting Panel and patient panel members, which in the GRADE system is rated as "very-low-quality" evidence.

Recommendations for pharmacologic interventions

Active PsA in treatment-naive patients (Table 1 and Figure 3). *All recommendations for treatment-naive patients with active PsA are conditional based on low- to very-low-quality evidence.*

In treatment-naive patients with active PsA, a TNFi biologic agent is recommended over an OSM as a first-line option (Table 1). OSMs may be used instead of a TNFi biologic in patients without severe PsA and without severe psoriasis (as defined in Methods and Figure 2; final determination of severity to be made by the patient and the health care provider), those who prefer an oral drug instead of parenteral therapy, or those with contraindications to TNFi treatment, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.

For treatment-naive patients with active PsA, the use of a TNFi biologic or OSM is recommended over an interleukin-17 inhibitor (IL-17i) or IL-12/23i biologic. An IL-17i or IL-12/23i biologic may be used instead of TNFi biologics in patients with severe psoriasis or contraindications to TNFi biologics, and may be used instead of OSMs in patients with severe psoriasis or severe PsA. MTX is recommended over NSAIDs in treatment-naive patients with active PsA. NSAIDs may be used instead of MTX after consideration of possible contraindications and side effect profile in patients without evidence of severe PsA or severe psoriasis and in those at risk for liver toxicity (Table 1 and Figure 3). An IL-17i biologic is recommended over an IL-12/23i biologic. IL-12/23i biologics may be used in patients who have concomitant IBD or who desire less frequent drug administration.

Active PsA despite treatment with an OSM (Table 2 and Figure 4). *All recommendations for patients with active PsA despite treatment with an OSM are conditional based on mostly low- to very-low-quality evidence and, in a few instances, moderate-quality evidence.*

In patients with active PsA despite OSM therapy, switching to a TNFi, an IL-17i, or an IL-12/23i biologic is recommended over switching to a different OSM (Table 2 and Figure 4). A different OSM may be used rather than a TNFi, IL-17i, or IL-12/23i in patients who prefer an oral medication or those without evidence of severe PsA or severe psoriasis; a differ-

Table 1. Recommendations for the initial treatment of patients with active psoriatic arthritis who are OSM- and other treatment–naive (PICOs 9–15)*

	Level of evidence (evidence [refs.] reviewed)†
In OSM- and other treatment–naive patients with active PsA,	
1. **Treat with a TNFi biologic over an OSM** (MTX, SSZ, LEF, CSA, or APR) (PICO 10a–e) **Conditional recommendation** based on low-quality evidence; may consider an OSM if the patient does not have severe PsA,‡ does not have severe psoriasis,§ prefers oral therapy, has concern over starting a biologic as the first therapy, or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (53–66)
2. **Treat with a TNFi biologic over an IL-17i biologic** (PICO 14) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-17i biologic if the patient has severe psoriasis or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
3. **Treat with a TNFi biologic over an IL-12/23i biologic** (PICO 13) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has severe psoriasis, prefers less frequent drug administration, or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
4. **Treat with an OSM over an IL-17i biologic** (PICO 12) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-17i biologic if the patient has severe psoriasis and/or severe PsA.	Very low
5. **Treat with an OSM over an IL-12/23i biologic** (PICO 11) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD and/or severe psoriasis and/or severe PsA or prefers less frequent drug administration.	Very low
6. **Treat with MTX over NSAIDs** (PICO 9) **Conditional recommendation** based on very-low-quality evidence; may consider NSAIDs before starting MTX in patients with less active disease, after careful consideration of cardiovascular risks and renal risks of NSAIDs.	Very low (67)
7. **Treat with an IL-17i biologic over an IL-12/23i biologic** (PICO 15) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD or prefers less frequent drug administration.	Very low

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), cyclosporine (CSA), or apremilast (APR) and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. OSM- and other treatment–naive is defined as naive to treatment with OSMs, tumor necrosis factor inhibitors (TNFi,) interleukin-17 inhibitors (IL-17i), and IL-12/23i; patients may have received nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, and/or other pharmacologic and nonpharmacologic interventions.

† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

‡ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.

§ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

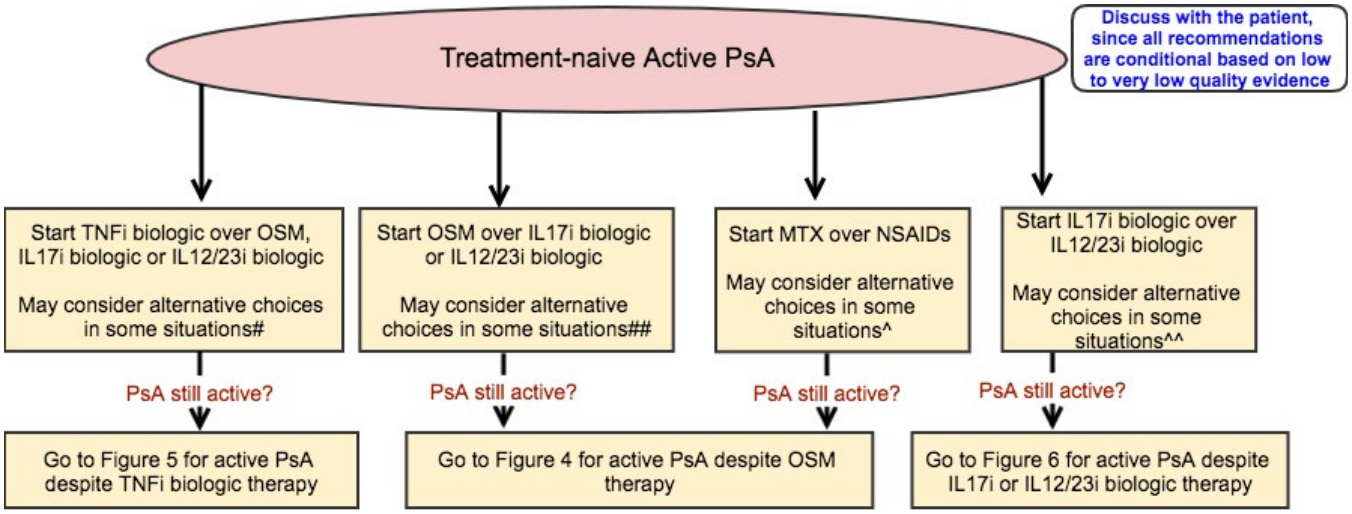

Figure 3. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) who are treatment-naive (no exposure to oral small molecules [OSMs] or other treatments). All recommendations are conditional based on low- to very-low-quality evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 1 and the related section in the Results. This figure is derived from recommendations based on PICO (population/intervention/comparator/outcomes) questions that are based on the common clinical situations. Active PsA was defined as symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining health care provider to be due to PsA based on the presence of at least 1 of the following: actively inflamed joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and/or extraarticular manifestations such as uveitis or inflammatory bowel disease (IBD). TNFi = tumor necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor; MTX = methotrexate; NSAIDs = nonsteroidal antiinflammatory drugs.

ent OSM may be used rather than a TNFi in the presence of contraindications to TNFi biologics. A TNFi biologic is recommended over an IL-17i biologic, an IL-12/23i biologic, abatacept, or tofacitinib. An IL-17i biologic is recommended over an IL-12/23i biologic, abatacept, or tofacitinib. An IL-12/23i is recommended over abatacept or tofacitinib. In patients with contraindications to TNFi agents, an IL-12/23i, an IL-17i, abatacept, or tofacitinib may be used instead of a TNFi. In patients with severe psoriasis, an IL-12/23i or an IL-17i may be used instead of a TNFi. Tofacitinib may be used instead of a TNFi in patients preferring oral medication who do not have severe psoriasis.

Switching to another OSM is recommended over adding another OSM to the current treatment (except in the case of apremilast). Adding another OSM (except apremilast) to current treatment may be considered if the patient has exhibited partial response to the current OSM. Adding apremilast to the current OSM therapy is recommended over switching to apremilast monotherapy since most evidence for benefits of apremilast pertains to apremilast combination therapy. Switching to apremilast monotherapy may be considered instead of apremilast combination therapy if the patient has intolerable side effects with the current OSM.

Biologic monotherapy is recommended over biologic combination therapy with MTX (the most commonly used OSM in combination therapy). When switching to biologic monotherapy, stopping the OSM or tapering of the OSM are both reasonable options and depend on patient and health

Table 2. Recommendations for treatment of patients with active psoriatic arthritis despite treatment with an OSM (PICOs 16–25; 67–69; 76–78)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA despite treatment with an OSM,	
1. **Switch to a TNFi biologic over a different OSM** (PICO 23) **Conditional recommendation** based on moderate-quality evidence; may consider switching to a different OSM if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, if the patient prefers an oral versus parenteral therapy, or in patients without evidence of severe PsA‡ or severe psoriasis.§	Moderate (62–66,69–86)
2. **Switch to a TNFi biologic over an IL-17i biologic** (PICO 17) **Conditional recommendation** based on moderate-quality evidence; may consider an IL-17i if the patient has severe psoriasis and/or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, and/or a family history of demyelinating disease such as multiple sclerosis.	Moderate (62–66, 72–78, 87–97)
3. **Switch to a TNFi biologic over an IL-12/23i biologic** (PICO 16) **Conditional recommendation** based on moderate-quality evidence; may consider an IL-12/23i if the patient has severe psoriasis and/or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers less frequent drug administration.	Moderate (62–66, 72–78, 97–102)
4. **Switch to a TNFi biologic over abatacept** (PICO 67) **Conditional recommendation** based on low-quality evidence; may consider abatacept if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (62–66, 72–78, 103, 104)
5. **Switch to a TNFi biologic over tofacitinib** (PICO 76) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers oral medication.	Low (62–66, 72–78, 105)
6. **Switch to an IL-17i over a different OSM** (PICO 25) **Conditional recommendation** based on low-quality evidence; may consider switching to a different OSM if the patient prefers an oral versus parenteral therapy or in patients without evidence of severe PsA or severe psoriasis.	Low (79–87, 89–95)
7. **Switch to an IL-17i biologic over an IL-12/23i biologic** (PICO 18) **Conditional recommendation** based on moderate-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD or prefers less frequent drug administration.	Moderate (87, 89–95, 98–100, 106, 107)
8. **Switch to an IL-17i biologic over abatacept** (PICO 69) **Conditional recommendation** based on low-quality evidence; may consider abatacept in patients with recurrent or serious infections.	Low (89–95, 103, 104)
9. **Switch to an IL-17i biologic over tofacitinib** (PICO 78) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy or has a history of recurrent *Candida* infections.	Low (89–95, 105)
10. **Switch to an IL-12/23i biologic over a different OSM** (PICO 24) **Conditional recommendation** based on low-quality evidence; may consider switching to a different OSM if the patient prefers an oral versus parenteral therapy or in patients without evidence of severe PsA or severe psoriasis.	Low (79–86, 98–100)
11. **Switch to an IL-12/23i biologic over abatacept** (PICO 68) **Conditional recommendation** based on low-quality evidence; may consider abatacept in patients with recurrent or serious infections.	Low (98–100, 103, 104)

Table 2. *(Cont'd)*

	Level of evidence (evidence [refs.] reviewed)†
12. **Switch to an IL-12/23i biologic over tofacitinib** (PICO 77) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy.	Low (98–100, 105)
13. **Add apremilast to current OSM therapy over switching to apremilast** (PICO 22b) **Conditional recommendation** based on low-quality evidence; may consider switching to apremilast if the patient has intolerable side effects with the current OSM.	Low (83, 84, 108)
14. **Switch to another OSM (except apremilast) over adding another OSM (except apremilast) to current treatment** (PICO 22a) **Conditional recommendation** based on low-quality evidence; may consider adding another OSM (except apremilast) to current treatment if the patient has demonstrated partial response to the current OSM.	Low (83, 84, 108)
15. **Switch to a TNFi biologic monotherapy over MTX and a TNFi biologic combination therapy** (PICO 19) **Conditional recommendation** based on low-quality evidence; may consider MTX and TNFi biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, has concomitant uveitis (since uveitis may respond to MTX therapy), and if the current TNFi biologic is infliximab or adalimumab.	Low (109–111)
16. **Switch to an IL-17i biologic monotherapy over MTX and an IL-17i biologic combination therapy** (PICO 21) **Conditional recommendation** based on very-low-quality evidence; may consider MTX and an IL-17i biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, or has concomitant uveitis (since uveitis may respond to MTX therapy).	Very low
17. **Switch to an IL-12/23i biologic monotherapy over MTX and an IL-12/23i biologic combination therapy** (PICO 20) **Conditional recommendation** based on very-low-quality evidence; may consider MTX and an IL-12/23i biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, or has concomitant uveitis (since uveitis may respond to MTX therapy).	Very low

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine, leflunomide, cyclosporine, or apremilast and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. TNFi = tumor necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor.

† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

‡ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.

§ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

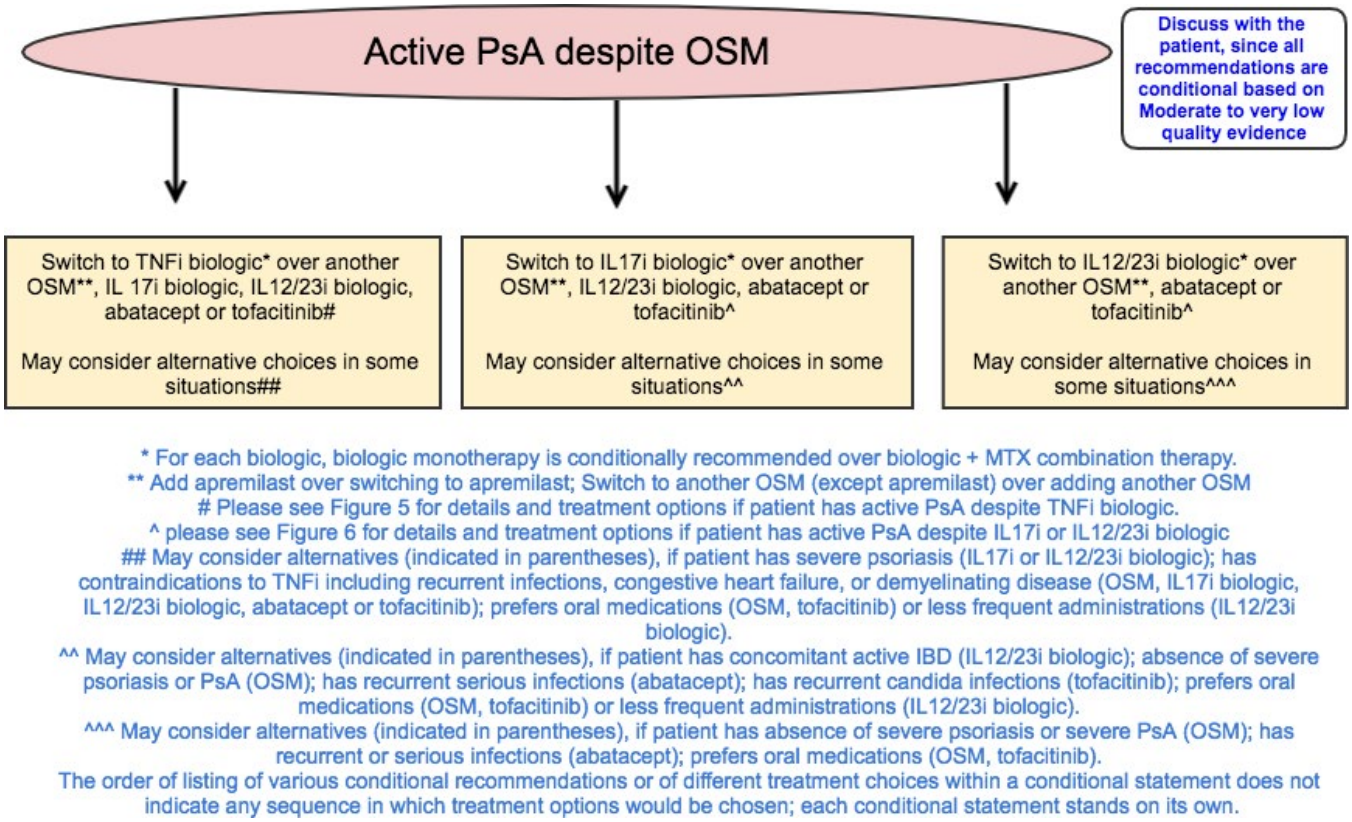

Figure 4. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with oral small molecules (OSMs). All recommendations are conditional based on low- to very-low-quality evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 2 and the related section in the Results. TNFi = tumor necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor; MTX = methotrexate.

care provider preferences. A biologic agent in combination with MTX may be used instead of biologic monotherapy if the patient has severe psoriasis, has had a partial response to current MTX therapy, or has concomitant uveitis (since uveitis may respond to MTX therapy), or in patients receiving treatment with a monoclonal antibody TNFi biologic, especially infliximab and adalimumab, to potentially delay or prevent the formation of antidrug antibodies.

Active PsA despite treatment with a TNFi biologic agent as monotherapy or in combination therapy (Table 3 and Figure 5). *All recommendations for patients with active PsA despite TNFi biologic treatment are conditional based on low- to very-low-quality evidence.*

In patients with active PsA despite treatment with TNFi biologic monotherapy, switching to a different TNFi biologic monotherapy is recommended over switching to IL-12/23i biologic, an IL-17i biologic, abatacept, or tofacitinib monotherapy or adding MTX to the current TNFi biologic (Table 3 and Figure 5). An IL-12/23i biologic, IL-17i biologic, abatacept, or tofacitinib may be used instead of a different TNFi biologic monotherapy in the case of a primary TNFi biologic failure or a serious adverse event due to the TNFi biologic. An IL-17i or IL-12/23i biologic may be used instead of a different TNFi biologic, particularly in the presence of severe psoriasis. Abatacept may be used instead of a TNFi biologic in patients with recurrent or serious infections in the absence of severe psoriasis, based on indirect evidence of fewer hospitalized infections with abatacept compared to TNFi biologics in a population with rheumatoid arthritis (33). Tofacitinib may be used instead of a TNFi biologic if oral therapy is preferred by the patient.

In patients with active PsA despite treatment with TNFi biologic monotherapy, an IL-17i biologic is recommended over an IL-12/23i biologic, abatacept, or tofacitinib, and an IL-12/23i biologic is recommended over abatacept or tofacitinib. An IL-12/23i biologic may be considered instead of an IL-17i biologic if the patient has IBD or desires less frequent drug administration. Abatacept may be considered instead of an IL-

Table 3. Recommendations for treatment of patients with active psoriatic arthritis despite treatment with a TNFi biologic, as monotherapy or in combination with MTX (PICOs 26–35; 70–75)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA despite treatment with a TNFi biologic monotherapy,	
1. **Switch to a different TNFi biologic over switching to an IL-17i biologic** (PICO 28) **Conditional recommendation** based on low-quality evidence; may consider an IL-17i if the patient had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse event or severe psoriasis.‡	Low (72, 73, 90–93, 95)
2. **Switch to a different TNFi biologic over switching to an IL-12/23i biologic** (PICO 27) **Conditional recommendation** based on low-quality evidence; may consider an IL-12/23i if the patient had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse effect or prefers less frequent drug administration.	Low (72, 73, 99, 100)
3. **Switch to a different TNFi biologic over switching to abatacept** (PICO 70) **Conditional recommendation** based on low-quality evidence; may consider abatacept if the patient had a primary TNFi biologic efficacy failure or TNFi biologic–associated serious adverse effect.	Low (72, 73, 103, 104)
4. **Switch to a different TNFi biologic over switching to tofacitinib** (PICO 73) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy or had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse effect.	Low (62–66, 72–78, 105)
5. **Switch to a different TNFi biologic (with or without MTX) over adding MTX to the same TNFi biologic monotherapy** (PICO 26 and 26A) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX when patients have demonstrated partial response to the current TNFi biologic therapy,especially if the TNFi biologic is a monoclonal antibody.	Very low
6. **Switch to an IL-17i biologic over switching to an IL-12/23i biologic** (PICO 29) **Conditional recommendation** based on low-quality evidence; may consider an IL-12/23i if the patient has IBD or if the patient prefers less frequent drug administration.	Low (90–93, 95, 99, 100)
7. **Switch to an IL-17i biologic over abatacept** (PICO 72) **Conditional recommendation** based on low-quality evidence; may consider abatacept if the patient prefers IV dosing or in patients with recurrent or serious infections.	Low (90–93, 95, 103, 104, 112)
8. **Switch to an IL-17i biologic over tofacitinib** (PICO 75) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy or in patients with concomitant IBD or a history of recurrent *Candida* infections.	Low (90–93, 105)
9. **Switch to an IL-12/23i biologic over abatacept** (PICO 71) **Conditional recommendation** based on of low-quality evidence; may consider abatacept if the patient prefers IV dosing or in patients with recurrent or serious infections.	Low (99, 100, 103, 104)
10. **Switch to an IL-12/23i biologic over tofacitinib** (PICO 74) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy.	Low (98–100, 105)
11. **Switch to a different TNFi biologic monotherapy over switching to a different TNFi biologic and MTX combination therapy** (PICO 30) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a TNFi biologic and MTX combination therapy if the current TNFi biologic is infliximab.	Very low
12. **Switch to an IL-17i biologic monotherapy over switching to an IL-17i biologic and MTX combination therapy** (PICO 32) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-17i biologic and MTX combination therapy in patients with concomitant uveitis, as uveitis may respond to MTX therapy.	Very low

Table 3. *(Cont'd)*

	Level of evidence (evidence [refs.] reviewed)†
13. **Switch to an IL-12/23i biologic monotherapy over switching to an IL-12/23i biologic and MTX combination therapy** (PICO 31) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-12/23i biologic and MTX combination therapy if the patient has severe psoriasis.	Very low
In adult patients with active PsA despite treatment with a TNFi biologic and MTX combination therapy,	
14. **Switch to a different TNFi biologic + MTX over switching to a different TNFi biologic monotherapy** (PICO 33) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a different TNFi biologic monotherapy if the patient has demonstrated MTX-associated adverse events, prefers to receive fewer medications, or perceives MTX as a burden.	Very low
15. **Switch to an IL-17i biologic monotherapy over an IL-17i biologic and MTX combination therapy** (PICO 35) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-17i biologic and MTX combination therapy if the patient had had a partial response to the existing regimen or in patients with concomitant uveitis, as uveitis may respond to MTX therapy. Continuing MTX during the transition to an IL-17i biologic was discussed as potentially beneficial to allow the new therapy time to work.	Very low
16. **Switch to IL-12/23i biologic monotherapy over IL-12/23i biologic and MTX combination therapy** (PICO 34) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-12/23i biologic and MTX combination therapy if the patient had had a partial response to the existing regimen or in patients with concomitant uveitis, as uveitis may respond to MTX therapy. Continuing MTX during the transition to an IL-12/23i biologic was discussed as potentially beneficial to allow the new therapy time to work.	Very low

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). TNFi = tumor necrosis factor inhibitor; MTX = methotrexate; IL-17i = interleukin-17 inhibitor; IV = intravenous.
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
‡ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

17i or IL-12/23i biologic in patients with recurrent or serious infections. Tofacitinib may be considered instead of an IL-17i biologic in patients who prefer oral therapy or have a history of recurrent or severe *Candida* infections. Tofacitinib may be considered instead of an IL-12/23i biologic in patients who prefer oral therapy. For each biologic (TNFi, IL-12/23i, or IL-17i), monotherapy is recommended over combination with MTX. Combination therapy with biologic and MTX may be used instead of biologic monotherapy in the presence of severe psoriasis, partial response to current MTX therapy, concomitant uveitis (since uveitis may respond to MTX therapy), and if the current TNFi biologic is infliximab or adalimumab (for immunogenicity prevention).

Under circumstances in which combination therapy with a TNFi biologic and MTX is used and active PsA persists, switching to a different TNFi with MTX is recommended over monotherapy with a different TNFi. Continuing MTX treatment during TNFi transition was seen as beneficial because TNFi biologics may have more sustained efficacy when used in combination with MTX, but evidence is limited (34). Monotherapy with a different TNFi biologic may be used if the patient has had MTX-associated adverse events, prefers to receive fewer medications, or perceives MTX treatment as a burden. IL-12/23i or IL-17i biologic monotherapy is recommended over either of these agents in combination with MTX. Combination therapy with an IL-17i or IL-12/23 biologic and MTX may be used instead of switching to biologic monotherapy

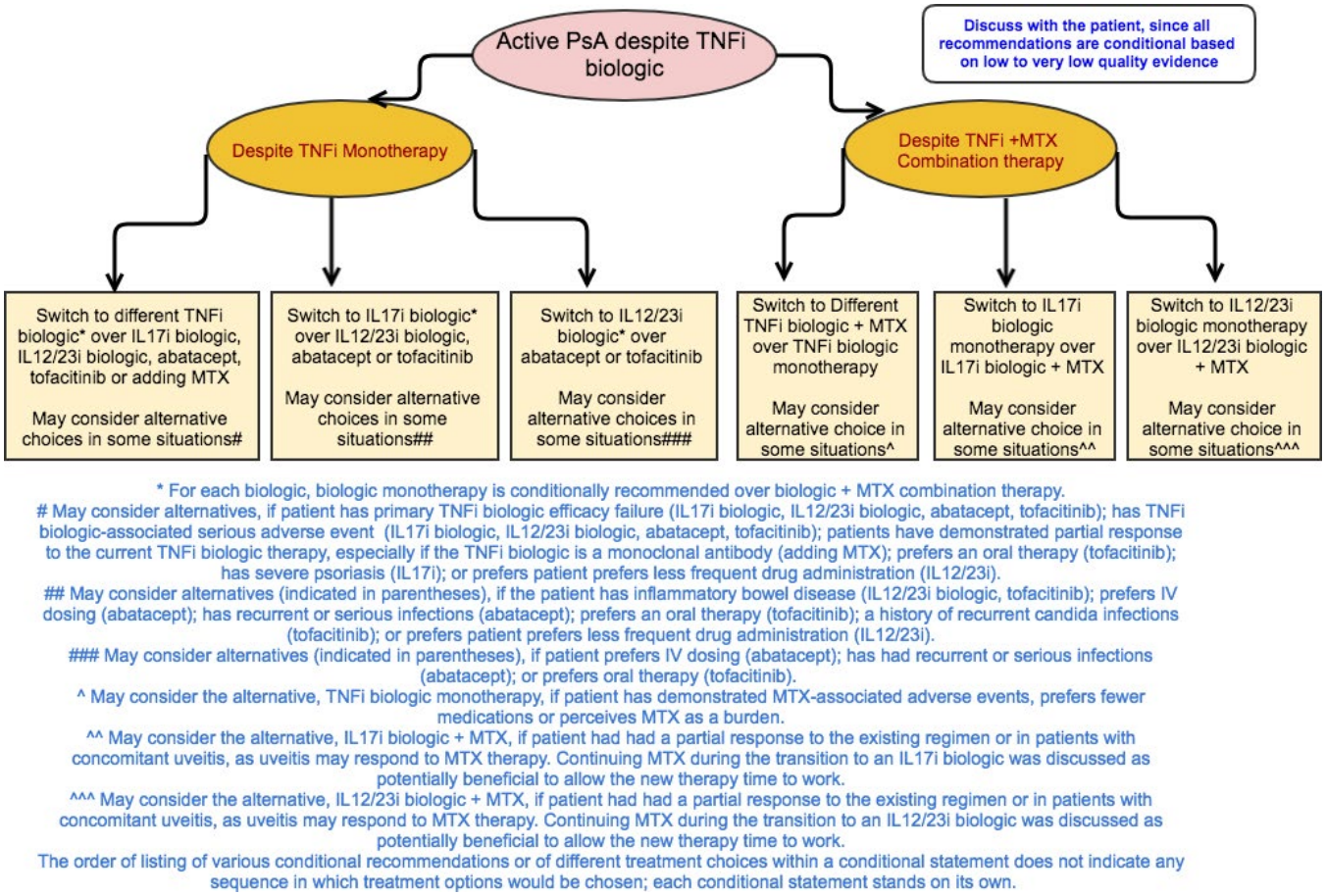

Figure 5. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with a tumor necrosis factor inhibitor (TNFi) as monotherapy or as combination therapy with methotrexate (MTX). All recommendations are conditional based on low- to very-low-quality evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 3 and the related section in the Results. IL-17i = interleukin-17 inhibitor; IV = intravenous.

if the patient had a partial response to the existing regimen and/or has concomitant uveitis that might respond to MTX therapy.

Active PsA despite treatment with an IL-17i biologic agent as monotherapy (Table 4 and Figure 6). *All recommendations for patients with active PsA despite IL-17i biologic treatment are conditional based on very-low-quality evidence.*

In patients with active PsA despite treatment with an IL-17i biologic, switching to a TNFi biologic is recommended over switching to an IL-12/23i biologic, adding MTX to the current IL-17i biologic, or switching to a different IL-17i biologic (Table 4 and Figure 6). Switching to an IL-12/23i biologic is recommended over adding MTX to the current IL-17i biologic or switching to a different IL-17i biologic. Treatment may be switched to an IL-12/23i biologic instead of a TNFi biologic if the patient has severe psoriasis or a contraindication to TNFi biologic treatment. Another IL-17i biologic may be used instead of switching to a TNFi or IL-12/23i biologic if the patient had a secondary efficacy failure with the current IL-17i biologic, severe psoriasis, or a contraindication to TNFi treatment. MTX may be added to the current IL-17i regimen instead of switching to a TNFi or IL-12/23i biologic in patients who have had a partial response to the current IL-17i biologic.

Active PsA despite treatment with an IL-12/23i biologic agent as monotherapy (Table 4 and Figure 6). *All recommendations for patients with active PsA despite IL-12/23i biologic treatment are conditional based on very-low-quality evidence.*

In patients with active PsA despite treatment with an IL-12/23i biologic, switching to a TNFi biologic is recommended over adding MTX to the current regimen or switching to an IL-17i biologic

Table 4. Recommendations for treatment of patients with active psoriatic arthritis despite treatment with an IL-17i or an IL-12/23i biologic monotherapy (PICOs 36–43)*

	Level of evidence†
In adult patients with active PsA despite treatment with an IL-17i biologic monotherapy,	
1. **Switch to a TNFi biologic over switching to an IL-12/23i biologic** (PICO 39) **Conditional recommendation** based on very-low-quality-evidence; may consider switching to IL-12/23i if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers less frequent drug administration.	Very low
2. **Switch to a TNFi biologic over switching to a different IL-17i biologic** (PICO 42) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a different IL-17i if the patient had had a secondary efficacy failure to current IL-17i, or severe psoriasis, or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
3. **Switch to a TNFi biologic over adding MTX to an IL-17i biologic** (PICO 41) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX to an IL-17i if the patient had had a partial response to the existing regimen or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
4. **Switch to an IL-12/23i biologic over switching to a different IL-17i biologic** (PICO 43) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a different IL-17i if the patient had had a secondary efficacy failure to current IL-17i or severe psoriasis,‡ or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
5. **Switch to an IL-12/23i biologic over adding MTX to an IL-17i biologic** (PICO 40) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX to an IL-17i if the patient had had a partial response to the existing regimen.	Very low
In adult patients with active PsA despite treatment with an IL-12/23i biologic monotherapy,	
6. **Switch to a TNFi biologic over switching to an IL-17i biologic** (PICO 38) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-17i if the patient has severe psoriasis or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
7. **Switch to a TNFi biologic over adding MTX to an IL-12/23i biologic** (PICO 36) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX in patients in whom the severe psoriasis is not responding to the current therapy, or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
8. **Switch to an IL-17i biologic over adding MTX to an IL-12/23i biologic** (PICO 37) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX in patients with only partial response to the current therapy or in those who potentially have not had enough time to adequately respond.	Very low

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease. IL-17i = interleukin-17 inhibitor; TNFi = tumor necrosis factor inhibitor; MTX = methotrexate.

† When there were no published studies—as was the case with all of the recommendations presented in this table—we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

‡ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

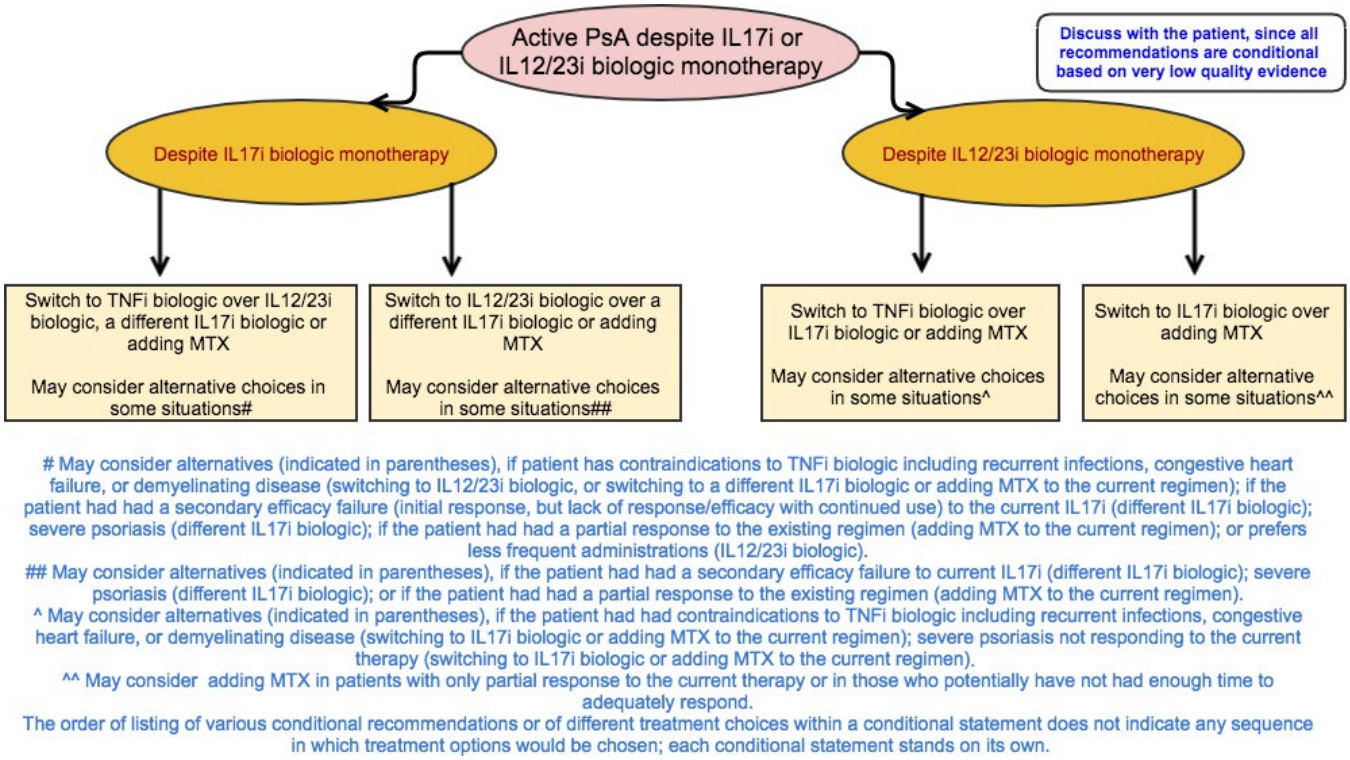

Figure 6. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with interleukin-17 inhibitor (IL-17i) or IL-12/23i biologic monotherapy. All recommendations are conditional based on low- to very-low-quality of evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 4 and the related section in the Results. TNFi = tumor necrosis factor inhibitor; MTX = methotrexate.

(Table 4 and Figure 6). Switching to an IL-17i biologic is recommended over adding MTX to the current therapy. Treatment may be switched to an IL-17i biologic instead of a TNFi biologic if the patient has severe psoriasis or a contraindication to TNFi biologic treatment. MTX may be added to the current IL-12/23i biologic therapy instead of switching to a TNFi or an IL-17i biologic in patients with a partial response to the current therapy; MTX may also be added to the current IL-12/23i biologic therapy instead of switching to a TNFi biologic in the presence of contraindications to TNFi biologics.

Treat-to-target (Table 5). *This recommendation for patients with active PsA is conditional based on low-quality evidence.*

In patients with active PsA, using a treat-to-target strategy is recommended over not following a treat-to-target strategy. One may consider not using a treat-to-target strategy in patients in whom there are concerns related to increased adverse events, costs of therapy, and patient burden of medications associated with tighter control.

Active PsA with psoriatic spondylitis/axial disease despite treatment with NSAIDs (Table 5). *All recommendations for patients with active PsA with psoriatic spondylitis/axial disease despite NSAID treatment are conditional based on very-low-quality evidence.*

The ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for patients with axial spondyloarthritis (35) should be followed for patients with axial PsA. OSMs are not effective for axial disease (35). In patients with active axial PsA despite NSAID treatment, a TNFi biologic is recommended over an IL-17i or IL-12/23i biologic, and an IL-17i biologic is recommended over an IL-12/23i biologic. An IL-17i biologic may be used instead of a TNFi biologic if the patient has severe psoriasis or a contraindication to TNFi biologic treatment (Table 5). We recommend *not using* an IL-12/23i biologic since 3 randomized trials of an IL-12/23i biologic (ustekinumab) in patients with axial spondyloarthritis (a related condition) were stopped because the key primary and secondary end points were not achieved (36–38); the safety profile was reportedly consistent with that observed in past ustekinumab studies.

Table 5. Recommendations for treatment of patients with active psoriatic arthritis including treat-to-target, active axial disease, enthesitis, or active inflammatory bowel disease (PICOs 44–55; 58–62)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA,	
1. **Use a treat-to-target strategy over not following a treat-to-target strategy** (PICO 44) **Conditional recommendation** based on low-quality evidence; may consider not following a treat-to-target strategy in patients in whom higher frequency and/or severity of adverse events, higher cost of therapy, or higher patient burden of medications with tighter control are a concern.	Low (113)
In patients with active PsA with psoriatic spondylitis/axial disease despite treatment with NSAIDs,‡	
2. **Switch to a TNFi biologic over switching to an IL-17i biologic** (PICO 46) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-17i biologic if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or if the patient has severe psoriasis.§	Very low
3. **Switch to a TNFi biologic over switching to an IL-12/23i biologic** (PICO 45) **Conditional recommendation** based on very-low-quality evidence; switching to an IL-12/23i biologic is *not* considered since recent trials in axial SpA were stopped.	Very low
4. **Switch to an IL-17i biologic over switching to an IL-12/23i** (PICO 47) **Conditional recommendation** based on very-low-quality evidence; switching to an IL-12/23i biologic is *not* considered since recent trials in axial SpA were stopped.	Very low
In adult patients with active PsA and predominant enthesitis who are both OSM- and biologic treatment–naive,¶	
5. **Start oral NSAIDs over an OSM (specifically apremilast)** (PICO 48) **Conditional recommendation** based on very-low-quality evidence; may consider starting an OSM (specifically apremilast) if the patient has active joint disease and/or skin disease or contraindications to the use of NSAIDs, including cardiovascular disease, peptic ulcer disease, or renal disease or impairment.	Very low
6. **Start a TNFi biologic over an OSM (specifically apremilast)** (PICO 48A) **Conditional recommendation** based on very-low-quality evidence; may consider starting an OSM (specifically apremilast) if the patient prefers an oral treatment as the first therapy or the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
7. **Start tofacitinib over an OSM (specifically apremilast)** (PICO 55) **Conditional recommendation** based on very-low-quality evidence; may consider starting an OSM (specifically apremilast) if the patient has recurrent infections.	Very low
In adult patients with active PsA and predominant enthesitis despite treatment with OSM,	
8. **Switch to a TNFi biologic over an IL-17i biologic** (PICO 53) **Conditional recommendation** based on low-quality evidence; may consider switching to an IL-117i if the patient has severe psoriasis or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (72, 73, 76, 89, 90, 92)
9. **Switch to a TNFi biologic over an IL-12/23i biologic** (PICO 52) **Conditional recommendation** based on low-quality evidence; may consider switching to an IL-12/23i if the patient has severe psoriasis or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or if the patient prefers less frequent drug administration.	Low (72, 73, 76, 98, 100)
10. **Switch to a TNFi biologic over switching to another OSM** (PICO 49) **Conditional recommendation** based on low-quality evidence; may consider switching to another OSM# if the patient prefers an oral medication over an injection, or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (72, 73, 76, 83–85)

Table 5. *(Cont'd)*

	Level of evidence (evidence [refs.] reviewed)†
11. **Switch to an IL-17i biologic over an IL-12/23i biologic** (PICO 54) **Conditional recommendation** based on low-quality evidence; may consider switching to an IL-12/23i if the patient has concomitant IBD or if the patient prefers less frequent drug administration.	Low (89, 90, 92, 93, 98–100)
12. **Switch to an IL-17i biologic over switching to another OSM** (PICO 51) **Conditional recommendation** based on low-quality evidence; may consider switching to another OSM if the patient prefers an oral medication.	Low (83–86, 89, 90, 92, 93)
13. **Switch to an IL-12/23i biologic over switching to another OSM** (PICO 50) **Conditional recommendation** based on low-quality evidence; may consider switching to another OSM# if the patient prefers an oral medication over an injection, or if there are contraindications to an IL-12/23i, such as severe recurrent infections.	Low (83–86, 98, 100)
In adult patients with active PsA and concomitant active IBD who are both OSM- and biologic treatment–naive,	
14. **Start a monoclonal antibody TNFi biologic over an OSM** (PICO 62) **Conditional recommendation** based on very-low-quality evidence; may consider starting an OSM if the patient prefers an oral medication, or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low (114)
In adult patients with active PsA and concomitant active IBD despite treatment with an OSM,	
15. **Switch to a monoclonal antibody TNFi biologic over a TNFi biologic soluble receptor biologic (i.e., etanercept)** (PICO 58)	Moderate (115–117)
Strong recommendation supported by moderate-quality evidence, showing TNFi monoclonal antibody biologics are effective in IBD but indirect evidence shows a TNFi biologic soluble receptor biologic is not effective for the treatment of IBD.	
16. **Switch to a TNFi monoclonal antibody biologic over an IL-17i biologic** (PICO 59)	Moderate (50)
Strong recommendation supported by moderate-quality evidence showing monoclonal antibody TNFi biologics are effective for IBD while an IL-17i biologic is not effective for IBD.	
17. **Switch to a TNFi biologic monoclonal antibody biologic over an IL-12/23i biologic** (PICO 61) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-12/23i biologic if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers less frequent drug administration.	Very low
18. **Switch to an IL-12/23i biologic over switching to an IL-17i biologic** (PICO 60)	Moderate (50)
Strong recommendation supported by moderate-quality evidence showing IL-12/23i biologic is effective for IBD while an IL-17i biologic is not effective for IBD.	

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD).

† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

‡ Axial disease is generally treated according to the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for spondyloarthritis (SpA).

§ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

¶ Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine, leflunomide, cyclosporine, or apremilast and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. OSM- and biologic treatment–naive is defined as naive to treatment with OSMs, tumor necrosis factor inhibitors (TNFi,), interleukin-17 inhibitors (IL-17i), and IL-12/23i; patients may have received nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, and/or other pharmacologic and nonpharmacologic interventions.

It should be noted that for the enthesitis questions (PICO 49, 50, and 51), the existing evidence was mainly drawn from the apremilast studies, as no randomized controlled trial report described enthesitis outcomes for the other OSMs.

Active PsA with predominant enthesitis in treatment-naive patients and despite treatment with an OSM (Table 5). *All recommendations for patients with active PsA with predominant enthesitis are conditional based on low- to very-low-quality evidence. (This section names apremilast among all OSMs specifically for recommendations, since of the OSMs, only apremilast has shown efficacy for enthesitis.)*

In treatment-naive PsA patients with predominant enthesitis, a TNFi biologic is recommended over an OSM as a first-line option. Apremilast may be used instead of a TNFi biologic if the patient prefers an oral therapy or has contraindications to TNFi. Oral NSAIDs are recommended over starting an OSM unless the patient has cardiovascular disease, peptic ulcer disease, renal disease (or impairment), or severe psoriasis or PsA, in which case apremilast may be given instead of NSAIDs. Tofacitinib is recommended over apremilast for treatment-naive patients with predominant enthesitis. Apremilast may be used instead of tofacitinib in patients with recurrent infections.

In patients with active PsA with predominant enthesitis despite treatment with an OSM (used for other manifestations of PsA), a TNFi biologic, an IL-17i biologic, or an IL-12/23i biologic is recommended over switching to another OSM. Apremilast may be used in patients who prefer oral therapy or who have recurrent infections or contraindications to TNFi biologics. A TNFi biologic is recommended over an IL-17i or IL-12/23i biologic. An IL-17i or IL-12/23i biologic may be used instead of a TNFi biologic in patients with severe psoriasis or contraindications to TNFi. An IL-17i biologic is recommended over an IL-12/23i biologic. An IL-12/23i biologic may be used instead of a TNFi biologic in patients who prefer less frequent drug administration, and instead of an IL-17i biologic in patients with concomitant IBD or who prefer less frequent drug administration.

Active PsA with concomitant active IBD (Table 5). *All recommendations for patients with active PsA with concomitant active IBD are strong based on moderate-quality evidence, except for 2 conditional recommendations based on very-low-quality evidence.*

Active PsA in OSM- and biologic treatment–naive patients with concomitant active IBD. In patients with active PsA with concomitant active IBD who have not received OSM or biologic treatment, a monoclonal antibody TNFi biologic (excludes etanercept, which is a fusion molecule/soluble receptor biologic) is recommended over an OSM (Table 5). An OSM may be used in patients without severe PsA who prefer oral therapy or have contraindications to TNFi biologics.

Active PsA despite treatment with an OSM in patients with concomitant active IBD. In patients with active PsA with concomitant active IBD despite treatment with an OSM, a monoclonal antibody TNFi biologic or an IL-12/23i biologic *should be used* over an IL-17i biologic, and a monoclonal antibody TNFi biologic *should be used* over a TNFi soluble receptor biologic (etanercept) (*all strong recommendations* [Table 5]). A monoclonal antibody TNFi biologic is recommended over an IL-12/23i biologic (conditional recommendation). An IL-12/23i biologic may be used instead of a monoclonal antibody TNFi biologic in patients with contraindications to TNFi biologics or who prefer less frequent drug administration.

Active PsA with comorbidities (Table 6). *All recommendations for patients with active PsA with comorbidities are conditional based on low- to very-low-quality evidence, except those for patients with serious infections, which are strong based on moderate-quality evidence.*

Active PsA in OSM- and biologic treatment–naive patients with concomitant diabetes. In patients with active PsA with concomitant active diabetes who have not received OSM or biologic treatment, an OSM other than MTX is recommended over a TNFi biologic, due to the concern about the higher prevalence of fatty liver disease and liver toxicity with MTX use in this patient population (39,40) (Table 6). A TNFi biologic may be used instead of an OSM in the presence of severe PsA or severe psoriasis or when diabetes is well controlled (i.e., with a potentially lower risk of infections).

Active PsA in OSM- and biologic treatment–naive patients with frequent serious infections. In patients with active PsA who have frequent serious infections and have not received OSM or biologic treatment, an OSM *should be used* over a TNFi biologic as a first-line treatment since there is a black box warning against the use of a TNFi biologic in patients with frequent serious infections (*strong recommendation*). An IL-12/23i or IL-17i biologic is recommended over a TNFi biologic (conditional recommendation [Table 6]). A TNFi biologic may be used instead of an IL-12/23i biologic in patients with severe PsA and instead of an IL-17i biologic in patients with concomitant IBD.

Active PsA in patients requiring killed or live attenuated vaccinations when starting biologic treatment (Table 7). *All recommendations for vaccinations in patients with active PsA are conditional based on very-low-quality evidence.*

It is recommended that the biologic treatment be started and the killed vaccines administered (as indicated based on patient age, sex, and immunization history per recommendations of the Centers for Disease Control and Prevention [41]) in patients with active PsA over delaying the biologic to give the killed vaccines. Delaying the start of the biologic is recommended over not delaying to administer a live attenuated vaccination in patients with active PsA (Table 7). If PsA manifestations are severe and delaying the start of the biologic is not desirable, starting the biologic and administering the live attenuated vaccines at the same time might be considered.

Table 6. Recommendations for treatment of patients with active psoriatic arthritis and comorbidities, including concomitant diabetes and recurrent serious infections (PICOs 63–66)*

	Level of evidence (evidence [refs.] reviewed) †
In adult patients with active PsA and diabetes who are both OSM- and biologic treatment–naive,‡	
1. **Start an OSM other than MTX over a TNFi biologic** (PICO 63a) **Conditional recommendation** based on very-low-quality evidence; may consider starting a TNFi, if the patient has severe PsA§ or severe/active skin disease,¶ when diabetes is well controlled.	Very low (118, 119)
In adult patients with active PsA and frequent serious infections who are both OSM- and biologic treatment–naive,	
2. **Start an OSM over a TNFi biologic** (PICO 64) **Strong recommendation** supported by moderate-quality evidence, including a black box warning against the use of a TNFi biologic with regard to increased risk of serious infection.	Moderate (33, 120)
3. **Start an IL-12/23i biologic over a TNFi biologic** (PICO 65) **Conditional recommendation** based on very-low-quality evidence; may consider starting a TNFi if the patient has severe PsA.	Very low (33)
4. **Start an IL-17i biologic over a TNFi biologic** (PICO 66) **Conditional recommendation** based on very-low-quality evidence; may consider starting a TNFi biologic in patients with concomitant IBD.	Very low

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD).
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
‡ Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine, leflunomide, cyclosporine, or apremilast and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. OSM- and other treatment–naive is defined as naive to treatment with OSMs, tumor necrosis factor inhibitors (TNFi), interleukin-17 inhibitors (IL-17i), and IL-12/23i; patients may have received nonsteroidal antiinflammatory drugs, glucocorticoids, and/or other pharmacologic and nonpharmacologic interventions.
§ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.
¶ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

Recommendations for nonpharmacologic interventions in patients with active PsA regardless of pharmacologic treatment status (Table 8)

All recommendations for nonpharmacologic interventions for patients with active PsA are conditional based on low- to very-low-quality evidence, except that for smoking cessation, which is a strong recommendation.

It is recommended that patients with active PsA use some form or combination of exercise, physical therapy, occupational therapy, massage therapy, and acupuncture over not using these modalities as tolerated. Low-impact exercise (e.g., tai chi, yoga, swimming) is recommended over high-impact exercise (e.g., running). High-impact exercises may be performed instead of low-impact exercises by patients who prefer the former and

Table 7. Recommendations for vaccination in patients with active psoriatic arthritis (PICOs 56–57)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA needing vaccinations,‡	
1. **Start the biologic and administer killed vaccines over delaying the start of biologic to administer killed vaccines** (PICO 56) **Conditional recommendation** based on very-low-quality evidence; may consider delaying the start of biologic to administer killed vaccines due to patient preference based on patient belief about vaccine efficacy.	Very low (121–126)
2. **Delay the start of biologic to administer live attenuated vaccines over starting the biologic and administering live attenuated vaccines** (PICO 57) **Conditional recommendation** based on very-low-quality evidence; may consider starting the biologic and administering live attenuated vaccines in patients with very active severe joint§ or skin¶ disease who prefer no delay in biologic initiation.	Very low (127)

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease.
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
‡ Vaccines as indicated by patient age, sex, and immunization history per recommendations from the Centers for Disease Control and Prevention and available at: https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf.
§ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.
¶ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

have no contraindications to high-impact exercises (Table 8). Clinicians *should* encourage patients to stop smoking, offering cessation aids, due to a demonstrated effectiveness of smoking cessation in randomized trials in other conditions and in the general population (42–44) (*strong recommendation*). In PsA patients who are overweight or obese, weight loss is recommended in order to potentially increase pharmacologic response.

All strong recommendations in this guideline are also listed separately in Supplementary Appendix 6, at http://onlinelibrary.wiley.com/doi/10.1002/acr.23789/abstract.

DISCUSSION

We present herein the first ACR/NPF guideline for the treatment of psoriatic arthritis. The goal of this guideline is to assist health care providers in managing active PsA in their patients, including optimizing therapy. PsA is a heterogeneous and multifaceted inflammatory disease, and its different clinical features (e.g., peripheral arthritis, psoriasis, nail disease, enthesitis, dactylitis, axial disease) sometimes respond differently to therapy. Despite an expansion in the number of new therapies for PsA, there remains limited comparative efficacy/effectiveness evidence to inform treatment decisions. Thus, most of our recommendations are based on low-quality evidence and are conditional. The conditional recommendations convey that, although the suggested course of action will be best for many patients, there will be some patients in whom, considering their comorbidities and/or their values and preferences, the alternative represents the best choice. The guideline will be updated as new evidence from comparative studies becomes available.

A Patient Panel meeting was held prior to the Voting Panel meeting to gain insight into patients' values and preferences for the pharmacologic/nonpharmacologic intervention comparisons being addressed. We recognize that patient preferences are an important part of our treatment recommendations. Findings from the Patient Panel meeting were discussed throughout the Voting

Table 8. Recommendations for treatment of patients with active psoriatic arthritis with nonpharmacologic interventions (PICOs 1–8)*

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA,	
1. **Recommend exercise over no exercise** (PICO 1) **Conditional recommendation** based on low-quality evidence; may consider no exercise in patients with existing muscle/tendon injury or multiple inflamed symptomatic joints with worsening pain with exercise.	Low (128)
2. **Recommend low-impact exercise (e.g., tai chi, yoga, swimming) over high-impact exercise (e.g., running)** (PICO 2) **Conditional recommendation** based on very-low-quality evidence; may consider high-impact exercise due to patient preference.	Very low
3. **Recommend physical therapy over no physical therapy** (PICO 3) **Conditional recommendation** based on very-low-quality evidence; may consider no physical therapy due to patient preference, out-of-pocket cost, distance to physical therapy site, or lack of transportation.	Very low
4. **Recommend occupational therapy over no occupational therapy** (PICO 4) **Conditional recommendation** based on low-quality evidence; may consider no occupational therapy due to patient preference, out-of-pocket cost, distance to occupational therapy site, or lack of transportation.	Low (129, 130)
5. **Recommend weight loss over no weight loss for patients who are overweight/obese** (PICO 5) **Conditional recommendation** based on low-quality evidence; may consider no weight loss due to additional patient burden involved with weight-loss program.	Low (131–133)
6. **Recommend massage therapy over no massage therapy** (PICO 7) **Conditional recommendation** based on very-low-quality evidence; may consider no massage therapy due to associated costs.	Very low (134)
7. **Recommend acupuncture over no acupuncture** (PICO 8) **Conditional recommendation** based on very-low-quality evidence; may consider no acupuncture due to associated costs.	Very low (135)
8. **Recommend smoking cessation over no smoking cessation** (PICO 6) **Strong recommendation** supported by moderate-quality evidence, rated down for indirectness.	Moderate (136, 137)

***** Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease.
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

Panel meeting to ensure that patient input was incorporated into the final PsA guideline. Examples of patient feedback included strong value on therapies that are effective (e.g., prevent further damage, and improve quality of life, social participation, and function) and safe (especially having low adverse event profiles). In particular, patients discussed the negative impact of adverse events (e.g., fatigue, nausea, and malaise) on quality of life and social participation, and thus the risk for these adverse events weighed heavily in patients' decision-making. The concept of treat-to-target was challenging for patients. Although they saw value in improved outcomes, they also thought this strategy could increase costs to the patient (e.g., copayments, time traveling to more frequent appointments, etc.) and potentially increase adverse events. Therefore, a detailed conversation with the patient is needed to make decisions regarding treat-to-target. To help ensure that the recommendations were patient-centered, 2 patients were members of the Voting Panel.

While using a treat-to-target approach over not using a treat-to-target approach was discussed by the Voting Panel, we did not address specific targets to be recommended or used. There have been 2 international meetings to discuss potential targets: the use of either minimal disease activity (MDA) or disease activity in psoriatic arthritis (DAPSA) (45,46). The treatment target for PsA would likely be MDA or DAPSA, although a different target may be chosen through patient–provider discussion.

The ACR/NPF PsA guideline conditionally recommends a TNFi biologic over an OSM agent in patients with active PsA.

The available low-quality evidence is inconclusive regarding the efficacy of OSMs in management of PsA, whereas there is moderate-quality evidence of the benefits of TNFi biologics, in particular regarding their impact on the prevention of disease progression and joint damage. In making their recommendation, the panel recognized the cost implications, but put considerations of quality of evidence for benefit over other considerations. This guideline provides recommendations for early and aggressive therapy in patients with newly diagnosed PsA.

The recommendation is, however, conditional, and the panel recognized several potential exceptions to it. Circumstances in which a patient may choose an OSM over a TNFi biologic may include mild-to-moderate disease, a preference of oral over parenteral therapy, or concerns regarding adverse effects of a biologic. A TNFi biologic would not be a good choice in patients with contraindications, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.

During the development of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recommendations (47) and the European League Against Rheumatism (EULAR) recommendations (48) for the treatment of PsA, panel members also challenged the decision to put OSMs first in those recommendations. For the EULAR recommendations, the final decision was made based on the lower cost of these medications, a consideration our panel placed lower than the quality of evidence for benefit.

In patients with concomitant IBD, the Voting Panel made strong recommendations favoring a monoclonal antibody TNFi or an IL-12/23i biologic over an IL-17i biologic or a TNFi receptor biologic (etanercept). This was based on moderate-quality evidence showing that TNFi biologics and ustekinumab (an IL-12/23i biologic) are effective for the management of IBD, whereas etanercept (a TNFi receptor biologic) and secukinumab (an IL-17i biologic) are not (49,50).

When the evidence was low or very-low quality, the panel could not be confident in the judgment of net benefit—thus the conditional recommendation. Often, low- or very-low-quality evidence came from indirect evidence, for instance from rheumatoid arthritis (33) or, in the absence of studies, from clinical experience (Supplementary Appendix 5, on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23789/abstract). When data on comparative benefits and comparative harms were similar between two medications, the panel explicitly preferred and recommended the medication for which longer-term harms were more well-known, and in which the physician experience in patients with PsA was longer, supplementing with harms data/experience from related rheumatic conditions, where these medications are commonly used. In each case, judgments of net benefit involved explicit consideration of values and preferences, including input from Patient Panel members of the Voting Panel as well as the full Patient Panel that met prior to the Voting Panel meeting.

We recognize that these recommendations do not account for the full complexity of PsA or the full range of possible therapies (e.g., glucocorticoids were not addressed). The high degree of heterogeneity in the presentation and course of PsA coupled with the involvement of multiple domains in a single patient cannot be captured in a single algorithm. In addition, reporting of disease measures and differences in inclusion/exclusion criteria in PsA clinical trials makes it difficult to compare therapies across trials. The impact of alternative therapies on important outcomes such as joint damage still remains to be elucidated. Vaccination recommendations with tofacitinib were not included, as it was not yet approved for PsA when the PICO questions were drafted and only a limited number of PICO questions could be feasibly included for voting. Additional topics, including vaccination in the setting of tofacitinib, will be addressed in a subsequent guideline update.

The ACR has decided to use GRADE methodology in the development of guidelines for the management of rheumatic diseases. The GRADE methodology specifies that panels make recommendations based on a consideration of the balance of relative benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the evidence based on the lowest quality of the critical outcomes—high, moderate, low, or very low), and patients' values and preferences. The rating of the quality of evidence for each clinical situation (PICO question) helped to inform the strength of the recommendation (strong or conditional) (51).

The use of GRADE (not used in other PsA treatment recommendations) allowed an explicit consideration of the overall evidence, including the balance of benefits and harms of treatments, the incorporation of patient values and preferences, and cost considerations to judge the tradeoff. This approach led to transparency in decision making by the Voting Panel for each clinical scenario and the formulation of these recommendations. Consistent with GRADE guidance, the Voting Panel usually offered a strong recommendation in the presence of moderate- or high-quality rating of the evidence, and a conditional recommendation in the presence of very-low or low-quality evidence (although recommendations can also be conditional in the setting of moderate-quality evidence, and in certain circumstances strong in the face of low-quality evidence) (15). The other merits of the ACR/NPF process undertaken included a comprehensive literature search, the consideration of each comparison in light of the available evidence, the diverse composition of the Voting Panel, the inclusion of all of the available therapies (e.g., IL-17i biologics, an IL-12/23i biologic, abatacept, and tofacitinib) in the decision-making process (including those approved for psoriasis or rheumatoid arthritis but not yet for PsA, ensuring that the guideline would not be out of date by the time it was published), and the inclusion of population subsets, such as those with predominant enthesitis and/or IBD.

Limitations of the guideline include the limited comparative evidence to inform selection of therapies (i.e., primary comparative benefit/efficacy and harms evidence) and the inability to include all possible clinical scenarios due to the necessity of keeping the task feasible. Because the American Academy of Dermatology and the NPF are currently developing a guideline addressing therapy for psoriasis, our guideline did not address treatment of isolated psoriasis. Another limitation is that we searched only English-language literature. The major limitation of the work arises from the limitations in the evidence.

In this guideline, we often used indirect comparisons among trials/therapies, frequently relying on network meta-analysis. Stratified analyses among subgroups (e.g., treatment-naive, inadequate response to a TNFi biologic agent) were rarely reported separately in primary trials, limiting our ability to perform network meta-analyses in these important subgroups. For most clinical scenarios (PICO questions) there were few or no head-to-head comparison studies identified in the literature review. Thus, the quality of evidence was most often low or very low, and only occasionally moderate (Supplementary Appendix 5; http://onlinelibrary.wiley.com/doi/10.1002/acr.23789/abstract). This led to nearly all recommendations being conditional, with a few strong recommendations in cases in which there was sufficient evidence (including that from outside of PsA) to make the Voting Panel confident in selecting one option over the comparator. A flow chart or ranking of treatments requires strong recommendation; when recommendations are conditional/weak it means that the right course of action differs between patients. When the right course of action differs between patients, it is inappropriate to make the flow chart and establish treatment ranking or a hierarchy of treatment options (14).

The 2018 ACR/NPF guideline for the treatment of PsA will assist patients and their health care providers in making challenging disease management decisions. More comparative data are needed to inform treatment selection. Several ongoing trials, including a trial to compare a TNFi biologic combination therapy with a TNFi biologic monotherapy and MTX monotherapy (52), will inform treatment decisions. We anticipate future updates to the guideline when new evidence is available.

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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. Dr. Singh 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. Singh, Guyatt, Ogdie, Gladman, Deal, Deodhar, Husni, Kenny, Mease, Merola, Miner, Gottlieb, Magrey, Nowell, Orbai, Reddy, Scher, M. Siegel, Walsh, Turner, Reston.

Acquisition of data. Singh, Ogdie, Gladman, Deal, Dunham, Husni, Mease, Jonsson, Shah, Sullivan, Turgunbaev, Gottlieb, Orbai, Scher, E. Siegel, M. Siegel, Reston.

Analysis and interpretation of data. Singh, Guyatt, Ogdie, Gladman, Deal, Deodhar, Dubreuil, Dunham, Husni, Kenny, Kwan-Morley, Lin, Marchetta, Mease, Merola, Miner, Ritchlin, Siaton, Smith, Van Voorhees, Jonsson, Shah, Sullivan, Turgunbaev, Coates, Gottlieb, Magrey, Nowell, Orbai, E. Siegel, M. Siegel, Walsh, Reston.

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Quantitative Signal Intensity Alteration in Infrapatellar Fat Pad Predicts Incident Radiographic Osteoarthritis: The Osteoarthritis Initiative

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Objective. To determine whether infrapatellar fat pad (IPFP) signal intensity measures are predictive of incident radiographic osteoarthritis (ROA) over 4 years in the Osteoarthritis Initiative study.

Methods. Case knees (n = 355), as defined by incident ROA, were matched 1:1 with control knees, according to sex, age, and radiographic status. T2-weighted magnetic resonance images were assessed at P0 (the visit when incident ROA was observed on a radiograph), P1 (1 year prior to P0), and baseline and used to assess IPFP signal intensity semiautomatically. Conditional logistic regression analyses were performed to assess the risk of incident ROA associated with IPFP signal intensity alteration, after adjustment for covariates.

Results. The mean age of the participants was 60.2 years, and most (66.7%) were female and overweight (mean body mass index 28.3 kg/m^2). Baseline IPFP measures including the mean value and standard deviation of IPFP signal intensity, the mean value and standard deviation of IPFP high signal intensity, median and upper quartile values of IPFP high signal intensity, and the clustering effect of high signal intensity were associated with incident knee ROA over 4 years. All P1 IPFP measures were associated with incident ROA after 12 months. All P0 IPFP signal intensity measures were associated with ROA.

Conclusion. The quantitative segmentation of high signal intensity in the IPFP observed in our study confirms the findings of previous work based on semiquantitative assessment, suggesting the predictive validity of semiquantitative assessment of IPFP high signal intensity. The IPFP high signal intensity alteration could be an important imaging biomarker to predict the occurrence of ROA.

INTRODUCTION

Osteoarthritis (OA) is a chronic disease characterized by articular cartilage loss and osteophyte formation as well as abnormal changes in other structures within the joint, such as synovitis, damage to the menisci, ligament tears, and infrapatellar fat pad (IPFP) alterations, eventually leading to joint failure and, in some cases, total knee replacement (1).

The IPFP is a local fat pad situated inferior to the patella and filling the anterior knee compartment (2). The IPFP has a buffering and lubricating function in the knee joint and is extensively vascularized and innervated (3). The IPFP interacts with surrounding joint tissue. Sports and trauma can cause IPFP damage, including edema, inflammation, synovial proliferation, and fibrosis, which may induce pain and restriction of knee movement (4). Based on the fact that the anatomic cleft within the IPFP is lined with synovium (5), high signal intensity alterations observed on water-sensitive fat-suppressed magnetic resonance imaging (MRI) are widely used as a surrogate for synovitis; however, it remains to be determined whether these signals represent inflammation or other pathologic changes and whether they play a major role in the early stage of OA (2).

This article was prepared using an Osteoarthritis Initiative (OAI) public-use data set, and its contents do not necessarily reflect the opinions or views of the OAI Study Investigators, the NIH, or the private funding partners of the OAI. The OAI is a public–private partnership between the NIH (contracts N01-AR-2-2258, N01-AR-2-2259, N01-AR-2-2260, N01-AR-2-2261, and N01-AR-2-2262) and private funding partners (Merck Research Laboratories, Novartis Pharmaceuticals, GlaxoSmithKline, and Pfizer, Inc.) and is conducted by the OAI Study Investigators. Private sector funding for the OAI is managed by the Foundation for the NIH. Image acquisitions were funded by the OAI.

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SIGNIFICANCE & INNOVATIONS

- We developed a novel quantitative method for measuring infrapatellar fat pad (IPFP) signal intensity alterations.
- Using this novel quantitative method, we demonstrated that IPFP signal intensity alterations are associated with the incidence of radiographic osteoarthritis.

Previous MRI studies have demonstrated an association between synovitis, as measured using IPFP signal intensity alteration, and knee pain or cartilage loss in patients with OA (6,7). Han et al (8) reported that high signal intensity in the IPFP was associated with knee pain, joint structural changes, and knee radiographic OA (ROA) in older adults, suggesting it may serve as an important imaging biomarker in knee OA. A nested case–control study showed that Hoffa-synovitis, in which IPFP signal intensity alteration was assessed on a manual semiquantitative scale from 0 to 3 (9), was strongly associated with the development of incident knee ROA (10). However, the reproducibility of the manual semiquantitive method is not high (9). It also cannot detect heterogeneity of the signal that might be indicative of ongoing biomechanical perturbation of the region. There is a need for a reliable and valid method to quantify IPFP signal intensity. Recently, we developed a semiautomatic, quantitative method to measure signal intensity changes in the IPFP. This method is reproducible and has concurrent and clinical construct validity (11), but its predictive validity needs to be examined.

The current case–control study is nested within the Osteoarthritis Initiative (OAI) study, which includes data for individuals who have or are at high risk for developing symptomatic knee OA. The aim of this study was to investigate whether signal intensity alteration within the IPFP predicts incident ROA over a 4-year follow-up period during which IPFP signal intensity was measured using our novel semiautomatic quantitative method.

SUBJECTS AND METHODS

Study design and subjects. Study participants were selected from the OAI study, which is a multicenter, longitudinal, prospective observational study focusing primarily on knee OA. In that study 4,796 participants (ages 45–79 years) were enrolled from February 2004 to May 2006 and followed up for 4 years. The follow-up included annual clinical assessments, at which radiographs and MR images were obtained. Our data were derived from the incidence subcohort, in which participants had characteristics that placed them at increased risk for developing symptomatic knee OA.

Demographic information (age, sex, and ethnicity) had been recorded at the first visit. Height and weight were measured twice while the participant was wearing light clothing and was not wearing shoes. Body mass index (BMI) was calculated at the same visit. Inclusion criteria were frequent knee symptoms and frequent prescription of medications to treat knee symptoms. Other screening risk factors were weight, history of knee injury and surgery, bony enlargement of fingers, frequent knee bending, and total knee replacement (TKR) in a parent or sibling. Exclusion criteria were bilateral TKR, plans to have bilateral TKR, rheumatoid and inflammatory arthritis, contraindications to receiving 3.0T-weighted MRI, nonambulatory status, serious comorbid conditions that are likely to interfere with participation, plans to relocate, or participation in another clinical trial. Signed consent forms were obtained from all participants.

Cases and controls. Case knees (n = 355) were defined by incident ROA (Kellgren/Lawrence [K/L] grade ≥2) on knee radiographs at any assessment after baseline but prior to the 48-month visit. This sample includes all such case knees with available images, except knees in which ROA developed by the first follow-up visit (12 months) and were K/L grade 1 at baseline and K/L grade 2 or higher in the contralateral knee. Both knees of a participant could be included if ROA developed in both. Each knee was matched with a control knee (1:1) by sex, age (±5 years), and radiographic status (K/L grade 0 or 1 in the index knee and K/L grade 0 or 1 or 2+ in the contralateral knee). Incident ROA did not develop in control knees between baseline and 48 months.

Knee injury and surgery history were ascertained by self-report at the enrollment visit (according to the OAI study protocol). Knee injury was defined as a history of injury causing difficulty walking for at least 1 week, and surgery was defined as a history of any knee surgery such as meniscal and ligamentous repairs. Repetitive knee-bending activity was assessed by a questionnaire that included climbing up a total of 10 or more flights of stairs, kneeling for 30 minutes or more, squatting or deep knee bending for 30 minutes or more, moving a heavy (25 pounds or more) object, or going into/out of a squat more than 10 times. A 0–5-point scale was used to measure the sum of each activity described above.

Radiography. Fixed-flexion radiography in both knees of all participants was performed at baseline and all annual follow-up visits. In all participants, bilateral standing films of the knee were obtained in posteroanterior projection, with knees flexed to 20–30° and feet internally rotated 10°. Knee radiographs were read by central readers using standard protocols including K/L grade and the Osteoarthritis Research Society International grades for joint space narrowing. ROA was defined as a K/L grade of ≥2 (12).

Measurements of signal intensity in the IPFP. MR images were assessed at P0 (the visit when ROA was observed on a radiograph), 1 year prior to P0 (P1), and at baseline. Sagittal plane intermediate-weighted turbo spin-echo MR images (3.0T-weighted scanner) were used to assess IPFP signal intensity semiautomatically, using MatLab X.Y. (The MathWorks, Inc.) (11).

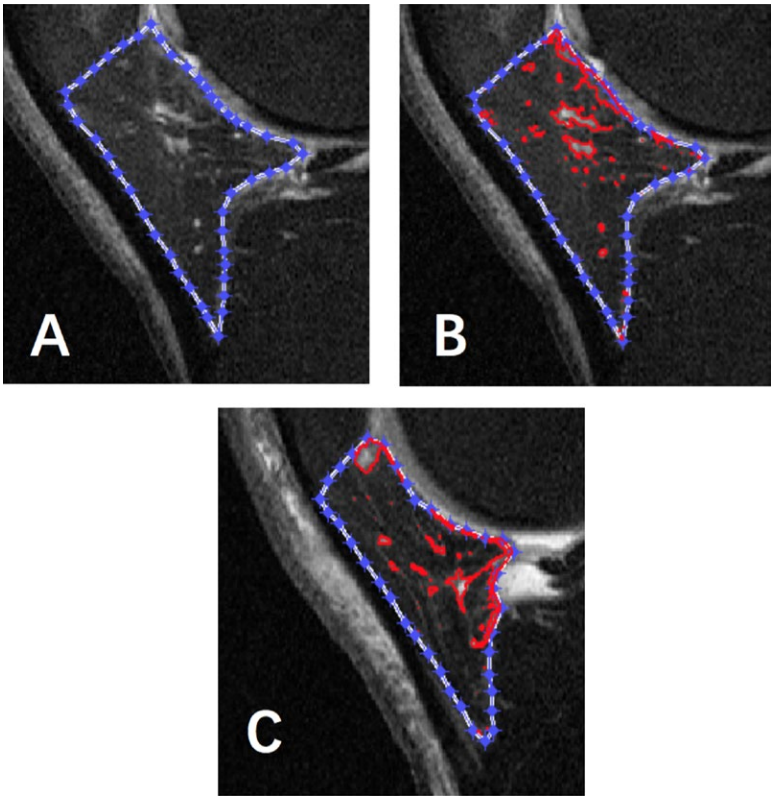

Figure 1. Segmentation of the infrapatellar fat pad (IPFP) and high signal intensity measurements on sagittal T2-weighted images, using MatLab. **A,** The outer contour of the IPFP was contracted inward using the new algorithm of the software. **B,** The high signal intensity region was selected automatically (red circle). **C,** The clustering effect of high signal intensity regions shown was different from that shown in **B**, in which the clustering effect of high signal intensity regions was lower.

The reader manually created an initial lasso around the IPFP by choosing a set of points in sequence near the outer contour of the IPFP; the lasso contracted inward to the actual edge of the IPFP automatically (Figure 1A). By using this new algorithm, it was easy to distinguish fake edges from real edges and to more accurately identify the IPFP boundary. IPFP regions with high signal intensity were also identified subsequently based on the algorithm (11). The algorithm was used to calculate the neighboring pixels of initial seed points to determine whether the pixel neighbors should be added to the area of high intensity signal (Figures 1B and C).

The algorithm automatically calculated the signal intensity of the IPFP. Measures of IPFP signal intensity included the mean value (Mean [IPFP]) and standard deviation (sDev [IPFP]) of IPFP signal intensity, mean value (Mean [H]) and standard deviation (sDev [H]) of IPFP high signal intensity, median value (Median [H]) and upper quartile value (UQ [H]) of high signal intensity, volume of high signal intensity regions of IPFP (Volume [H]), and the ratio of Volume (H) to volume of whole IPFP (Percentage [H]), and Clustering factor (H) representing the clustering effect of high signal intensity.

The sDev (IPFP) was introduced to represent signal intensity variation in the whole IPFP. The UQ (H) was used to represent the highest quartile of the signal. The UQ value means the highest quartile cut point value of the signal. The Volume (IPFP) and Volume (H) were calculated according to the slice thickness and the area on each slice, and the Percentage (H) was used to represent the adjusted quantity of these regions. The clustering regions with high signal intensity in the IPFP differed in patients, which may have different clinical significance. Clustering factor (H) was therefore introduced to represent this clustering effect. The greater the clustering effects, the higher aggregation of the high signal intensity even if the clustering effects had the same volume of high signal intensity (11).

These signal intensity measures were selected to represent IPFP signal intensity heterogeneity, extent, and clustering effect based on the concurrent validity and the clinical construct validity we previously reported (11) (Figures 1B and C). The intraclass correlation coefficients and interobserver correlation coefficients for all measures are high (>0.90) (11). Significant correlations between the semiquantitative score and quantitative measures were observed. The Pearson's correlation coefficients were as follows: for Mean (IPFP), r = 0.30; for sDev (IPFP), r = 0.74; for Median (H), r = 0.58; for UQ (H), r = 0.60; for Volume (H), r = 0.19; for Percentage (H), r = 0.37; and for Clustering factor (H), r = 0.49 (all $P < 0.001$) (11).

Statistical analysis. The *t*-test, chi-square test, and Fisher's exact test were used to test the difference between the case and control groups. Conditional logistic regression accounting for the correlation between both knees of an individual was applied to assess the risk of ROA with regard to signal intensity alteration before

and after adjustment for covariates measured at baseline. These covariates were self-reported knee injury, self-reported knee surgery, BMI (normal, overweight, obese), and the number of knee-bending activities (none, 1–3, 4–5). We re-scaled the values of the IPFP measurements by dividing them by 3, 4, or 10 when performing the analyses, in order to make the hazard ratios (HRs) at the same order of magnitude. Models were run at 3 time points: baseline, P1, and P0. Analyses were conducted using SAS version 9.4.

RESULTS

One knee lacked readable MRI data and was removed from the analysis, along with its matched knee; thus, 708 knees were used in the analysis. The mean ± SD age of the participants (n = 677) was 60.2 ± 8.6 years; most of the subjects were female (66.7%) and overweight (mean ± SD BMI 28.3 ± 4.5 kg/m^2). The characteristics of the participants are shown in Table 1. The case and control groups were comparable with respect to age, sex, height, and knee-bending activities, but weight and BMI were higher in the case group, and more subjects in the case group were overweight. Among case knees, the percentages of baseline knee injury (38.4%) and knee surgery (15.3%) were higher than those among control knees (19.8% and 6.8%, respectively). The case-defining visit was 12 months for 119 knees (33.6%), 24 months for 82 knees (23.2%), 36 months for 103 knees (29.1%), and 48 months for 50 knees (14.1%). The case group had higher values for sDev (IPFP), Percentage (H), UQ (H), and Clustering factor (H) than the control group at baseline, P1, and P0 (Figure 2). All differences between these 2 groups were significant, except baseline Percentage (H) (P = 0.06).

Associations between IPFP signal intensity measures at baseline and incident ROA are shown in Table 2. In unadjusted analyses, baseline IPFP measures including sDev (IPFP), Mean (H), sDev (H), Median (H), UQ (H), and Clustering factor (H) were

Table 1. Baseline characteristics of the case and control participants and the case and control knees*

	All	Cases	Controls	P
Participants†				
Age, mean ± SD years	60.2 ± 8.6	60.3 ± 8.7	60.1 ± 8.4	0.8061
BMI, mean ± SD kg/m^2	28.3 ± 4.5	28.9 ± 4.5	27.7 ± 4.4	0.0006
Height, mean ± SD mm	1,670.0 ± 87.9	1,671.7 ± 91.0	1,668.3 ± 85.0	0.6114
Weight, mean ± SD kg	79.1 ± 15.2	80.8 ± 15.0	77.5 ± 15.3	0.0053
BMI, no. (%)				
Normal	167 (25.0)	62 (19.3)	105 (30.4)	0.0031
Overweight	267 (40.0)	135 (41.9)	132 (38.3)	
Obese	233 (34.9)	125 (38.8)	108 (31.3)	
Sex, no. (%)				
Male	222 (33.3)	109 (33.9)	113 (32.8)	0.8053
Female	445 (66.7)	213 (66.1)	232 (67.2)	
Knee-bending activities in last 30 days, no. (%)				
None	63 (9.5)	26 (8.1)	37 (10.7)	0.0631
1, 2, or 3	497 (74.5)	234 (72.7)	263 (76.2)	
4 or 5	107 (16.0)	62 (19.3)	45 (13.0)	
Knees‡				
K/L class (grade in index knee/grade in contralateral knee), no. (%)				
1 (0/0)	126 (17.8)	63 (17.8)	63 (17.8)	1.0000
2 (0/1)	152 (21.5)	76 (21.5)	76 (21.5)	
3 (1/1)	166 (23.4)	83 (23.4)	83 (23.4)	
4 (0/2+)	118 (16.7)	59 (16.7)	59 (16.7)	
5 (1/2+)	146 (20.6)	73 (20.6)	73 (20.6)	
Baseline knee injury	206 (29.1)	136 (38.4)	70 (19.8)	<0.0001
Baseline knee surgery	78 (11.0)	54 (15.3)	24 (6.8)	0.0004

* Group differences were determined by *t*-test, chi-square test, and Fisher's exact test.
† For all, n = 677; for cases, n = 322; for controls, n = 355. BMI = body mass index; K/L = Kellgren/Lawrence.
‡ For all, n = 708; for cases, n = 354; for controls, n = 354.

significantly associated with increased incident ROA over 4 years, and these associations remained unchanged after adjustment for BMI, number of knee-bending activities, self-reported injury, and self-reported knee surgery (HR 5.2 [95% CI 1.1–23.6], 5.7 [95% CI 2.2–14.5], 3.3 [95% CI 1.7–6.4], 3.1 [95% CI 1.3–7.7], 3.2 [95% CI 1.6–6.2], 2.9 [95% CI 1.6–5.2], 1.6 [95% CI 1.2–2.1], respectively). Baseline Mean (IPFP) was not significantly associated with incident ROA in univariable analysis, but this association became significant after adjustment for the above-described covariates. In contrast, baseline Percentage (H) was not significantly associated with incident ROA in both univariable and multivariable analyses. The risk for incident ROA in case knees was 1.6–5.2 higher than that in control knees with regard to the different IPFP measurements.

Associations between IPFP signal intensity and incident ROA at P1 are shown in Table 3. All P1 IPFP measures were significantly and positively associated with incident ROA, both before and after adjustment for BMI, number of knee-bending activities, self-reported injury, and self-reported knee surgery (HR 12.6 [95% CI 2.8–57.2], HR 8.1 [95% CI 3.2–20.4], HR 5.1 [95% CI 2.6–9.9], HR 2.8 [95% CI 1.1–6.7], HR 4.8 [95% CI 2.5–9.2], HR 4.0 [95% CI 2.2–7.2], HR 5.0 [95% CI 1.6–15.7], and HR 2.7 [95% CI 2.0–3.7], respectively). These HRs were higher than those at baseline.

Associations between IPFP signal intensity measures and incident ROA assessed at the same time are shown in Table 4. Similar to the P1 IPFP measures, all P0 IPFP measures were significantly and positively associated with concurrent ROA in unadjusted analyses and after adjustment for the covariates (HR 8.8 [95% CI 2.0–39.0], HR 5.7 [95% CI 2.5–12.9], HR 3.2 [95% CI 1.7–6.0], HR 2.8 [95% CI 1.3–6.4], HR 3.5 [95% CI 1.9–6.6], HR 3.0 [95% CI 1.7–5.3], HR 9.7 [95% CI 2.9–32.5], and HR 2.6 [95% CI 1.9–3.5], respectively).

DISCUSSION

To the best of our knowledge, this study is the first to demonstrate that IPFP signal intensity alterations are associated with incident ROA, using a novel method to measure IPFP signal intensity alterations quantitatively. We observed that except for Percentage (H), the baseline IPFP signal intensity measures were all significantly associated with incident ROA over 4 years. All IPFP measures at P1 predicted incident ROA after 12 months and at P0 were associated with concurrent incident ROA. These findings suggest that our quantitative measurements of IPFP signal intensity alterations have predictive validity. IPFP signal intensity alterations, which can be regarded as an important imaging marker (similar to bone marrow lesions, cartilage defects, mensical tears, and effusion synovitis) may play a role in the pathogenesis of early OA.

Usually IPFP signal intensity alteration was assessed semi-quantitatively (0–3), with a grade of ≥1 termed Hoffa-synovitis

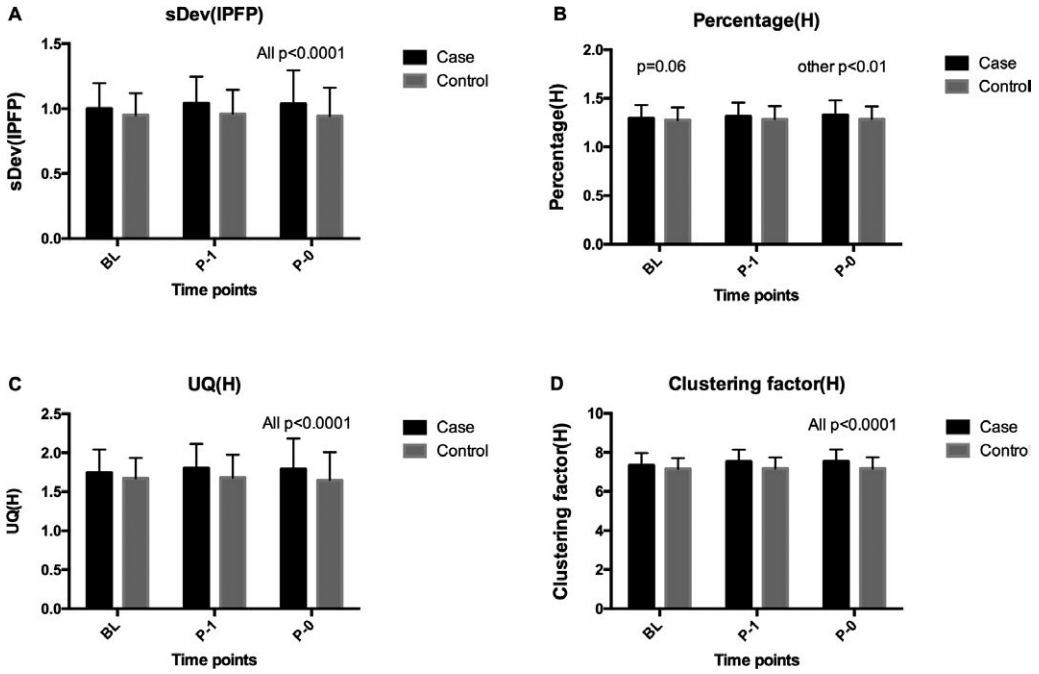

Figure 2. Comparison of major infrapatellar fat pad (IPFP) signal intensity measures between the case and control groups. **A,** Standard deviation of IPFP signal intensity (sDev [IPFP]). **B,** Ratio of volume of high signal intensity region/whole IPFP volume (Percentage [H]). **C,** Upper quartile value of high signal intensity region (UQ [H]). **D,** Clustering factor of high signal intensity (Clustering factor [H]); BL = baseline; P0 = the visit when incident radiographic osteoarthritis was observed on a radiograph; P1 = 1 year prior to P0. Bars show the mean ± SD.

Table 2. Associations between IPFP signal intensity measures at baseline and P1*

	Univariable analysis	Multivariable analysis†
Mean (IPFP)	3.8 (0.9–16.4)‡	5.2 (1.1–23.6)
sDev (IPFP)	5.2 (2.1–12.9)	5.7 (2.2–14.5)
Mean (H)	2.9 (1.5–5.6)	3.3 (1.7–6.4)
sDev (H)	2.6 (1.1–6.3)	3.1 (1.3–7.7)
Median (H)	2.9 (1.5–5.5)	3.2 (1.6–6.2)
UQ (H)	2.7 (1.5–4.7)	2.9 (1.6–5.2)
Percentage (H)	2.8 (1.0–8.4)‡	2.7 (0.9–8.2)‡
Clustering factor (H)	1.7 (1.3–2.1)	1.6 (1.2–2.1)

* All cases and controls (n = 708) were included in the analysis. IPFP = infrapatellar fat pad; P1 = 1 year prior to P0 (the visit when radiographic osteoarthritis [OA] was observed on a radiograph); Mean (IPFP) = mean value of IPFP intensity; sDev (IPFP) = standard deviation of IPFP signal intensity; Mean (H) = mean value of IPFP high intensity; sDev (H) = standard deviation of IPFP high signal intensity; Median (H) = median value of high signal intensity region; UQ (H) = upper quartile value of high signal intensity region; percentage (H) = ratio of volume of high signal intensity region/whole IPFP volume; Clustering factor (H) = clustering factor of high signal intensity. Values are the hazard ratio (95% confidence interval). Except where indicated otherwise, all associations were significant at $P < 0.05$.
† Adjusted for body mass index, number of knee-bending activities, self-reported injury, and self-reported knee surgery.
‡ Not significant.

(9,13), even though IPFP signal intensity alteration may also represent other pathologic changes such as vascular neoformation, edema, or fibrosis (4). The roles of IPFP signal intensity alteration or Hoffa-synovitis in knee OA remain unclear. A 2.6-year longitudinal study demonstrated that baseline IPFP signal intensity was positively associated with knee pain when going up/down stairs, cartilage defects, and bone marrow lesions but was negatively associated with lateral tibial cartilage volume in older adults (8). A case–control study in which a semiquantitative method (grades 0–3) was used showed that baseline Hoffa-synovitis was associated with incident ROA over 4 years (10).

Results from the Multicenter Osteoarthritis Study (MOST) study showed that Hoffa-synovitis was an independent cause of incident knee OA over 84 months of follow-up (14). In contrast, a 30-month follow-up study showed that Hoffa-synovitis did not predict cartilage loss in subjects at high risk of knee OA (15). Similar results were observed in a study in patients with symptomatic knee OA, in which IPFP signal intensity changes were not associated with cartilage loss at the 15- and 30-month follow-up assessments but were significantly associated with a change in pain as assessed on a visual analog scale (6). Although the findings of these studies were not consistent, they suggest that IPFP signal intensity alteration was potentially a biomarker for knee OA development; however, the semiquantitative assessment was insensitive to change, which would not be an ideal outcome measure for interventions.

Table 3. Associations between IPFP signal intensity measures at P1 and P0*

	Univariable analysis	Multivariable analysis†
Mean (IPFP)	9.4 (2.4–40.5)	12.6 (2.8–57.2)
sDev (IPFP)	8.5 (3.4–21.1)	8.1 (3.2–20.4)
Mean (H)	5.1 (2.6–9.8)	5.1 (2.6–9.9)
sDev (H)	2.8 (1.2–6.8)	2.8 (1.1–6.7)
Median (H)	4.8 (2.5–9.2)	4.8 (2.5–9.2)
UQ (H)	4.0 (2.3–7.2)	4.0 (2.2–7.2)
Percentage (H)	4.8 (1.5–15.3)	5.0 (1.6–15.7)
Clustering factor (H)	2.7 (2.0–3.6)	2.7 (2.0–3.7)

* A total of 658 cases and controls were included. IPFP = infrapatellar fat pad; P1 = 1 year prior to P0 (the visit when radiographic osteoarthritis [OA] was observed on a radiograph); Mean (IPFP) = mean value of IPFP intensity; sDev (IPFP) = standard deviation of IPFP signal intensity; Mean (H) = mean value of IPFP high intensity; sDev (H) = standard deviation of IPFP high signal intensity; Median (H) = median value of high signal intensity region; UQ (H) = upper quartile value of high signal intensity region; Percentage (H) = ratio of volume of high signal intensity region/whole IPFP volume; Clustering factor (H) = clustering factor of high signal intensity. Values are the hazard ratio (95% confidence interval). All associations were significant at $P < 0.05$.
† Adjusted for body mass index, no. of knee-bending activities, self-reported injury, and self-reported knee surgery.

Previous studies have focused on a special region of the IPFP, the superolateral Hoffa's fat pad (SHFP), based on the hypothesis that SHFP edema (grades 0–3) was caused by friction

Table 4. Associations between IPFP signal intensity measures at the same time as incident radiographic OA*

	Univariable analysis	Multivariable analysis†
Mean (IPFP)	6.4 (1.5–26.6)	8.8 (2.0–39.0)
sDev (IPFP)	5.5 (2.4–12.4)	5.7 (2.5–12.9)
Mean (H)	3.0 (1.6–5.7)	3.2 (1.7–6.0)
sDev (H)	2.8 (1.2–6.6)	2.8 (1.3–6.4)
Median (H)	3.2 (1.7–6.1)	3.5 (1.9–6.6)
UQ (H)	2.9 (1.6–5.1)	3.0 (1.7–5.3)
Percentage (H)	9.8 (3.0–31.4)	9.7 (2.9–32.5)
Clustering factor (H)	2.7 (2.0–3.6)	2.6 (1.9–3.5)

* A total of 666 cases and controls were included in the analysis. IPFP = infrapatellar fat pad; Mean (IPFP) = mean value of IPFP intensity; sDev (IPFP) = standard deviation of IPFP signal intensity; Mean (H) = mean value of IPFP high intensity; sDev (H) = standard deviation of IPFP high signal intensity; Median (H) = median value of high signal intensity region; UQ (H) = upper quartile value of high signal intensity region; Percentage (H) = ratio of volume of high signal intensity region/whole IPFP volume; Clustering factor (H) = clustering factor of high signal intensity. Values are the hazard ratio (95% confidence interval). All associations were significant at $P < 0.05$.
† Adjusted for body mass index, physical activities, self-reported injury, and self-reported knee surgery.

between the patellar tendon and the lateral femoral condyle and by patellofemoral joint malalignment (16,17). Results based on the MOST study showed that SHFP hyperintensity was significantly associated with cartilage damage and bone marrow lesions in the lateral patellofemoral joints and with worsening bone marrow lesions in the medial patellofemoral joint (18). SHFP may be a local marker of patellofemoral joint structural damage. Edema in superolateral Hoffa's fat pad bone marrow lesions may be an important indicator of underlying patellofemoral joint maltracking or impingement in younger, symptomatic patients (19). Because the current study was designed to include older rather than younger adults, we focused on signal intensity in the whole IPFP rather than regions.

Our newly developed quantitative method has concurrent and clinical construct validity for measuring IPFP signal intensity alterations (compared with the semiquantitative method) and for examining the associations with joint structural outcomes, respectively (11). This method was also reproducible, with high intraclass correlation coefficients. However, our study was preliminary and was limited by a small sample size and the cross-sectional design, and significant associations between IPFP measures and structural changes in patients with knee OA were not all consistent (11). Furthermore, the predictive validity of this new method was not reported. We presented IPFP signal intensity measures that represent aspects of signal intensity, but these measures are highly correlated. Future work should explore whether a composite score for these measures can be established for a valid IPFP assessment in studies of OA.

In the current study, we observed that all IPFP measures assessed at P0 were significantly associated with incident ROA, further confirming the clinical construct validity of this method. Furthermore, we observed that IPFP measures assessed at P1 were all significantly associated with incident ROA, and all measures assessed at baseline (except Percentage [H]) were associated with incident ROA, suggesting the predictive validity of this quantitative measure. The more heterogeneous signal intensity in the whole IPFP, the higher signal intensity quantity, and more clustering of high signal intensity, the more likely that these measures predict incident OA. The associations for baseline IPFP measures were not as strong as those for P1 IPFP measures, indicating that IPFP signal intensity measures would be more strongly associated with incident ROA in a fixed, shorter time interval (1 year) than in variable time intervals (1–4 years).

The underlying mechanisms for the association between IPFP signal intensity alteration and incident ROA remain to be elucidated. IPFP signal intensity alteration can be a sign of synovial inflammation (6,20). Synovial tissue from patients with early OA were characterized by increased mononuclear cell infiltration and overproduction of proinflammatory cytokines (21). These cytokines diffused into cartilage through the synovial fluid and influenced cartilage metabolism by producing proteases and other catabolic factors such as nitric oxide, causing other structural changes associated with the disease process (22) and followed by the development of ROA.

The IPFP has been identified as a potential source of cytokines and adipokines (23–25). In vitro studies have demonstrated that the IPFP has an anabolic phenotype, and that the inflammatory factors secreted by the IPFP can influence cartilage metabolism and mesenchymal stem cell–derived cartilage repair (4,26,27). The IPFP is also enriched with immune cells toward a proinflammatory phenotype (25,27), which can be influenced by the proinflammatory environment in the joint (23). Activated immune cells (e.g., macrophages) produce various growth factors, cytokines, and enzymes that enhance osteophyte formation, mitigate cartilage breakdown by matrix metalloproteinase activity, induce joint effusion by vasodilation, and might influence subchondral bone metabolism (4). We recently reported that the serum interleukin-17 level was positively associated (and serum adiponectin was negatively associated) with IPFP signal intensity alteration in patients with knee OA (28), suggesting that the association between IPFP signal intensity alteration and incident ROA may be related to dysregulated cytokines and adipokines.

Our study is unique because we looked at multiple time points prior to the diagnosis of ROA in a well-designed nested case–control study, with cases matched with controls by sex, age, and baseline radiographic disease status in both knees, which ensured maximal comparability of baseline characteristics between cases and controls. There were also some potential limitations. First, the signal intensity alterations in the IPFP observed on nonenhanced MRI were sensitive but nonspecific for detecting inflammatory changes (as compared with contrast-enhanced MR images) in OA (7); however, nonenhanced MRI is more economical and less invasive, and the signal intensity changes on nonenhanced MRI have been widely used as a synovitis surrogate and are correlated with chronic synovitis (13). Second, pathologic examinations could not be performed in our epidemiologic study; therefore, the pathologic changes associated with IPFP high signal intensity alteration are unknown. Third, our new method included only high signal intensity alterations. Although the low signal alterations may also be associated with the outcomes of knee OA (29), further modifications to our technique to identify such alterations are needed in the future. Last, the percentages of obesity, surgery, and injury were higher than those in the control group, which could influence our results; however, we have added them as potential confounders into the analyzing models, and therefore our findings should not be greatly affected by these factors.

The quantitative segmentation of high signal in the IPFP has confirmed previous work based on semiquantitative assessment of IPFP high signal intensity, suggesting its predictive

validity. These findings emphasize the importance of IPFP pathology on the structural pathogenesis of OA. The quantitative measures of IPFP signal intensity are sensitive to changes and could be ideal end points for intervention. Targeting inflammation or synovitis may have the potential to delay the development of knee OA.

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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. Dr. Ding 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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Association of Knee Effusion Detected by Physical Examination With Bone Marrow Lesions: Cross-Sectional and Longitudinal Analyses of a Population-Based Cohort

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Objective. To determine the association of effusion detected by physical examination with the prevalence of bone marrow lesions (BMLs) on magnetic resonance imaging (MRI), and the incidence/progression of BMLs over 3 years in subjects with knee osteoarthritis.

Methods. A population-based cohort with knee pain (n = 255) was assessed for effusion on physical examination. On MRI, BMLs were graded 0–3 (none, mild, moderate, severe), and incidence/progression was defined as a worsening of the sum of BML scores over 6 surfaces by ≥1 grade. We analyzed the full cohort and a mild disease subsample with a Kellgren/Lawrence (K/L) grade <3. Cross-sectional logistic and longitudinal exponential regression analyses were performed, adjusted for age, sex, body mass index (BMI) and pain. We calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for effusion detected by physical examination versus BMLs (prevalence and incidence/progression).

Results. The weighted mean age was 56.7 years, the mean BMI was 26.5, 56.3% were women, 20.1% had effusion on physical examination, and 80.7% had a K/L grade <3. Effusion on physical examination was significantly associated with prevalent BMLs in the full cohort (odds ratio [OR] 6.10 [95% confidence interval (95% CI) 2.77–13.44]) and in the K/L grade <3 cohort (OR 6.88 [95% CI 2.76–17.15]). In the full cohort, sensitivity, specificity, PPV, and NPV were 34.6, 92.5, 79.9, and 62.1%, respectively, and in the K/L <3 cohort 31.7, 94.0, 75.5, and 70.1%, respectively. Longitudinally, effusion on physical examination was not significantly associated with BML incidence/progression in the full cohort (hazard ratio [HR] 1.83 [95% CI 0.95–3.52]) or in the K/L grade <3 cohort (HR 1.73 [95% CI 0.69–4.33]). In the two cohorts, sensitivity, specificity, PPV, and NPV were 32.0, 82.2, 42.2, and 74.9%, respectively, and 21.2, 85.6, 30.1, and 78.8% respectively.

Conclusion. BMLs on MRI can be predicted from physical examination effusion cross-sectionally, with a high PPV of 79.9%. Assessment for knee effusion on physical examination is useful for determining potential candidates with BMLs before costly MRI screening for recruitment into clinical trials.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis among Canadians, affecting 11% of the 2001 population and nearly one-third of those ages 65–69 years (1). More recently, among US adults, nearly 27 million persons had clinically diagnosed OA in 2008 (increased from 21 million in 1995) (2). With the increasing average age and adiposity of these populations, and strongly related to age and body mass index (BMI), OA constitutes a substantial and increasing public health burden (3–6).

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SIGNIFICANCE & INNOVATIONS

- Knee effusion on clinical examination was significantly associated with a 6-fold increased risk of bone marrow lesions (BMLs) on magnetic resonance imaging (MRI).
- The presence of a knee effusion on clinical examination had a positive predictive value of 79.9% for the presence of BMLs on MRI, which highlights the utility of this inexpensive clinical examination for potential recruitment of subjects with BMLs into clinical trials.
- When adjusted for age, sex, body mass index and baseline pain, clinical knee effusion was not significantly associated with incidence/progression of BMLs over 3 years.

Effusion is an important marker for inflammation and is common in knee OA. Moderate to large effusion on magnetic resonance imaging (MRI) was seen in 55% of patients with radiographic OA (7) and was present in 67% of patients in a population-based study of subjects with early and radiographic OA (8). We have recently reported that physical examination effusion was highly correlated with MRI effusion, particularly moderate-to-large MRI effusion (9). While a systematic review reported that some studies have poor inter- and intrarater reliability of clinical tests of effusion (10), other studies, including ours, have reported good-to-excellent interrater reliability of knee effusion on examination (11–13). Furthermore, the predictive utility of a combination of clinical examinations for bulge sign, ballottement, and patellar tap versus ultrasound effusion has been shown to have high sensitivity and moderate specificity in senior residents (14).

Bone marrow lesions (BMLs) are an important feature of knee OA and are the target of certain therapeutic interventions (15,16). Both effusion and BMLs have been independently associated with OA as well as pain in OA (17–19). This fact underscores the relevance of identifying subgroups of OA patients who may have BMLs for inclusion in clinical trials that seek to target this feature. While MRI is a useful tool for identifying BMLs, it is not cost-effective when used solely for the purpose of screening for BMLs for recruitment into a clinical trial targeting BML reduction. This fact suggests the need for a less expensive, easier test that could prescreen those most likely to have BMLs. A positive association between MRI effusion and BMLs was previously reported in cross-sectional (8,20,21) and longitudinal (8,21) studies. Additionally, Yusup et al (22) reported on the cross-sectional association of BMLs with histologically confirmed synovitis in patients with end-stage OA. These studies raise the possibility of using knee examination as a prescreening tool, since effusion can be detected easily by physical examination.

No studies have yet evaluated the association of physical examination effusion with BMLs, but given our previous findings of its high correlation with MRI effusion (9), this association does seem a likely candidate. Detection of effusion on physical examination is easily done in clinical practice and could prove highly useful in preidentifying patients with likely BMLs before sending them for costly confirmatory MRIs. This 2-stage approach (physical examination before MRI to find BMLs) could enhance recruitment of subjects with BMLs into clinical trials in a more cost-efficient manner.

We established a population-based cohort of subjects with knee pain with longitudinal follow-up over 3 years (23). This cohort consisted of patients with the full spectrum of disease from no OA to preradiographic OA to advanced radiographic OA. In this study, we were interested separately in the full cohort (all Kellgren/Lawrence [K/L] grades), as well as those subjects with only mild disease (K/L grades 0–2), since the latter may represent a potential future target population for randomized controlled trials (24). The objectives of this study were to evaluate the cross-sectional and longitudinal association of effusion detected by physical examination with prevalent BMLs and with the incidence/progression of BMLs, while additionally providing an example of potential cost savings associated with using physical examination for knee effusion as a prescreening tool for knee BMLs, before costly MRIs are performed.

MATERIALS AND METHODS

Study population. The population for this cohort study was recruited between 2002 and 2005 and has been described previously in detail (25). Briefly, subjects ages 40–79 years with knee pain were recruited as a random population sample in the Greater Vancouver area in Canada. Recruitment was conducted using stratified sampling to achieve equal representation within age decades and sex. Subjects were excluded at baseline if they had inflammatory arthritis or fibromyalgia, previous knee arthroplasty, knee injury or surgery within the previous 6 months, or knee pain referred from hips or back, or if they were unable to undergo MRI.

All subjects were invited for follow-up. Exclusion criteria at follow-up were total knee arthroplasty, inflammatory arthritis, inability to undergo MRI, comorbidity, and inability to attend the study center. Reasons for nonparticipation at follow-up have been described previously and included loss to follow-up (9.8%), death (0.4%), lack of interest (13.7%), ineligibility (11.0%), and incomplete MRI (1.2%). All subjects provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Board, University of British Columbia.

Clinical evaluation. Subjects were evaluated comprehensively at baseline and follow-up with questionnaires to assess demographics, knee symptoms, OA risk factors, and general health. A standardized knee examination was performed (11). Effusion detected by physical examination was assessed using the bulge sign (present/absent) and the patellar tap (present/absent). If ei-

ther sign was positive, knee effusion was considered present. The interrater reliability for knee effusion has previously been shown to be high, with a reliability coefficient of 0.97 for bulge sign and a prevalence-adjusted, bias-adjusted $\kappa = 0.78$ for patellar tap (11). Subjects completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) VA 3.1 (26). Pain, stiffness, and function scores were normalized to a 0–100 scale.

Radiographic evaluation. Baseline and follow-up knee radiographs were obtained using a fixed-flexion technique, with the Synaflexer (Synarc) positioning frame and a skyline view with the subject in the supine position. Radiographs were scored blinded to clinical and MRI information by 2 independent readers (JC and SN) using the K/L 0–4 grading scale (24). The interrater reliability was good, with an intraclass correlation coefficient (ICC) of 0.79 (25). Differences in readings were adjudicated by consensus scores of the 2 readers.

MRI evaluation. MRI was performed with a GE 1.5T magnet (GE Healthcare) using a transmitter–receiver extremity knee coil. The imaging protocol included 4 MRI sequences: 1) fat-suppressed T1-weighted 3-dimensional spoiled gradient-recalled acquisition in the steady state sequence with images obtained in the sagittal plane with reformat images in the axial and coronal planes (repetition time [TR] 52 msec, time to echo [TE] 10 msec, flip angle 60°, field of view [FOV] 12 cm, matrix 256 × 128, section thickness 1–1.5 mm, with 1 signal averaged); 2) fat-suppressed T2-weighted fast spin-echo (FSE) sequence with images obtained in the coronal plane (TR 3,000 msec, TE 54 msec, echo train length [ETL] 8, FOV 14 cm, matrix 256 × 192, section thickness 4 mm, with an intersection gap of 1 mm with 2 signals averaged); 3) T1-weighted FSE sequence with images obtained in the oblique sagittal plane (TR 450 msec, TE minimum full, ETL 2, band width 20 Hz/pixel, FOV 16 cm, matrix 384 × 224, section thickness 4 mm, with an intersection gap of 1 mm with 2 signals averaged); and 4) T2-weighted FSE sequence with images obtained in the oblique sagittal plane (TR 4,025 msec, TE 102 msec, ETL 17, band width 20 Hz/pixel, FOV 16 cm, matrix 320 × 288, section thickness 3 mm, with an intersection gap of 0 mm with 4 signals averaged). Baseline and follow-up MR images were read side-by-side, blinded to time sequence, by a single reader (AG) who was also blinded to radiographic and clinical information.

BML assessment. BMLs were scored on a scale of 0–3 (0 = none [0% of the site], 1 = mild [<25% of the site], 2 = moderate [25–49% of the site], and 3 = severe [≥50% of the site]) at 6 sites within the knee (lateral femoral condyle, lateral tibial plateau, medial femoral condyle, medial tibial plateau, patella, and trochlear groove) as previously described (27). The overall joint BML score was determined by the highest score of any of the 6 sites. The ICC for intrarater reliability of BML readings ranged from 0.81 to 0.93 for different joint sites, with the exception of patellar BML, where the ICC was 0.58. Prevalent BML was defined as grade ≥1. For the longitudinal analysis, incidence/progression of BMLs was defined as an increase in the sum of BML scores across 6 surfaces by ≥1 grade. Those who had no change in the BML sum or regression of BML sum were classified as nonprogressors.

Statistical analysis. Data were summarized using frequencies or means ± SDs. Analyses were performed on the full cohort and on the subsample with baseline K/L grade <3. For the cross-sectional analysis, we performed logistic regression with BML (present/absent) as the outcome variable and effusion on physical examination as the predictor variable, adjusted for age, sex, BMI, and baseline WOMAC pain, to determine the odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association of physical examination effusion with BML prevalence. For the longitudinal analysis, we used exponential regression models, which take into account the differential follow-up time, adjusted for age, sex, baseline BMI, and baseline WOMAC pain, to determine the hazard ratios (HRs) and 95% CIs for the association of physical examination effusion with BML incidence/progression. We calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for physical examination effusion versus BMLs (prevalence and incidence/progression). To obtain population-based estimates, all analyses were performed using age decade–sex stratum sampling weights (25). All analyses were performed using SAS software, version 9.4.

Using the results of the above analyses, we estimated the cost for enrollment in a clinical trial that targets patients with knee BMLs, using initial prescreening with effusion on physical examination prior to obtaining MRI. Our assumptions in this calculation include the fact that the estimated cost of an MRI is $500, and a trained examiner, responsible solely for joint examination in a randomized controlled trial, can conservatively perform 10 physical examinations for knee effusion per hour in a clinic, at a combined cost of $200 per hour, including support staff to handle patient scheduling.

RESULTS

Of the weighted 255.0 subjects seen at baseline, 205.7 (80.7%) had a K/L grade <3 (mild disease cohort). Of 163.0 subjects seen at follow-up, all subjects were able to progress and thus were included in the longitudinal analysis of the full cohort. Of those 163 subjects, 133.3 (81.8%) had a baseline K/L grade <3 (mild disease cohort). The median follow-up time was 3.2 years (range 2.5–5.1 years). Baseline characteristics of the study population are shown in Table 1. For the full cohort (n = 255.0), the mean age at baseline was 56.7 years, mean BMI was 26.5, and 56.3% were women. Physical examination effusion was present in 20.1% of subjects. The majority of subjects had preradiographic disease, i.e., K/L grade 0 or 1, 41.1% and 20.4%, respectively. K/L grade 2 was seen in 19.1%. BML grade 0 was

Table 1. Sample-weighted baseline characteristics of cross-sectional and longitudinal study populations*

	Cross-sectional		Longitudinal	
	Full cohort (n = 255.0)†	Mild disease (n = 205.7)†	Full cohort (n = 163.0)†	Mild disease (n = 133.3)†
Age, mean ± SD years	56.7 ± 10.4	55.0 ± 10.0	57.6 ± 10.1	56.0 ± 9.7
Women	143.7 (56.3)	117.0 (56.9)	88.1 (54.0)	73.9 (55.4)
BMI, mean ± SD kg/m^2	26.5 ± 4.9	25.9 ± 4.4	26.1 ± 4.2	25.8 ± 4.2
WOMAC pain mean ± SD (range 0–100)	20.5 ± 17.7	19.2 ± 18.2	19.6 ± 16.8	18.4 ± 16.9
WOMAC stiffness mean ± SD (range 0–100)	24.4 ± 23.6	21.5 ± 22.9	23.6 ± 22.0	20.9 ± 20.6
WOMAC function mean ± SD (range 0–100)	18.7 ± 18.3	16.8 ± 18.4	17.4 ± 17.0	15.8 ± 17.0
K/L grade				
0	104.9 (41.1)	104.9 (51.0)	65.0 (39.9)	65.0 (48.8)
1	52.1 (20.4)	52.1 (25.3)	33.8 (20.7)	33.8 (25.3)
2	48.7 (19.1)	48.7 (23.7)	34.5 (21.2)	34.5 (25.9)
3	26.9 (10.6)	0.0 (0.0)	16.3 (10.0)	0.0 (0.0)
4	22.3 (8.8)	0.0 (0.0)	13.4 (8.2)	0.0 (0.0)
Physical examination effusion	51.2 (20.1)	32.0 (15.6)	35.6 (21.9)	21.3 (16.0)
Bone marrow lesion				
0	136.8 (53.6)	129.6 (63.0)	82.0 (50.3)	79.0 (59.3)
1	54.6 (21.4)	42.3 (20.6)	40.8 (25.1)	29.5 (22.1)
2	45.7 (17.9)	28.3 (13.8)	30.7 (18.9)	23.1 (17.3)
3	17.9 (7.0)	5.5 (2.7)	9.4 (5.8)	1.7 (1.3)

* Values are the number (%) unless indicated otherwise. Mild disease cohort is defined as K/L grade <3. BMI = body mass index; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; K/L = Kellgren/Lawrence.
† Number given as a weighted value.

seen in 53.6%, grade 1 in 21.4%, grade 2 in 17.9%, and grade 3 in 7.0%. Baseline demographic characteristics were similar for the baseline mild disease cohort, as well as for the longitudinal study population (Table 1).

In cross-sectional analyses, BMLs were highly prevalent in subjects with effusion on physical examination compared to those without effusion on physical examination (79.9% versus 38.0%; chi-square $P < 0.001$). We found a significant association of effusion on physical examination with prevalent BMLs both in unadjusted logistic regression and after adjustment for age, sex, BMI and WOMAC pain (adjusted OR 6.10 [95% CI 2.77–13.44]) (Table 2). In the baseline K/L grade <3 sample, the relationship was similar (adjusted OR 6.88 [95% CI 2.76–17.15]). In the full cohort, sensitivity and specificity were 34.6% (95% CI 26.0–43.2) and 92.5% (95% CI 88.1–96.9), respectively, while PPV and NPV were 79.9% (95% CI 68.9–90.9) and 62.1% (95% CI 55.4–68.7), respectively. In the mild disease cohort, sensitivity was slightly lower and specificity was slightly higher, while PPV and NPV were also slightly lower and higher, respectively.

In longitudinal analyses, the incidence/progression of BMLs was seen in 28.9% of subjects. There was no significantly increased risk of BML incidence/progression in subjects with physical examination effusion in the whole cohort (HR 1.83 [95% CI 0.95–3.52]) or in the mild disease subsample with K/L grade <3, after adjusting age, sex, BMI, and WOMAC pain (Table 3). There was, however, a crude unadjusted association in the full

Table 2. Effusion as a risk factor for prevalent bone marrow lesions using logistic regression analysis*

	Crude OR	Adjusted OR†	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Full cohort	6.49 (3.10–13.61)	6.10 (2.77–13.44)	34.6 (26.0–43.2)	92.5 (88.1–96.9)	79.9 (68.9–90.9)	62.1 (55.4–68.7)
Mild disease cohort	7.23 (3.03–17.24)	6.88 (2.76–17.15)	31.7 (21.3–42.2)	94.0 (89.9–98.1)	75.5 (60.6–90.4)	70.1 (63.3–76.9)

* All values are shown with the 95% confidence interval. Mild disease cohort is defined as Kellgren/Lawrence grade <3. OR = odds ratio; PPV = positive predictive value; NPV = negative predictive value.
† Analyses adjusted for age, sex, body mass index, and baseline Western Ontario and McMaster Universities Osteoarthritis Index pain.

Table 3. Effusion as a risk factor for bone marrow lesion incidence/progression using exponential regression analysis*

	Crude HR	Adjusted HR†	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Full cohort	2.00 (1.08–3.71)	1.83 (0.95–3.52)	32.0 (18.6–45.3)	82.2 (75.3–89.2)	42.2 (26.0–58.4)	74.9 (67.3–82.4)
Mild disease cohort	1.58 (0.66–3.80)	1.73 (0.69–4.33)	21.2 (6.6–35.8)	85.6 (78.8–92.4)	30.1 (10.6–49.6)	78.8 (71.2–86.4)

* All values are shown with the 95% confidence interval. Mild disease cohort is defined as Kellgren/Lawrence grade <3. HR = hazard ratio; PPV = positive predictive value; NPV = negative predictive value.
† Analyses adjusted for age, sex, body mass index, and baseline Western Ontario and McMaster Universities Osteoarthritis Index pain.

sample only, with HR 2.00 (95% CI 1.08–3.71). In the full cohort, sensitivity and specificity were 32.0% (95% CI 18.6–45.3) and 82.2% (95% CI 75.3–89.2), respectively, while PPV and NPV were 42.2% (95% CI 26.0–58.4) and 74.9% (95% CI 67.3–82.4), respectively. In the mild disease cohort, sensitivity was slightly lower and specificity was slightly higher, while PPV and NPV were also slightly lower and higher, respectively.

To estimate the cost for enrollment in a clinical trial that targets patients with knee BML, using initial prescreening with physical examination for knee effusion prior to obtaining MRI, we estimate from our sample that the prevalence of BMLs in the population with knee pain is 46.4%. Thus, under the assumptions listed in the Methods section, without prescreening, acquiring 100 knees with BMLs would require 216 MRIs, at a cost of $108,000. Alternatively, among those with effusion detected by physical examination, 79.9% have BMLs, and thus in a prescreened sample, acquiring 100 knees with BMLs would require only 125 MRIs, at a cost of $62,500. The prevalence of knee effusion on physical examination from our sample is an estimated 20.1%. Therefore, to obtain the 125 patients with knee effusions needed would require physical examinations of 622 knees, which could be accomplished in 62 hours at a cost of $12,400. The prescreening approach therefore provides a net savings of $108,000 – $62,500 – $12,400 = $33,100, which is 30.6%.

DISCUSSION

In this study, we report that effusion detected by physical examination was significantly cross-sectionally associated with BMLs on MRI, with a 6- or 7-fold increased risk (depending on the subgroup) in those subjects with effusion compared to those without effusion, adjusted for age, sex, BMI, and WOMAC pain. Unadjusted associations were quite similar. Interestingly, this relative risk is stronger than that previously reported by Wang et al (8) on MRI effusion versus whole-joint BMLs (prevalence ratio 1.28 [95% CI 1.13–1.44]), although Wang et al analyzed MRI-based effusion rather than physical examination effusion. They also adjusted their model for radiographic OA, which we did not, because we consider radiographic OA to be too immersed in the causal chain along which effusion and BMLs lie, and a primary intended application of our findings is to preclude costly screening MRIs for BMLs by use of inexpensive clinical examinations only (i.e., without the need for radiographic information). Meredith et al (20) also reported a cross-sectional association, although they reported this as Spearman's rank correlation (0.36). Longitudinally, physical examination effusion at baseline was not significantly associated with incidence/progression of BMLs, after adjusting for age, sex, BMI, and baseline pain. However, in the unadjusted model on the full cohort, we did find a significant 2-fold association. Previous longitudinal studies evaluating MRI-based effusion found mixed results, 1 showing a positive association (21), and 1 finding no significant association with BMLs (8).

The cross-sectional findings have various implications, first, for trials that use effusion as either a source population or outcome. Knowing that the majority (79.9%) of a population with physical examination effusion is likely to also have BMLs could be considered when designing treatments for these groups. Another application of our findings is cost savings. For the purpose of recruiting subjects with knee BMLs into clinical trials, reducing the number of costly screening MRIs may be desirable. For example, in 1 study, Pelletier at al (16) estimated the disease-modifying effect of strontium ranelate on BMLs and cartilage loss. In a cost analysis (under a plausible hypothetical scenario), we found that the high PPV for the cross-sectional association between effusion on physical examination and knee BMLs could be leveraged to achieve a substantial cost savings of nearly one-third. While the various costs assumed in this calculation could vary depending on location, MRI is likely the dominant expense in most such scenarios, and thus the potential savings would remain substantial. The unadjusted longitudinal association that we found (baseline effusion predictive of BML incidence/progression) may also be leveraged, specifically in studies aiming to reduce BML incidence/progression with an intervention, by recruiting a sample at higher risk of BML incidence/progressions and therefore more likely to show an effect of an intervention.

There are, of course, situations concerning BMLs that our study does not purport to address. Specifically, with regard to patient care, we are not proposing a physical examination for effusion in lieu of a diagnostic MRI for BMLs or other features. Rather, we propose examination for effusion as a precursor to a screening MRI for BMLs, in a very specific situation where the objective is to recruit a sample with BMLs for research.

Joint inflammation, detected as an effusion, is a key feature of OA and can occur early or late in the disease course

(28). Our findings of a cross-sectional association of effusion on physical examination with BMLs suggests that these features of OA are pathogenetically linked and may be related to underlying inflammation. Wang et al (8) showed in their cohort, ages 50–80 years, that effusion/synovitis assessed on MRI was a risk factor for BML progression, which may have been mediated by cartilage damage. This observation is in keeping with our findings of increased HRs for BML incidence/progression in those subjects with effusion, although only of borderline significance in the adjusted analysis and only in the full cohort. Even though effusion is important at all stages of disease, it may be a stronger risk factor for BML progression in more advanced OA. The causal pathways that are pertinent in OA, particularly in early disease, have not yet been clearly defined. Our study provides some insight, but this is an area where further research is needed.

The strengths and limitations of our study deserve comment. While our study is population-based (a strength), it should be noted that the target population is not the overall population, but those subjects with knee pain, ages 40–79 years at baseline, who were successfully followed up over an average of 3 years. Thus, we cannot be sure that the results of this study are applicable to a more general population that includes persons without baseline knee pain, or those outside the target age range of ≥40 years. Another important strength of our study is that we specifically analyze effusion detected on physical examination, rather than MRI-based effusion, which is directly relevant for the intended application of precluding subjects from unnecessary MRIs during recruitment for clinical trials involving patients with BMLs. However, one potential limitation of using physical examination to detect effusion as a prescreening tool for knee BML studies is that all the recruited subjects will have effusions, and thus the patient population will not be perfectly representative of all patients with knee BMLs generally (BML patients without physical examination effusion would be missing). On the other hand, the potential cost savings is large, and the individual researcher would ultimately decide how important including BMLs without knee effusion may or may not be in their particular research questions. Another limitation relates to the use of semiquantitative assessment of BMLs, which may not be as sensitive to change as a quantitative measurement of BML size or volume, and this lack of sensitivity may have limited our ability to detect an association with BML incidence/progression.

In summary, in this population-based study, effusion detected by physical examination was cross-sectionally associated with a significantly increased risk of BMLs on MRI. We found a high PPV of 79.9% of physical examination effusion to predict BMLs on MRI in a patient sample with knee pain representing the full range of knee OA (from preradiographic through advanced radiographic disease), and 75.5% in a mild disease subsample, excluding those subjects with advanced radiographic OA. This study highlights the potential utility of physical examination for knee effusion for the purpose of prescreening, before administering costly MRIs for clinical trials that require subjects with knee BMLs.

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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. Cibere 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. Cibere, Guermazi, Nicolaou, Esdaile, Thorne, Singer, Wong, Kopec, Sayre.

Acquisition of data. Cibere, Guermazi, Nicolaou.

Analysis and interpretation of data. Cibere, Esdaile, Thorne, Singer, Wong, Kopec, Sayre.

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Qualitative Evaluation of Evidence-Based Online Decision Aid and Resources for Osteoarthritis Management: Understanding Patient Perspectives

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Objective. To qualitatively examine the experiences with, and impact of, evidence-based online resources in self-management among Australians with osteoarthritis.

Methods. Telephone interviews were conducted with 36 users of a novel osteoarthritis resource, the Osteoarthritis Awareness Hub. Rogers' 5 attributes of innovation (relative advantage, compatibility, complexity, trialability, and observability) and outcomes guided the semistructured interview and analysis. Maximum variation sampling was used, and data saturation occurred after 33 interviews. A coding scheme was agreed upon and all interview data were entered into NVivo for qualitative content analysis.

Results. Study participants had high levels of literacy and health literacy. For adoption and implementation of an innovation, the participants' narratives confirmed and underscored the fact that it was important that it come from an authoritative and trusting voice and that its perceived benefits align with participants' values and existing practices (relative advantage and compatibility). The participants also valued seeing the practical benefits of the innovation, such as its capacity to impart quality and balanced new insights and information, and to maintain and monitor their personal progress. Notably, many participants spoke about the mental and physical health benefits that they derived from engagement with the online resources.

Conclusion. Our study findings confirm that web-based tools can be a useful adjunct to patients adopting self-management strategies. Rogers' theory provides a framework for a deeper appreciation of the how, why, and what questions concerning the adoption and implementation processes, especially among people with good technology and health literacy.

INTRODUCTION

Osteoarthritis (OA) is one of the most common chronic conditions, and its prevalence is increasing rapidly, largely due to growing obesity and aging of the population (1). OA affects 1 in 11 Australians (9%) and is a disabling condition that significantly impacts individuals and society at large, with physical, psychosocial, workforce, and economic ramifications (2). Compared to people without OA, patients with OA have poorer health and quality-of-life, higher levels of psychological distress, and severe pain. They are also more likely to have comorbidities such as cardiovascular disease, back pain, and mental health issues (2,3).

Numerous clinical guidelines recommend efficacious conservative treatments, including allied health support and lifestyle modifications such as exercise and weight loss (4–8). However, the predominant approach to OA management still focuses primarily on symptom management to address pain and joint dysfunction using pharmaceuticals and surgery (9–11). Such clinical practice is in contrast to how patients wish to manage their OA. Most are neither satisfied with their current treatment, nor ready

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SIGNIFICANCE & INNOVATIONS

- A web-based resource from an authoritative and trusted source, combined with tangible practical benefits, aids adoption and implementation processes.
- Increased understanding of osteoarthritis management through active engagement with a web-based resource provides patients with a sense of control and empowerment.
- The utility of a decision aid tool (DAT) goes beyond its potential in shared decision-making processes, which require clinicians' input; the DAT supports the patient's desire to be an autonomous decision-maker in self-management.
- This is the first qualitative inquiry that explicates the intricacies and complexities involved in the adoption of innovation among people with good technology and health literacy.

for or acquiescent to total joint replacement, and they look for other treatments (12).

Reasons for the incongruity between evidence-based OA care and what occurs in clinical practice are multifaceted, involving patient, clinician, and system factors (13). Key issues include the inadequacy of guidelines to change clinicians' behaviors, low OA literacy in the community (14), insufficient patient education (15), patient dissatisfaction with the information from health professionals (16), lack of patient involvement in decision-making (17), and the complexity and time-intensive nature of OA management for older people who are likely to have coexisting multimorbidity and polypharmacy (18,19).

It is important for patients to understand treatment risks and benefits and to be understood by health professionals about their values and preferences in OA management. Such understanding is key to ensuring patient confidence and improving satisfaction with their management decision (20–22). However, short clinical encounters are a common barrier to the effective communication process necessary to help the patient make informed decisions (23). OA management is also complex due to marked variations in weight, tolerance for physical activity, the risk for adverse antiinflammatory events, including both gastrointestinal and cardiovascular toxicity, and frequent concomitant comorbidities, including depression, hypertension, and/or diabetes mellitus. Patient decision aids can reduce the level of uncertainty, increase patients' knowledge about the risks and benefits of therapeutic alternatives, help clarify their values and preferences, and prepare them for the clinical encounter and treatment choices (24,25).

This qualitative study formed part of a larger study evaluating the effects of the Osteoarthritis Awareness Hub (OA-Hub), an evidence-based online program created in partnership with patients, clinical experts, and Arthritis Australia. The OA-Hub was developed to address the lack of reliable, easily accessible, and affordable resources for patients with OA to guide informed decision-making. Given the uncertainty surrounding the tradeoffs between benefits and harms for OA management, we aimed to explore the experiences and perceptions of users of the OA-Hub concerning OA self-management and decision support. A key research question was "How do users of the OA-Hub experience and perceive the adoption and implementation processes of the OA-Hub?"

PATIENTS AND METHODS

The OA-Hub. The online program OA-Hub contains a website, MyJointPain.org.au (MJP), providing information and self-management resources for OA of the hip and/or knee (26), and a web-based decision aid tool (DAT) using a software platform called Annalisa (27). The primary objective of the OA-Hub was to help people with OA achieve measurable improvements in health outcomes and health care utilization, informed by the most up-to-date evidence available. A unique feature of the DAT allowed patients to compare different treatments, based on factors that were most important to them, in reference to their clinical characteristics and preferences about the benefits and harms associated with the alternative options. Nineteen treatment options were shown, ranging from cardiovascular exercise to surgery, based on the best OA management evidence available. The factors important to patients were based on qualitative and patient preference studies as well as input from the research team. By combining OA management evidence with the user's chosen weighting for each treatment option (elicited graphically at the point of decision), the best course of action for each patient was shown by a quantified score for each option. The use of the DAT was elective for the OA-Hub users.

Methodology. This qualitative evaluation focuses on the adoption and implementation of the innovation, the OA-Hub, from the perspectives of patients with OA who accessed it. According to Rogers' diffusion of innovation theory (28), successful innovation adoption is determined by 5 attributes: relative advantage, compatibility, complexity, trialability, and observability. Rogers' theory informed this qualitative inquiry, and in particular the development of semistructured interview guides and data analysis. As part of the evaluation study, we also examined the outcomes of the innovation and factors influencing the adoption and outcomes (consequences) of the innovation (Table 1).

Recruitment. Ethics approval was granted by the University of Sydney Human Research Ethics Committee (2014/017). Potential participants were eligible for the study if they were age <40 years, had OA in at least 1 hip or knee joint, and had an active e-mail account and access to the internet. Participants were recruited from the broader OA community via Arthritis Australia

Table 1. Semistructured interview guides*

Attributes of adoption	Interview questions
Overall point of consideration in diffusion of innovation theory, thinking about diffusion as a social process	Tell me about your experience with OA? This will help us to put your experience into context. What's your experience with OA been like? How do you usually find more information about OA and its management?
Relative advantage: the degree to which an innovation is perceived as better than the idea it supersedes	Thinking now about the MJP and/or the DAT, what benefits did you anticipate in using the website [relative to not using the website]? How has the internet mediated the way in which you see self-management of your OA?
Compatibility: the degree to which an innovation is perceived as being consistent with the values, past experiences, and the needs of possible adopters	What are your expectations/needs when looking for information? Is the name of the website meaningful to you?
Trialability: the degree to which an innovation can be experimented with before a commitment to adopt is made	What did you think of the instructions/advice from the website? Have you tried to follow them? (Explore "why" and "what happened")
Simplicity and ease of use (or complexity): how difficult or easy an innovation is to understand and/or use	What are the difficulties/barriers in using the website in terms of managing your OA (i.e., application of its messages in real life)?
Observability: the extent to which an innovation provides tangible results	What do you think of the MJP and/or the DAT in terms of its usefulness? What made you think this? Do you find it easy to see how it helped you or others? Could you tell me a story or any situation where you thought using the website was beneficial to your management of osteoarthritis?
Anticipated versus unanticipated consequences/ outcomes	Looking back on your experience of using the website, has it helped you achieve what you thought it might help you to achieve? Was this something you expected? What else did you think happened since you started using the website? Looking back before you started using the website, and compared with the present, could you tell me if there has been any change in your management of OA and that change could be a result of what you have learned from the website?
Factors that influence the adoption of the innovation	Do you think your life circumstances have made it easier or harder to use the website? Are there any other factors that may have affected the way information from the website has influenced your management of OA? What are the difficulties/barriers in using the MJP and/or the DAT?

* OA = osteoarthritis; MJP = MyJointPain website; DAT = decision aid tool.

and included research participants of the OA-Hub quantitative evaluation (26). As part of their survey, these participants were invited to indicate whether or not they would be interested in a follow-up interview to talk about their experience with the OA-Hub. From the list of those interested in the interview, we selected and invited participants using maximum variation sampling, considering age, sex, rurality, the severity of the condition, and engagement of the OA-Hub with or without the DAT component. Saturation of data occurred after 33 interviews, and we continued 3 more interviews to ensure that no additional insights emerged from the interviews.

Participants. Thirty-six users of the OA-Hub took part in the one-on-one telephone interview, which took on average 40 minutes (ranging from 20 to 60 minutes). All participants had been accessing the OA-Hub for >2 months, and most had used the DAT (n = 22). Participants' ages ranged from 40 to 86 (median 63) years, and approximately three-fourths were women (n = 26). Time since diagnosis of OA ranged from several months to 35 years (median 12 years). The majority of participants were Australian-born (n = 28), with other regions of birth including central Europe, Germany, the UK, and New Zealand. Seventeen participants were in some form of paid employment, one was between jobs, and another was a homemaker. The remaining 17 participants were retired or in the process of retiring; 6 reported retiring because of their OA symptoms. One-fourth of the participants were currently working or had worked in the health care industry. Only 2 participants reported speaking a language other than English at home.

Analysis. All interviews were transcribed verbatim and then entered into NVivo for qualitative content analysis (29). The focus of the analysis was on meaning-making and representation of how participants adopted the innovation, using Rogers' attributes of the innovation as an overarching frame. The first and second authors (Y-HJ and IF) compared initial coding of 10

Table 2. Examples concerning relative advantage of the adoption of the innovation*

Key themes	Relevant quotes from the interviews
Gaining new insights and empowerment	Well, I think knowledge is empowerment, isn't it? If you know what's happening. I mean that's the whole purpose of it [the DAT], isn't it? To know more. I looked at all those...the little videos of people...doctors talking and I thought they were really helpful. Just an idea of what to expect and the physio and I thought they were good. So what I would expect to get out of it is knowledge to enable me to cope with it better. (FP10, age 68 years, OA for 10 years) It's [the MJP] achieved way beyond my expectation. And why I say that is when I found the website I did not know what I was looking for. I was trying to increase my basic knowledge. I was totally unaware of this dimension of treatment that is available for osteo. Totally unaware. (FP8, age 64 years, OA for 7 years)
Accessing quality, sensible and balanced information through an authoritative voice	This is perhaps where the MyJointPain website comes in, because there's so much information and misinformation about osteoarthritis and people are always trying to help retell you, you know, urban myths, and what their aunty finds helpful. I think that the main benefit was that I was confident that it would be a reliable, authoritative source of advice. (FP22, age 46 years, OA for 5 years) You [the MJP] very openly gave focused information to me. You didn't go off on a tangent about pills and tablets and all this other business. But it was just good, serious conversation between your website and myself, regarding my condition. There was no extraneous material involved. It was pure. So, it felt like no one was having a lend of me. You weren't trying to sell me some sort of tablet. (MP3, age 64 years, OA for 3 years) I thought it would be a bit of a self-help site, because of experience with one of my children. I was very, very surprised at the quality, just so sensible and so balanced. (FP20, age 67 years, OA for 20 years) Because there's such a dearth of information for younger people who are suffering from this [OA], and so this was not age-prescriptive, it wasn't kind of geared towards any particular age bracket, so I found that quite attractive too. (FP24, age 40 years, OA for 10 years)
Preserving and tracking information	I've used it [the MJP] mainly, I guess, to track my pain levels. Because memory is a terrible thing when it comes to that and I know it's very individual to assess the pain, et cetera. And it's not very objective. But I can track what I thought the pain was. And this week was better than last week, or this week's worse than last week and I wonder what I did that caused that to be. (MP4, age 66 years, OA for 2 years) I think it's the monitoring more than anything, because you tend to just forget about it, you don't ever monitor your pain levels and deterioration. (FP13, age 56 years, OA for 15 years)

* DAT = decision aid tool; FP = female participant; OA = osteoarthritis; MJP = MyJointPain website; MP = male participant.

interviews for consistency, and an agreed coding scheme was developed. All of the interview data were then coded by IF according to the agreed coding scheme.

Credibility and rigor. We established credibility and rigor of the study following the method described by Patton's work (29) through purposive sampling and obtaining high-quality data (e.g., interview questions piloted, data quality check, systematic data management, and data saturation); keeping reflective notes, ensuring consistency of data analysis and looking for alternative experiences; and involvement of highly experienced qualitative researchers.

RESULTS

Relative advantage. For most participants, the relative advantage of the OA-Hub was described in relation to its practical benefits, as shown in Table 2. Using the OA-Hub provided most participants with additional insights beyond those gained during the medical encounter, for example, using exercise as a treatment option to relieve hip pain, which became a means of empowerment. For those participants who embraced the information and advice from the MJP website, the relative advantage was seen in the authoritative and quality information of the nonmercantile nature of the MJP, in comparison with other inexpert sources of information or profit-driven sites. Presentation of information by professionals, in a sensible and balanced way, was particularly helpful and facilitative of meaningful interaction with the OA-Hub. Participants saw the MJP as supplementing their memory, with its capacity to preserve and track information on pain levels and other symptoms, as well as monitoring deterioration of conditions. For some participants, the MJP served as a reminder regarding exercise, nutrition, education, and self-management; for others, the monitoring function served as a source of clarification to augment information provided by other expert sources and prompted reflection on practices that might have affected pain levels.

Compatibility. Compatibility of OA-Hub content that influenced the innovation adoption falls into 4 broad areas, shown in Table 3. First, participants who embraced the OA-Hub valued sourcing online information for its practical application of current research and access to the most up-to-date information.

Second, the trustworthiness and objectivity of web resources in the OA-Hub addressed concerns about other information being tainted by commercial interests, and beliefs that profit-driven web resources were biased. Noncommercial information was compatible with the perceived intent of the OA-

Table 3. Examples concerning compatibility of the adoption of the innovation*

Key themes	Relevant quotes from the interviews
Existing practices of sourcing online information	I think that [the internet] just gives you the really up-to-date stuff. And that's what I felt yours does. I thought, well, and it would have...your site would have to be the most up-to-date thing. Because there'd be people working on it and doing research and development on it. There couldn't be really necessarily old stuff, but it would be, like, the latest that there is on this condition. (FP14, age 70 years, OA for 16 years) I've done a lot of research on the web, and the general practitioner has given me some brochures and things and I'm a regular to the Arthritis Foundation and what I really found most useful was the web things, that Arthritis Foundation did with unit of joints and muscles or something, that's associated with the Sydney Uni., a webcast, and that was really good because it gave you a practical idea and it walked you through different options. (FP6, age 62 years, OA >3 years)
Trustworthiness and objectivity of web resources	Well I saw it [the MJP] as not leading to a product offer. I saw it as coming with some, I can't remember authority, Arthritis Australia or Commonwealth Government funding or some such thing. And I'd felt as if it was a resource which wasn't commercially linked. (MP4, age 66 years, OA for 2 years) When I saw that site, I thought, "Hey, this looks interesting. Let's check in on this." And because it's university-based, or tied in, you realize it's not just a commercial site, it's actually a site that's founded in, I'd say, good practice. I've got to say, I didn't read too many of the testimonials. I looked mainly at what the professionals were saying. I mean it's subjective isn't it, a testimonial? It's how you feel and all that stuff, where I feel with the professionals saying it, it's a bit more objective and scientific. (MP5, age 68 years, OA for 4 years)
Existing skills and knowledge of similar technology to the OA-Hub	I've found those things [decision aids] useful before, that's probably one of the reasons why I jumped at using something like that [DAT]. (FP24, age 40 years, OA for 10 years) I think I was tooling around, looking for information. And I came across the website. I think I sort of knew it was a little bit of a beta site. And I've been involved with beta software for 40 odd years, so I was fairly aware of it. (MP4, age 66 years, OA for 2 years) You could call it [DAT] a map, basically. You go out and you orienteer, you use your map. It gave me the map that plotted the course and I was able to work the other things in and I'm still working on it. (FP31, age 52 years, OA for 12 years)
Background in health care	I suppose because of my nursing, I tend to look at things that are medically oriented and if I'm looking at supplements, I always go online and look at the research...I think probably my nursing training is good, because I still have a very high level of curiosity about what is a medical issue, so you know, health issues in general. (FP23, age 69 years, OA for 5 years) I think that some of the options might have been other stuff or if I wasn't already in the health system and knew how to negotiate those kind of things, then perhaps, yeah, that might be quite daunting for other people. (FP24, age 40 years, OA for 10 years)

* FP = female participant; OA = osteoarthritis; MJP = MyJointPain website; MP = male participant; DAT = decision aid tool.

Hub, and its legitimacy came through affiliation with large academic institutions. The OA-Hub would provide best-practice advice and objective accounts of managing OA in contrast to subjective testimonials. The evidence backing the DAT selection mechanism also enhanced trust. Often these threads came together under a broader conceptualization of the best treatment for OA being based on conventional scientific methods, even among participants who also used complementary and alternative medicines.

Third, compatibility was expressed through the participants' own experience of similar technology, based on their vocational background and work life. Participants also observed the relatively objective nature of the DAT technology as compatible with their philosophy of managing OA and their need to find a range of evidence-based treatments.

Last, one-fourth of the participants had either worked or continued to work in health care. For these participants, compatibility was assessed through the lens of their health care background. For example, being a nurse or a sonographer made them insiders, i.e., already possessing some knowledge that would assist them in the use of the innovation.

Complexity, trialability, and observability. Complexity, trialability, and observability were described as being less of an issue for most participants (Table 4). While mixed responses were found regarding the need for good computer literacy when navigating the MJP, the majority of participants reported that the content of the MJP was straightforward, meaningful, and appealing to everyone. Furthermore, none of those who had used the DAT reported its interface as being too complex to engage with meaningfully. They expressed emphatically the ease with which they were able to engage with the DAT. Two participants tried using the DAT but did not adopt the technology, because it only served to reinforce already-held knowledge and practices (lack of relative advantage). Among the rest of the DAT users, a similar qualification arose regarding the accessibility or complexity of the interface; it was easy to use with the prerequisite computer literacy.

Table 4. Examples concerning complexity, trialability, and observability of the adoption of the innovation*

Key attributes	Relevant quotes from the interviews
Complexity	I found it [the DAT] fairly easy to use. I would probably say I'm fairly highly computer literate. (MP15, age 63 years, OA for 35 years) I thought it [the DAT] was quite easy, you know. I mean, I'm fairly computer literate, so, I didn't have a problem using it at all, really. (MP32, age 64 years, OA for 3 years) Perhaps I'm not the right person to ask in a way because I am highly literate and comfortable with jumping around doing things and teasing out, what does this question mean. So, I found it very easy and straightforward to use. (FP22, age 46 years, OA for 5 years) Well it's hard for me to say objectively, because I guess I already have a certain degree of, kind of, health literacy. I found it [the DAT] easy to use but there's certain parts to it, and if you think about when you're putting in your medications or your alternative medications, and stuff like that, not all the ones that you might necessarily be on are listed. (FP24, age 40 years, OA for 10 years) I don't think you need to have any kind of formal training. But if you're not computer literate, then it can be very difficult. (FP23, age 69 years, OA for 5 years)
Trialability	Where quite often decisions are emotive, I'm hurting like hell at the moment, I need to do something now, and it just takes all that emotiveness out of it. I know if I've got something, I can go to it, try and find the answer, if not, find something close to it, and it gives me control back. (FP6, age 62 years, OA for >3 years) Honestly, I tore the hell out of it [the DAT]. I adjusted things to, sort of, try to find, like a balancing scale, I kept on to the same work, I adjust that, where will that take me? What will that change? And I got to know what meds, what different activities, what choices, you know, and I was pretty much eliminating the drug, did not want to go down that path. So, I mucked around with it [DMA] until I found and was guided by it to learn what could be done, what couldn't be done and where I needed to work from other aspects. So, it's been a training tool. (FP31, age 52 years, OA for 12 years) The decision-making tool I really just used that one time. I used it several times in that one sitting though, 'cause I kind of increased my symptoms or reduced them just to look at whether or not it would change what the decision was. (FP24, age 40 years, OA for 10 years)
Observability	I have shared the information about the website with people at the support group. And everybody there is curious for information, which is fantastic. (FP23, age 69 years, OA for 5 years)

* DAT = decision aid tool; MP = male participant; OA = osteoarthritis; FP = female participant.

Trialability was reflected in the capacity of the OA-Hub to allow participants to experiment with the program. The MJP itself already had a high level of trialability, since all participants had previously used online resources. Some participants spoke about how the DAT had acted as an instructional tool for managing the symptoms of OA. Others experimented with the DAT by inputting different scenarios to see what the recommendations were, or how the outcomes of the DAT might change. Experimenting with the DAT allowed them to think about how they were going to manage OA symptoms in the context of a multiplicity of treatments. In this study, trialability was not a prominent theme; rather, participants typically used the DAT once and found it helpful.

Observability refers to whether the people who know the participant, their family, friends or colleagues, have observed changes in the participant as a result of their use of the MJP or DAT. However, limited accounts were found regarding observability, largely due to a relatively short period of exposure to the OA-Hub.

Outcomes. The MJP and DAT were seen as trusted sources of information about OA management that participants had not been sufficiently given by their general practitioners and other clinicians. This information then facilitated effective tangible and intangible outcomes, such as weight reduction and better symptom management. As shown in Table 5, participants reported a relationship between the advice from the MJP and weight loss, which then alleviated some of the symptoms of OA, including pain. Other participants also reported taking up the advice from the MJP regarding practices that they had not previously considered. One participant who had cut back her walking due to pain in her knees was now able to continue walking as part of her weight management plan after seeking advice from the MJP. Similarly, another participant attributed the reduction in pain levels to the advice he had followed from the MJP, which included seeking help from a physiotherapist.

Another key outcome following the use of the OA-Hub was an increased focus and motivation leading to lifestyle changes, by helping participants maintain attention on activities that aided in managing symptoms. Participants were able to use the information on the MJP as a reminder to try and stay positive despite the pain and discomfort associated with OA. One participant reported having difficulty in managing her weight despite her awareness of the deleterious impact of weight on OA symptoms. Nevertheless, the reminders from the MJP helped her to continue working on her weight. Another participant who had jobs requiring significant manual labor and long hours standing reported that the DAT had motivated her to start to retrain for an occupation that did not bring such significant physical demands and helped her continue to man-

Table 5. Examples concerning outcomes of the adoption of the innovation*

Key themes	Relevant quotes from the interviews
Weight reduction and better symptom management	They do your BMI, and stuff like that. I lost 14 kilos over the last 12 months, like, that was a really good incentive for me. And I can feel the difference in how much relief that has provided, just that one thing. (FP24, age 40 years, OA for 10 years) When I go on long walks now I do take a walking aid with me, also nutrition I found very useful, and it's helped me lose weight. As I said, just those little snippets that they give you on the side is quite useful, and a lot of them I've put into practice like the meditation. I sort of used to do it, but I never used to do it on a regular basis. (FP6, age 68 years, OA for >3 years) The pain levels went backwards. Because of either recommendations that were made there [on the MJP] and then you follow them through, you do some exercise and go and see a physio or exercise specialist, whatever. And I did that. (MP5, age 68 years, OA for 4 years)
Increased focus and motivation leading to lifestyle changes	It [the MJP] keeps your mind on what you should be doing, nutrition, the exercising and things. It does keep me focused on what I should be doing and not putting it off or…it's something that I will continue using. (FP10, age 68 years, OA for 10 years) I suppose it [the MJP] makes me stop and think about my frame of mind, you know, have I been as upbeat as I could be this week? Have I tried to be as positive as I could be? (FP12, age 66 years, OA for 26 years) Yeah, I think it's really helpful to have it said again. I don't think you can have it said too many times. I mean, especially when you struggle with keeping your weight under control, as so many people do. (FP23, age 69 years, OA for 5 years) Yes, because I mean I'm a lot more, happier and confident. And like I said, I used to walk backwards and forwards [to work] and when I couldn't, it was a real pain, because you need exercise. And I'm doing that. So, it's brought a positive into my lifestyle. (MP5, age 68 years, OA for 4 years) I guess a change of my attitude, a little bit in thinking that I have this pain and it's no use getting angry or anything like that. I've just got to find ways of dealing with it…and I think it's just basically accepting that I've got these degenerations in my body and just get on with it. (FP28, age 66 years, OA for 11 years) I almost got talked into having an arthroscope and having my worse hip all cleaned up, but then when I actually went looking at the evidence [through the MJP and the DAT], there's not really great evidence that that is going to give me any better quality of life or, you know, give me anything better than I'm already doing just with lifestyle factors. (FP24, age 40 years, OA for 10 years)
Resilience as an underlying factor	I'm just trying to learn to live with it [OA], and I know it's a cliché, but just accept the new normal, and not be living in the past and remembering how when I could just walk all day and not worry about it. (FP22, age 46 years, OA for 5 years) I talk to myself a lot about, you know, this [OA] is something that you live with, you don't live out of it. So, in other words it doesn't control my life, it's something I have to accept and live with but I don't let it control me. (FP12, age 66 years, OA for 26 years)

* BMI = body mass index; FP = female participant; OA = osteoarthritis; MJP = MyJointPain website; MP = male participant; DAT = decision aid tool.

age her symptoms through a variety of treatments, including exercise. Another participant characterized the improvement in managing her OA as meeting milestones, describing it as an ongoing process, facilitated by the information she found on the MJP.

Resilience was identified as an influencing factor in the overall outcomes of the adoption of the OA-Hub in this study. Some participants described their will to problem-solve and manage OA regardless of challenges and their determination not to be controlled by the symptoms of OA. Such resilience was highly likely to have influenced the way they managed their OA.

DISCUSSION

With a proliferation of web-based health care resources worldwide, it is important that we understand what determines a person's decision to accept, use, and implement a virtual innovation, as well as evaluate the impact of the innovation on their health and well being. In this study, we focused on the determinants and key outcomes of the adoption of a web-based innovation, the OA-Hub, using Rogers' diffusion of innovation theory. Narrative accounts of 36 patients with OA who accessed the OA-Hub underscore the importance of having perceived benefits about the innovation that align with their values and existing practices. For adoption and implementation, it was important that the innovation come from an authoritative and trusted source. The participants also valued seeing the practical benefits of the innovation, such as its capacity to impart quality and balanced new insights, above and beyond their prior knowledge, and maintain and monitor their progress. As in a recent UK qualitative study (n = 10), the notions of trustworthiness in the MJP and its facility for personalized information preservation, monitoring, and planning were found to be important elements that helped individuals' engagement in self-management (30).

Participants' familiarity with web-based information and technology, along with an appropriate level of computer and

health literacy, in particular, appear to have played a major role in their decision to adopt and meaningfully engage with the innovation. The innovation of the OA-Hub was described as a vehicle for putting current research, both that of the experts and that of the individual adopter, into practice, thus fulfilling their need to make abstract information concrete. Notably, most participants reported that both the content of the MJP and the accessibility and interface of the DAT were straightforward, meaningful, and appealing to everyone, reflecting the reasonably high level of the participants' perceived computer and health literacy. These findings corroborate conclusions reached in similar studies in the UK (30,31). However, MJP users with lower health literacy (n = 6) in the UK found the content confusing and complex (30), and the depth and breadth of the MJP content were seen to be excessive, hindering further engagement with the resource (31). None of these points were found to be problematic in our study, which reflects the difference in health literacy levels between participants in the 2 studies. Furthermore, 2 of the participants in our study decided not to continue with the OA-Hub because they saw the information as a validation of already-held knowledge, hence lacking the relevant advantage of the innovation.

Our most notable finding was the extent to which some participants were able to successfully adopt and implement the innovation, illustrating that their participation in the OA-Hub led to positive health outcomes such as weight reduction and improved pain management as well as behavior and lifestyle changes. This benefit was also demonstrated in the quantitative outcomes of the 12-month evaluation of the MJP website, where changes in education about self-management, lifestyle, and physical activity were significant (26). These findings were further corroborated in the 24-month outcomes, which showed sustained improvements in education about treatment alternatives and self-management (article in preparation). Further research is needed to establish the causal relationship between the OA-Hub and positive health outcomes.

Furthermore, resilience ("it's something I have to accept and live with but I don't let it control me") was shown to be an important element in the adoption of innovation that requires behavior and lifestyle changes. Participants often spoke in highly emotive terms about the information provided by the website and the DAT, especially because the website and DAT might inform their feelings of acceptance and control of the condition. This information was not limited to the management of symptoms but rather affected approaches to their life more generally. For these participants, the website and the DAT were described as vehicles for gaining or regaining control of their lives, even with the spectre of increasing symptoms with aging. This finding goes some way in addressing previous research (32), suggesting that more needs to be known about how these technologies may contribute to patient-centered care. Many of the participants in the current study highlighted how the website and the DAT focused on them as individuals, thereby offering a sense of control in their treatment beyond that which might be afforded by patient–clinician shared decision-making. This insight is significant, confirming that the utility of a DAT does not necessarily rely on the involvement of a clinician in decision-making but provides a mechanism for the patient to have more meaningful engagement with clinicians if they choose to do so. The onus is on the individual patient, not the clinician, meaning that the patient is no longer a passive recipient of care and health service, but rather an informed and empowered, active participant in their health management.

Our findings provide an interesting contrast to the utility of recent developments, such as option grids, designed to facilitate collaborative dialogues and shared decision-making during clinical encounters (33). Evidence concerning the role of patient decision aids in improving knowledge is strong, but debates exist around whether or not patient decision aids provided before clinical encounters actually improve shared decision-making (33). In this argument, the occurrence of shared decision-making becomes the ultimate goal of the clinical encounter, because it signifies the fact that the patient is supported by the clinician to make an informed decision, based on both evidence and the patient's preferences and values (34). In our qualitative exploration, we noted that what facilitates the self-management process clearly is the patient becoming more confident with the information provided, plus the way they gain some level of control over their health care decisions through the use of the web resources and/or the DAT. Therefore, questions regarding the effectiveness of patient decision aids should not be limited to their role in shared decision-making alone. Further research is warranted to understand the role of the DAT in shared decision-making, including the exploration of clinician perspectives on its use.

The value of a DAT lies partly in its ability to take the best available population-based evidence on the benefits, potential harms, and other effects and personalize that evidence to the individual. That means going beyond mean point estimates of effect and stratifying risk and benefit prediction based on the individual's clinical and other characteristics. Gigerenzer and Muir Gray propose that knowledge (or evidence) is just the beginning (35). The evidence needs to be related to the needs and conditions of the individual patients, including their values and preferences, as well as their networks, resources, and social contexts (36). In this study, particularly in relative advantage and compatibility, we have shown that evidence-based decision-making in OA is possible by relieving the patient of the cognitive burden of processing information about probability (of benefits and harms) and empowering them to express their preferences for different aspects of treatment options.

Our findings need to be interpreted with caution, given that it is difficult to completely avoid self-selection bias toward more positive experiences. The application of the findings in a broader OA community may also be limited, because most of the participants were women, highly literate in both health and technology,

and born in Australia or speaking English as their first language. Our evidence supports the idea that the adoption of maximum variation sampling, considering participants' age, sex, rurality, the severity of the OA condition, and the level of engagement with the online resources, combined with data saturation, enhanced the credibility of the findings, and the possibility of such limitations has been minimized. Furthermore, our participant profile appears to be typical of users of an online community reported in the UK (37). Inclusion of education levels in maximum variation sampling in future research may address the shortcoming encountered in this study.

In conclusion, our study provides further corroboration that web-based tools can be a useful adjunct to patients adopting self-management strategies. This is the first qualitative inquiry that explicates the intricacies and complexities involved in the adoption of innovation. The findings also highlight barriers and facilitators to the use of tools to assist self-management within the community. What we have uncovered using Rogers' 5 attributes of innovation provides a deeper appreciation of the how, why, and what questions concerning the adoption and implementation processes, especially among patients with good technology and health literacy.

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. Jeon 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. Jeon, Dickson, Salkeld, Hunter.
Acquisition of data. Flaherty, Urban, Wortley.
Analysis and interpretation of data. Jeon, Flaherty.

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BRIEF REPORT

Discordance Between Population Impact of Musculoskeletal Disorders and Scientific Representation: A Bibliometric Study

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Objective. Musculoskeletal disorders (MSDs) are a leading cause of healthy years lost due to premature mortality and disability. Our objective was to investigate whether MSDs were commensurably represented within the published health literature.

Methods. MEDLINE bibliometric data were retrieved for 2011 and 2016. The 25 disease branches, including MSDs, were ranked according to published article counts, proportion of all publications, and increase in publications from 2011 to 2016. Rankings were also considered within 5 groupings of general health journals: geriatrics and gerontology, general and internal medicine, multidisciplinary sciences, primary health care, and public health.

Results. There were 532,283 MEDLINE publications in 2016, a 16% increase over 2011. In 2016, MSDs ranked 13th in publication count, unchanged from 2011. The increase of 11% in MSD publications from 2011 was below the overall increase. Of 2016 publications, only 7% were MSD indexed, dropping from 7.3% in 2011. MSD-indexed publications had their highest ranking (8th) within geriatrics and gerontology, and lowest (19th) within public health.

Conclusion. MSDs appear underrepresented in the published health literature generally, and specifically within public health, despite their significant population impact. A broader focus on noncommunicable diseases associated with mortality omits noncommunicable diseases such as MSDs that are leading contributors to high morbidity and high costs, and such omission likely contributes to the neglect of recognizing MSDs as a health priority.

INTRODUCTION

Musculoskeletal disorders (MSDs) are conditions that can affect muscles, bones, and joints and that lead to pain and disability. MSDs are prevalent across all sociodemographic strata (1). One of the most widely used summary measures of population health is disability-adjusted life years (DALYs) (the sum of the years of life lost due to premature mortality and years of life lived with disability). One DALY represents 1 year of healthy life lost. Based on the Global Burden of Diseases, Injuries, and Risk Factors Study 2016 (1), globally over 140 million DALYs were attributed to MSDs in 2016, and MSDs ranked in the top 3 causes of years of healthy life lost among people in high-income countries. Of the 21 categories (communicable, maternal, neonatal, nutritional, and noncommunicable disease and injury) considered in the study, 7 experienced a drop, and 14 had an increase in associated all-age DALYs from 1990 to 2016. MSDs ranked second in the percentage of increase in DALYs over this time period, at 61.6% (2 percentage points behind the combined diabetes mellitus, urogenital, blood, and endocrine diseases group). MSDs affect >30% of the population in North America and Europe (2). In addition to negative personal health and social impacts, MSDs have broader and significant societal implications, with direct (i.e., health care expenditure) and indirect (e.g., lost productivity) economic costs. MSDs account for 60% of permanent work incapacity in Europe, for example, and the cost of lost productivity due to MSDs in the European Union workforce is equivalent to 1–2% of the Union's gross domestic product (GDP) (3). Proportionately from 2009 to 2011, costs directly attributable to MSDs (i.e., incremental costs) in the US represented 2.25% of the country's GDP (4).

These numbers give reason to pause and are of a magnitude to suggest that identifying MSDs as a public health priority is eas-

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SIGNIFICANCE & INNOVATIONS

- Musculoskeletal disorders (MSDs) represent one of the leading causes of years of healthy life lost and of health economic burden.
- Despite calls to recognize MSDs as a health priority, MSDs are significantly under-represented in the published health literature relative to their burden and are particularly neglected within the public health literature.

ily justifiable. However, perceptions can mask reality. MSDs often lack the profile and attention given to other headline-catching diseases for which mortality has long been a clear outcome risk. A recent publication showed that MSDs were considered in <0.5% of all poster and oral abstracts delivered at public health and epidemiology scientific conferences in North America over the last half decade (5), a clear underrepresentation relative to the prevalence of MSDs and their societal impact. Emerging evidence, however, suggests that for some MSDs, heart disease and mortality are potential outcomes (1,6). Furthermore, the role of MSDs (at least of arthritis and other rheumatic conditions) as a common comorbidity for important conditions like diabetes mellitus, heart disease, and obesity demands consideration. As a comorbidity that causes mobility problems, MSDs are likely to interfere with recommended management (i.e., physical activity) for these conditions and therefore have additional unmeasured impact. Theis et al (7) eloquently address the consequences of ignoring rheumatic diseases from this perspective. With increasing life spans among patients with MSDs, many of these MSDs are chronic con-

Table 1. Ranking of disease branches by publication counts, 2016 and 2011

	2016			2011		
Disease branch	Publications	Ranking	%*	Publications	Ranking	%*
Pathologic conditions, signs, and symptoms	212,503	1	39.9	180,567	1	39.2
Neoplasms	130,754	2	24.6	109,837	2	23.8
Nervous system	106,053	3	19.9	93,164	3	20.2
Cardiovascular	89,050	4	16.7	75,879	4	16.5
Digestive system	62,501	5	11.7	52,268	5	11.3
Nutritional/metabolic	52,937	6	9.9	45,979	6	10.0
Urogenital	48,622	7	9.1	44,271	8	9.6
Immune system	47,352	8	8.9	45,122	7	9.8
Skin and connective tissue	45,113	9	8.5	39,489	11	8.6
Bacterial infections and mycoses	44,589	10	8.4	39,580	10	8.6
Respiratory tract	44,488	11	8.4	41,017	9	8.9
Endocrine system	38,158	12	7.2	31,756	15	6.9
Musculoskeletal	37,387	13	7.0	33,674	13	7.3
Congenital, hereditary, and neonatal diseases and abnormalities	37,380	14	7.0	34,307	12	7.4
Animal diseases	36,436	15	6.8	27,882	17	6.1
Viral	35,627	16	6.7	32,385	14	7.0
Wounds and injuries	32,657	17	6.1	27,942	16	6.1
Hemic and lymphatic	25,014	18	4.7	23,943	18	5.2
Eye diseases	19,936	19	3.7	16,456	19	3.6
Chemically-induced disorders	16,241	20	3.1	14,452	20	3.1
Stomatognathic	14,250	21	2.7	14,364	21	3.1
Parasitic	13,186	22	2.5	11,449	22	2.5
Otorhinolaryngologic	11,425	23	2.1	10,748	23	2.3
Occupational	2,567	24	0.5	2,688	24	0.6
Disorders of environmental origin	45	25	0.0	77	25	0.0

* Because each article can be indexed under >1 branch, percentages do not total 100.

ditions, with the consequence that affected individuals may live for several decades with ongoing pain and disability. The current study examined whether the relative underrepresentation of MSDs was unique to scientific meetings, by investigating the extent to which MSDs were represented in the published health/scientific literature in 2016, as well as a half decade prior to that time, in 2011.

MATERIALS AND METHODS

Bibliometric data from MEDLINE were used to describe the representation of MSDs in the published health literature. MEDLINE articles are classified using medical subject headings (MeSH), which are organized in a tree structure consisting of 16 main branches, 1 of which is diseases. The diseases branch consists of 26 major disease branches. Publication counts for the current study stem from these 26 branches and were restricted to the years 2011 and 2016. Female and male urogenital diseases (2 of the 26 disease branches) were combined into a single urogenital disease branch. Within MEDLINE, indexers use MeSH to describe the subject content of journal articles, and a single journal article can possibly be indexed under >1 major disease branch. Thus, branches cannot be considered mutually exclusive.

The major disease categories were ranked based on their total publication counts, and the proportions of all publications represented by these major disease categories were calculated. The increase in the number of publications from 2011 to 2016 was determined overall and by major disease category.

MSD representation across disciplines of health was investigated by considering 5 groupings of general health–related journals (not specific to particular diseases): geriatrics and gerontology, general and internal medicine, multidisciplinary sciences, primary health care, and public health. To facilitate publication count comparisons across these journal groupings, journals within each grouping were ranked by 2011 and 2016 impact factors, and the top 10 journals by impact factor within the respective year and journal grouping were retained. Within each of these journal groupings, composed of their top 10 journals, the number of publications by major disease category was determined and then ranked. The number of MSD publications, their rank, and their proportion of all publications within each of the journal groupings was given.

Within the MSD disease branch, there are 11 categories with a combined 125 subcategories. Some of the subcategories appear under >1 category and therefore are not mutually exclusive. We provide numbers for some of the larger/more recognized groups, while understanding that there is sometimes use of variant terminology for the same concept. We give publication counts for 4 MSD categories (bone diseases, joint disease, rheumatic diseases, and muscular diseases) and 5 subcategories (arthritis, osteoarthritis, gout, psoriatic arthritis, and fibromyalgia). Publication counts are provided for 2011 and 2016. Bibliometric searches were performed by an academic library information specialist.

RESULTS

There were a total of 460,602 MEDLINE published articles in 2011 and 532,283 in 2016 (search finalized on November 30, 2017), which represents a 16% increase over the 5-year period. With 37,387 MSD publications in 2016 and 33,674 in 2011, the increase in MSD publications over the study period, 11%, was below the 16% overall average increase and ranked 15th overall in the magnitude of the increase when comparing all disease branches. MSD rankings were unchanged in disease branch publication ratings, ranking 13th in 2016 and 2011 (Table 1). A total of 7% of all publications were indexed under the MSD branch in 2016, and 7.3% of all publications were indexed under MSD in 2011.

Within the specific disciplines of health that were considered, MSD-indexed publications had their highest ranking within geriatrics and gerontology, ranking 8th in 2016 (versus 9th in 2011), and their lowest ranking within public health, ranking 19th in 2016 (versus 17th in 2011) (Table 2). Within the top 10 ranked (by impact factor) geriatrics and gerontology and public health journals, MSD-indexed publications represented 3.0% and 0.8% of all publications, respectively, in 2016. Table 3 shows publication counts for specific musculoskeletal categories and subcategories for 2011 and 2016, including their proportion of all MSD publications.

DISCUSSION

This study quantified the representation of MSDs in the published health literature relative to other major disease categories for 2011 and 2016. Within the broader diseases branch,

Table 2. Number and ranking of musculoskeletal disorder publications within health-related disciplines in 2016 and 2011*

	2016			2011		
Health-related discipline	No.	Ranking	%	No.	Ranking	%
Geriatrics and gerontology	73	8	3.0	45	9	2.6
Primary health care	66	13	3.4	59	12	3.7
General and internal medicine	356	15	3.2	289	17	3.1
Multidisciplinary sciences	199	16	1.5	114	17	1.2
Public health	7	19	0.8	22	17	1.2

* Ranking and percentage are based on the top 10 journals, selected based on impact factors within respective years, within discipline.

Table 3. Publications for specific musculoskeletal disorder (MSD) categories/subcategories in MEDLINE, 2016 and 2011*

	2016 (n = 37,387)		2011 (n = 33,674)	
	No.	%	No.	%
MSD categories				
Bone diseases	16,781	44.9	15,922	47.3
Joint diseases	13,580	36.3	11,346	33.7
Rheumatic diseases	8,754	23.4	7,457	22.1
Muscular diseases	6,205	16.6	5,519	16.4
MSD subcategories				
Arthritis	9,984	26.7	8,382	24.9
Rheumatoid arthritis	3,715	9.9	3,448	10.2
Osteoarthritis	3,474	9.3	2,664	7.9
Gout	425	1.1	321	1.0
Psoriatic arthritis	412	1.1	316	0.9
Fibromyalgia	436	1.2	451	1.3

* Categories and subcategories are not mutually exclusive.

MSDs ranked 13th of 25 by number of publications in 2016, a ranking unchanged from 2011. Irrespective of the metric considered, MSD-indexed publications were low-to-moderately ranked. MSD-indexed publications were ranked in the top 10 only in the geriatrics and gerontology category, ranked 8th, but only representing 3.0% of publications in this group.

These rankings are in sharp contrast to the well-documented significant disability and cost impacts of MSDs in the population, both regionally and globally (2–5). Several indicators have been used to determine the extent to which MSDs are considered a health priority. These include, but are not limited to, funds allocated to MSD research, MSD-related training in medical schools, and attention directed toward MSDs in the dissemination of research results. Our findings that MSDs rank from moderate to low in the published health literature are consistent with reports that MSDs are underrepresented in clinical trials relative to the burden they represent (8), and that they appear underrepresented in medical schools, where few clerkships specific to MSDs are offered (9).

The chronic pain and disability associated with MSDs lead to deteriorating physical, mental, and social well-being overall, with subsequent negative health and cost consequences (including direct and lost productivity/opportunity costs) for individuals and society (1–4). The societal burden is especially significant due to high MSD prevalence and the implications associated with aging populations with increasing life spans. Organizations such as the American Public Health Association (10), the Global Alliance for Musculoskeletal Health of The Bone and Joint Decade (11), and the European Musculoskeletal Conditions Surveillance and Information Network (12) have recognized that MSDs should be viewed as a public health issue. Against this backdrop, MSD publications notably ranked 19th in count among the top public health journals in 2016, a drop in rank from 17th place in 2011. We found that 0.8% of all MEDLINE publications within public health included an MSD indexation, a finding remarkably similar to that of a recent study that reported MSD-related presentations (poster and oral) at North American public health and epidemiology conferences amounted to no more than 0.5% of all presentations from 2011 to 2016. The relatively low ranking of MSDs compared to other conditions may in part be driven by a focus on diseases associated with mortality. For example, the World Health Organization's noncommunicable diseases program has prioritized cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes mellitus precisely because of their contribution to mortality (13). Such an approach omits noncommunicable diseases associated with high morbidity and high costs but lower mortality, of which MSDs are leading contributors. This approach also neglects the significant impacts of MSDs as common comorbidities and their role with other diseases in amplifying deteriorations in quality of life, and in functional, mental, and social outcomes, impacts that are often difficult to quantify (7).

Our findings need to be interpreted in light of some limitations. MEDLINE served as the only source of publications. While MEDLINE is one of the most widely used health research databases, it does not contain all of the world's published health-related literature. Our investigation considered MSDs specifically within the academic community's publications. It did not assess consideration of other domains of health and public policy that otherwise may target MSDs. However, if scientific findings are to provide the evidence base for the development and implementation of guidelines, public policies, and health practices to mitigate the considerable burden of MSDs, the relative neglect of MSDs in the scientific literature is concerning. In addition, because a single publication can have multiple MeSH disease branches assigned to it, the publication can contribute to counts within multiple branches. Therefore, while the numbers provided for the MSD branch in the current study reflect the number of publications for which an MSD designation was made, this fact does not mean that MSDs were necessarily the foci of the publications. Particularly for MSDs that are highly prevalent and are very common comorbidities, and therefore have a greater likelihood of being identified in health studies generally, the MSD counts as given may be an overestimation of attention directly focused on MSDs.

Despite their significant impact, MSDs appear underrepresented in the published health literature generally and within the public health arena specifically. While researching the clinical and basic science aspects of MSDs is crucial, a parallel and concerted effort to address, study, and disseminate findings regarding the public health impact of MSDs is critical to fostering recognition of MSDs as a necessary health priority. While we do not suggest that disease burden alone should define what the appropriate ranking of citations should be for any

1 disease or disease category (14,15), the disconnect between the burden of MSDs and the discourse around MSDs as reflected by health publications/presentations cannot be ignored.

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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. Perruccio 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. Perruccio, Yip, Power, Canizares, Badley.

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Effects of Aerobic and Resistance Exercise in Older Adults With Rheumatoid Arthritis: A Randomized Controlled Trial

Elvira Lange,[1] Daniel Kucharski,[1] Sara Svedlund,[1] Karin Svensson,[2] Gunhild Bertholds,[2] Inger Gjertsson,[1] and Kaisa Mannerkorpi[1]

Objective. To evaluate the effect of a moderate-to-high–intensity, aerobic and resistance exercise with person-centered guidance in older adults with rheumatoid arthritis (RA), through a randomized controlled multicenter trial.

Methods. Older adults (ages 65–75 years) with RA (n = 74) were randomized to either a 20-week exercise intervention at a gym (n = 36) or to home-based exercise of light intensity (n = 38). Assessments were performed at baseline, at 20 weeks, and at 12 months. The primary outcome was the difference in the Health Assessment Questionnaire disability index (HAQ DI) score, and the secondary outcomes were the differences in physical fitness assessed by a cardiopulmonary exercise test, an endurance test, the timed up and go test, the sit to stand test, and an isometric elbow flexion force measurement.

Results. No significant differences between the groups were found for the primary outcome, HAQ DI score. Within the intervention group there was a significant improvement in the HAQ DI score when compared to baseline ($P = 0.022$). Aerobic capacity ($P < 0.001$) and 3 of 4 additional performance-based tests of endurance and strength significantly improved ($P < 0.05$) in the intervention group when compared to the control group. In the intervention group, 71% of patients rated their health as much or very much improved compared to 24% of patients in the control group ($P < 0.001$). At the 12-month follow-up, there were no significant differences in change between the 2 groups on the HAQ DI score. A significant between-group difference was found for change in an endurance test ($P = 0.022$).

Conclusion. Aerobic and resistance exercise with person-centered guidance improved physical fitness in terms of aerobic capacity, endurance, and strength in older adults with RA.

INTRODUCTION

A major factor contributing to ill health in old age is the increase in systemic inflammation that occurs with physiologic aging, so-called inflamm-aging. Systemic inflammation also changes body composition, leading to increased fat mass and sarcopenia (1), with the latter contributing to impaired balance and falls, which are associated with deleterious outcomes (2). Physical activity has antiinflammatory effects by promoting the breakdown of fat, increasing the antiinflammatory and regulatory properties of the immune system, and increasing muscle-produced interleukin (3–6). Age-related decline of physical function and ability to perform desired activities is a concern for patients with rheumatoid arthritis (RA) (7), especially since patients with RA of all ages, despite disease control, show a disease-related loss of muscle mass and altered body composition (8) that is related to disability (9). Studies have shown improvements in aerobic capacity, muscle strength, and disability, as assessed with the Stanford Health Assessment Questionnaire disability index (HAQ DI), after an intervention involving aerobic and resistance training (3,5). Therefore, it has been proposed that physical activity should be included in the routine management of middle-aged patients with RA (5,10), and the World Health Organization recommends both aerobic and resistance exercise each week, preferably of moderate-to-vigorous intensity, for adults ages >65 years (11). However, knowledge about benefits of exercise in older adults (ages >65 years) with RA is scarce.

The physical activity level among patients with RA, especially among those ages >55 years, is lower than the level recommended by international guidelines for health-enhancing physical activity and is lower than that among healthy persons (12,13). The reduced physical activity level among patients with RA is partly due to a worry that exercise could damage

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SIGNIFICANCE & INNOVATIONS

- Aerobic and resistance exercise with person-centered guidance improved physical fitness in older adults with rheumatoid arthritis (RA).
- Seventy-one percent of patients in the intervention group rated their health as much or very much improved on the Patient's Global Impression of Change scale.
- Older adults with RA were able to perform both aerobic and resistance exercise at a high intensity without any serious adverse events.
- The intervention is recommended for inclusion as part of the management of RA for older adults with low-to-moderate disease activity.

the joints (14,15), but no harmful side effects from exercise have been documented (5), and no joint damage is seen at extended follow-up after high-intensity exercise (16). A person-centered approach (17) is suggested to help identify and assuage worries of this type (18). The principles underlying this approach include the establishment of a partnership between the care giver and the patient, based on the patient narrative, and shared information and decision-making, together with documentation (17). A person-centered approach that focuses on the context, history, and resources of the individual has been suggested as particularly suitable for managing long-term diseases (17).

Today >50% of patients with RA are ages >65 years (19), and their health care cost is increased 3–4-fold over comparators in the general population (20). We hypothesized that a moderate-to-high intensity aerobic and resistance exercise with person-centered guidance would decrease disability and improve physical fitness in older adults with RA.

PATIENTS AND METHODS

Patients were recruited from the rheumatology clinics at the Sahlgrenska University Hospital, Gothenburg, and Skaraborg Hospital, Skövde, Sweden via the Swedish Rheumatology Quality Register. The recruitment, intervention, and data collection were performed between January 2015 and November 2016. The study complied with the Declaration of Helsinki and was approved by the Regional Ethics Review Board in Gothenburg (2014-11-24/790-14). Informed, written consent was obtained from the patients before the baseline examinations.

The inclusion criteria were RA according to the American College of Rheumatology 1987/European League Against Rheumatism 2017 criteria (21), ages ≥65 years, disease duration >2 years, and low-to-moderate Disease Activity Score in 28 joints (DAS28 <5.1). The exclusion criteria were comorbidities such as unstable ischemic heart disease or arrhythmia that might preclude moderate intensity exercise, joint surgery within 6 months prior to inclusion, ongoing exercise of moderate-to-high intensity ≥2 times/week, inability to understand or speak Swedish, and inability to participate in physical testing that involved walking or bicycling.

A letter of invitation that contained comprehensive information on the study was sent out and was followed by a phone call, during which the patients could accept or decline the invitation (Figure 1). At the screening visit, a physical examination, resting electrocardiogram, and cardiopulmonary exercise testing (CPET) were performed to search for exclusion criteria. In total, 49 patients were included and examined at the Sahlgrenska University Hospital, Gothenburg, and 25 patients were included and examined at the Skaraborg Hospital, Skövde (Figure 1).

Randomization. After screening and enrollment, the participants were randomized separately for each site to groups of 6 subjects by a person not involved in the examinations or intervention. Sealed opaque envelopes were used with a computer-generated sequence of allocation, and the envelopes were divided by sex (men/women). The participants were informed of their group allocation by the physiotherapist leading the intervention (EL and GB).

Intervention. For the intervention group, the supervised exercise intervention consisted of gym-based, moderate-to-high–intensity, aerobic and resistance exercise 3 times a week and home-based exercise for 20 weeks (Figure 2). The person-centered approach implied that the intervention started with an individual meeting, to create an understanding of the person establishing goals for exercise in a partnership and reaching an agreement on how the intervention should be performed. The gym-based exercise was tailored based on the resources of the individual and consisted of warm-up, 27 minutes of aerobic exercise at 70–89% of maximum heart rate in intervals of 3 minutes, and 5 resistance exercises at 70–80% of 1 repetition maximum (RM). Introduction to exercise began at a low level and slowly increased over 6 to 9 weeks. The physiotherapist was present at 2 of 3 sessions each week, and adjustments were made continuously. The patients performed exercise independently but attended the gym at approximately the same times and formed an informal group. In the control group, patients attended 1 individual meeting with the physiotherapist, where they were encouraged to perform home-based exercise according to the same protocol as the intervention group, but with no gym-based exercise, for 20 weeks (Figure 2).

Assessment. Background data and outcomes, comprising medical examination, questionnaire results, and 5 performance-based tests, were assessed by blinded assessors (DK, SS, KS,

and IG) at baseline, at postintervention (at 20 weeks), and at follow-up (at 12 months). Follow-up included medical examination, questionnaire results, and 4 performance-based tests. The DAS28 was used to assess disease activity (22,23).

Primary and secondary outcomes. The primary outcome, disability, was assessed using the HAQ DI (24,25). The secondary outcome, physical fitness, was assessed by 5 performance-based tests. Assessment of aerobic capacity through CPET was performed according to a protocol that was modified from the American Heart Association guidelines (26). A bicycle endurance test was performed on a cycle ergometer (Monark Ergometer 839 E, Monark Exercise AB) (27). After a 2-minute warm-up period at 50W, the patients cycled at a constant power of 70% or 75% of the maximum achieved power, which was based on the estimation from the CPET, and the total time was registered when the level of exertion was rated "very hard" on the Borg rating of perceived exertion (28). Functional balance was assessed with the timed up and go (TUG) test, in which the following series were timed: rise from an armchair, walk a distance of 3 meters as quickly as possible but still safely, walk back, and sit down (29). Leg muscle strength was assessed us-

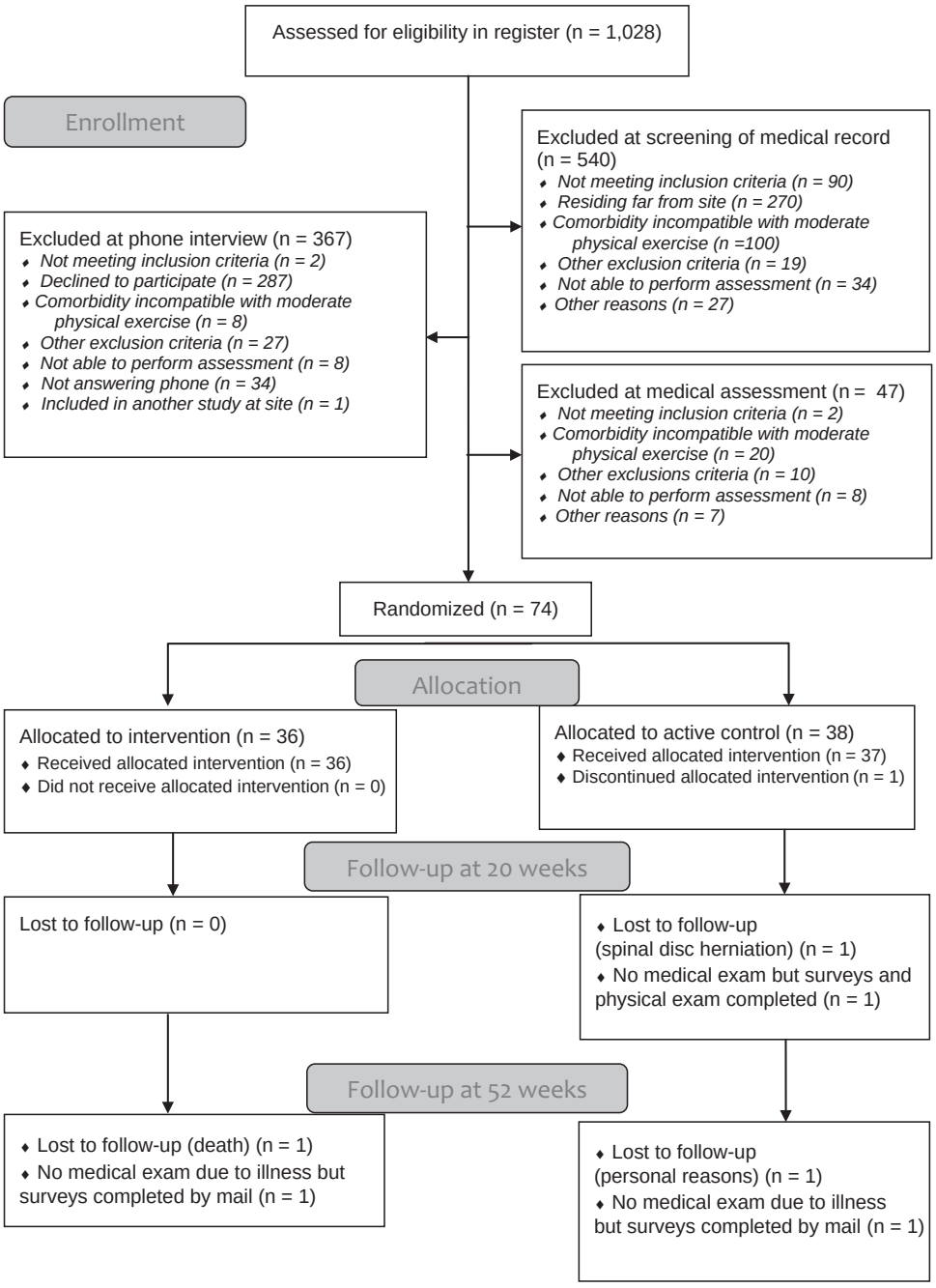

Figure 1. Consolidated Standards of Reporting Trials [CONSORT] diagram for the 2 groups in the randomized clinical trial.

ing the sit to stand (STS) test, in which the number of complete rises from a chair performed in 60 seconds was recorded (30). Isometric elbow flexion force was assessed with an electronic dynamometer (31). The patients were seated in a standardized position without back support and with legs stretched out. The forearm was supported by the trunk with the elbow at 90° flexion, and the maximum strength was measured over a period of 7 seconds. The Patient's Global Impression of Change (PGIC) (32) was measured at the postintervention examination and at the 12-month follow-up.

Measures of exercise load were performed using the Leisure Time Physical Activity Instrument (LTPAI), which assesses the amount of physical activity during a typical week, in terms of light, moderate, and vigorous activity. In this study, the sum of moderate and vigorous activity is given (33). Exercise load was registered by the physiotherapist leading the intervention (EL and GB). The patients were also asked to keep an exercise diary. During the follow-up period, patients in the intervention group were contacted by phone 2–3 times and the reported exercise was registered.

Statistical analysis. Statistical analyses were performed using the SPSS, version 24.0 (IBM). Descriptive statistics were used to characterize the 2 groups. Comparisons between groups were performed with the Mann-Whitney U test for ordinal variables and independent Student's *t*-test for continuous

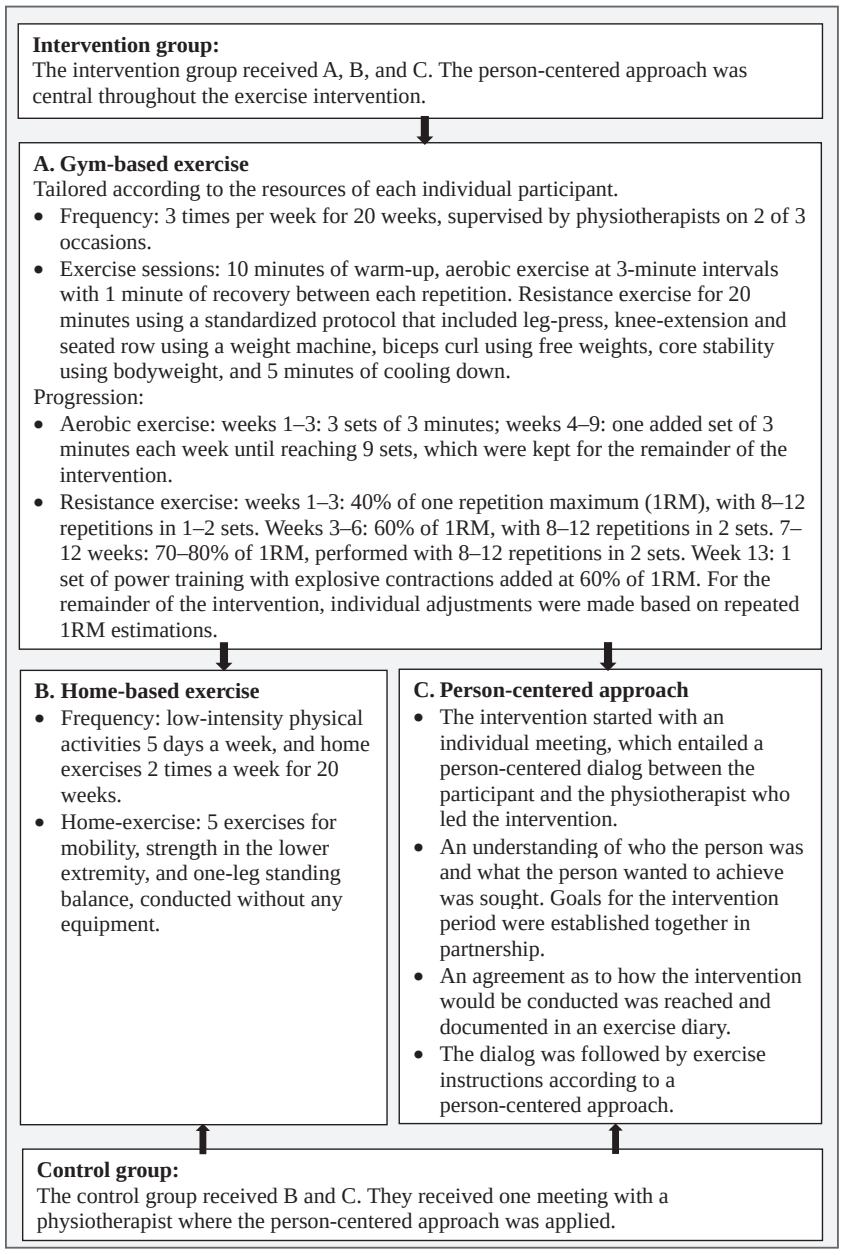

Figure 2. Intervention group and control group exercises.

variables, and the Mantel-Haenszel test was used for ordinal categorical variables. For comparisons between baseline and postintervention examinations within a group, Wilcoxon's signed rank test was used for ordinal variables, and the paired-sample *t*-test was used for continuous variables. All significance tests were 2-sided. Outcomes were analyzed according to intent-to-treat design, implying that all participants were invited to post-treatment examination, whether they had participated in the intervention or not. Only measured values were included in the analyses of changes over time between the 2 groups and within the groups, implying that missing cases were not included in the analyses. To evaluate the effect size, Cohen's *d* coefficient was calculated for between-group variables that showed a significant change (34). An effect size of 0.20 to <0.50 was regarded as small, 0.50 to <0.80 as medium, and >0.80 as large (34). To detect a clinically important difference of 0.2 on the HAQ DI score between groups, with an estimated SD of 0.5, 90% power, and 5% significance level using the Mann-Whitney U test, 35 participants were needed in each group.

RESULTS

Patients. The demographics and clinical characteristics of the participants are shown in Table 1. The groups were considered to be equivalent. A total of 73% of the patients were in remission (DAS28 <2.6) or had low disease activity (DAS28 <3.2) at baseline, and the disease activity was not significantly changed during the study.

In the intervention group, 50% of patients had a concomitant disease (from a total of 36 patients: cardiovascular disease 6, hypothyroidism 4, diabetes mellitus 2, pulmonary disease 2, previous cancers 8, and other diseases 3). Also in the intervention group, 19% of patients (n = 7) had a joint prosthesis. In the control group, 42% had a concomitant disease (from a total of 38 patients: cardiovascular disease 6, hypothyroidism 1, diabetes mellitus 3, pulmonary disease 1, previous cancers 5, and other diseases 3). In the control group, 26% of patients (n = 10) had a joint prosthesis.

Exercise attendance, level, and adverse effects. All patients in the intervention group completed the exercise intervention (Figure 1). Altogether, 72 patients (97%) completed the week 20 examinations. The mean attendance rate in the intervention group was 78%, with an average of 2.4 exercise sessions at the gym and 3.16 exercise sessions at home each week. The control group performed home exercise on average 2.84 times each week. The self-reported hours of moderate-to-vigorous physical activity on the LTPAI were increased significantly ($P = 0.001$) in the intervention group (2.4-hour increase) when the change was compared to that of the control group (0.3-hour increase). The majority of the intervention group, at 78%, reached the targeted level of 70–80% of 1 RM. The other 8 patients reached approximately 60% of 1 RM in 1–3 of the exercises. One patient performed at a lower load level than that intended in the aerobic exercise. Adverse effects were defined as increased pain that could be related to exercise. For 4 patients in the intervention group, adverse effects led to persistent exercise modifications in 1 exercise throughout the intervention. Nineteen patients encountered temporarily increased pain, which was managed with temporary exercise modifications for approximately 1 week or was managed without modifications.

Disability. No significant differences between the 2 groups were found on the primary outcome, HAQ DI score (Table 2). In the intervention group there was a significant within-group improvement ($P = 0.022$) of the HAQ DI score, corresponding to a 12% improvement of the scores. No such changes were found in the control group.

Physical fitness and global impression of change. Aerobic capacity (V_{O_2}/kg/minute) was significantly improved in the intervention group compared to the control group (Table 2). This improvement was accompanied by a significantly increased endurance, measured by the bicycle endurance test, compared between the 2 groups. Functional balance, assessed by TUG, was significantly improved between the 2 groups. In addition, leg muscle strength assessed with the STS was significantly improved between the 2 groups, but the isometric elbow flexion force did not differ significantly between groups. The PGIC rating was significantly different between the 2 groups at the postintervention examinations, with much or very much improved health among 71.4% of the intervention group and 24.3% of the control group after 20 weeks (Figure 3A).

Twelve-month follow-up. Altogether, 69 patients (93%) completed the entire 12-month follow-up examinations (Figure 1). Moderate-to-high–intensity activity, reported on the LTPAI, was increased compared to baseline, with 2.2 hours in the intervention group and 0.03 hours in the control group ($P = 0.005$). Based on phone calls and exercise diaries, 51% of patients in the intervention group (18 of 35) continued to exercise with the same intensity as during the intervention, and 34% (12 of 35) continued to exercise at a lower intensity. The members of the intervention group continued to perform home exercise on average 2.1 times/week and more strenuous exercise 1.4 times/week. The control group performed home exercise 1.9 times/week during the follow-up period.

No significant between- or within-group differences of change compared to baseline were found on HAQ DI score. There was a significant difference of change between groups on the endurance test ($P = 0.022$), with an increase of 4.7 minutes ($P = 0.008$) in the intervention group and 0.8 minutes ($P = 0.104$) in the control group compared to baseline. The STS score was significantly improved within both groups when compared to base-

Table 1. Characteristics of the study population*

	Intervention (n = 36)	Control (n = 38)
General information		
Women	27 (75)	29 (76.3)
Age, mean ± SD years	69.14 ± 2.61	70.11 ± 2.30
Disease duration, mean ± SD years	15.4 ± 10.7	17.4 ± 10.9
Body measurements, mean ± SD		
Body mass index	25.58 ± 4.43	28.01 ± 4.53
Length, cm	168.9 ± 8.51	166.4 ± 8.04
Weight, kg	73.3 ± 16.34	77.4 ± 12.81
Pain VAS current, mean ± SD mm	20.67 ± 19.09	23.20 ± 15.68
LTPAI, moderate + vigorous, mean ± SD hours	3.46 ± 2.60	3.11 ± 2.30
ESR, mean ± SD	14.22 ± 12.07	12.71 ± 8.26
CRP, mean ± SD	6.89 ± 15.94	4.05 ± 4.75
Disease activity by DAS28, mean ± SD	2.33 ± 1.10	2.41 ± 0.90
Disease activity by CDAI, mean ± SD	5.35 ± 4.41	5.47 ± 3.35
Education		
≤9 years	13 (36.1)	12 (31.6)
10–12 years	4 (11.1)	8 (21.1)
>12 years	14 (38.9)	11 (28.9)
Missing	5 (13.9)	7 (18.4)
Marital status, living with an adult	24 (66.7)	24 (63.2)
Cigarette smoking		
Current smoker	3 (8.3)	3 (7.9)
Former smoker	20 (55.6)	21 (55.3)
Never-smoker	13 (36.1)	14 (36.8)
Autoantibodies		
RF	25 (69.4)	26 (68.4)
Anti-CCP	26 (72.2)	21 (55.3)
Erosive	20 (55.6)	21 (55.3)
Medication		
No DMARD	0 (0)	4 (10.5)
Synthetic DMARD	34 (94.4)†	29 (76.3)†
Methotrexate	31 (86.1)	25 (65.8)
Other	5 (13.9)	5 (13.2)
Biologic DMARD	14 (38.9)†	17 (44.7)†
TNF inhibitors	12 (33.3)	9 (23.7)
Other DMARDs	2 (5.6)	8 (21.1)
Corticosteroids (oral)	6 (16.7)†	10 (26.3)†
NSAID	17 (47.2)†	22 (57.9)†
Paracetamol	15 (41.7)†	21 (55.3)†
Beta-blocker	5 (13.9)†	12 (31.6)†

* Values are the number (%) unless indicated otherwise. VAS = visual analog scale; LTPAI = Leisure Time Physical Activity Instrument ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; CDAI = Clinical Disease Activity Index; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor; NSAID = nonsteroidal antiinflammatory drug.
† Significant.

line (intervention group increased 2.5 [$P = 0.021$]; control group increased 1.5 [$P = 0.043$]), but no significant mean difference of change was found between groups. No significant differences were found on scores of TUG and isometric elbow flexion. The PGIC ratings were significantly different between the groups at the month 12 follow-up, with much or very much improved health

Table 2. Between-group analysis of the primary and secondary outcomes after 20 weeks*

	Intervention		Control		Between-group	
Measures	Baseline (n = 36)†	Post-treatment: baseline (n = 36)‡	Baseline (n = 38)†	Post-treatment: baseline (n = 37)‡	Analysis of change P	Effect size
Primary outcome						
HAQ DI, mean ± SD, median (range)	0.52 ± 0.5, 0.38 (0, 1.75)	−0.063 ± 0.16, 0 (−0.38, 0.13)§	0.6 ± 0.48, 0.44 (0, 1.5)	−0.0097 ± 0.27, 0 (−0.75, 0.75)	0.200	0.14
Secondary outcomes						
Vo_2/kg/minute, ml	18.6 ± 3.8	2.12 ± 1.93¶	17.8 ± 3.81	−0.16 ± 1.57	<0.001#	1.30
Endurance, minutes	11.4 ± 6.53	6.97 ± 7.79¶	9.7 ± 5.12	1.00 ± 4.76	<0.001#	0.93
TUG, seconds	7.6 ± 1.6	−0.68 ± 0.91¶	8.1 ± 1.7	−0.14 ± 1.35	0.049#	0.47
STS, no.	22.58 ± 4.2	3.11 ± 3.44¶	22.68 ± 5.49	0.49 ± 3.96	0.004#	0.71
Elbow flexion	15.55 ± 5.6	0.58 ± 1.9	15.57 ± 6.32	−0.12 ± 3.16	0.265	0.27

* Missing values at baseline: intervention group: Vo_2/kg/minute (n = 3), endurance (n = 1); control group: Vo_2/kg/minute (n = 1). Missing delta values: intervention group: Vo_2/kg/minute (n = 4), endurance and elbow force (n = 1); control group: Vo_2/kg/minute (n = 8), Clinical Disease Activity Index (n = 2). HAQ DI = Health Assessment Questionnaire disability index; TUG = timed up and go; STS = sit to stand.
† Mean ± SD.
‡ Δ ± SD
§ Shown as mean ± SD as well as median (range).
¶ *P* <0.05,
# *P* <0.001.
** Significant.

rated by 52.9% of the intervention group and 25.7% of the control group (Figure 3B).

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the effect of moderate-to-high intensity aerobic and resistance exercise for older adults with RA. The primary outcome, HAQ DI score, did not significantly improve when groups were compared. However, HAQ DI score showed a 12% within-group improvement in the intervention group. HAQ DI has been acknowledged as insufficient in capturing effects of resistance exercise (35). A limitation of HAQ DI is the floor effect (36), which is the most likely reason for the lack of significant results, because the majority of the patients already scored below 0.5 on HAQ DI score at baseline. A reason for floor effects might be the nature of activities included in the HAQ DI score, covering domestic tasks with a requirement of overall mobility rather than physical fitness (25). Almost all study patients had low disease activity or were in remission both at baseline and throughout the study, which is in line with the advances made in the treatment of RA in recent years (37).

The intervention group significantly improved their aerobic capacity when compared to the control group. Furthermore, they achieved the level of aerobic capacity of middle-aged to older adults with RA (38). Additionally, 3 of 4 other performance-based tests, assessing endurance, functional balance, and leg muscle strength, significantly improved when compared to the control group. The positive results of this study show that older adults with RA can improve their physical fitness, which is important knowledge, because reductions of muscle mass, muscle strength, and walking speed are common both in patients with RA (8) of all ages and in older adults independent of diagnosis (39).

Physical fitness is a key factor in predicting maintained or increased physical independence over time (40), which is particularly important for patients with RA, since becoming dependent on others is one of the concerns of aging with RA (7). The intervention did not have any significant impact on isometric elbow flexion force, which could be related to the main focus of the exercise protocol being the lower limbs. Another potential reason could be the design of the test, since the electronic dynamometer that was used has commonly been used to study shoulder strength (41).

The PGIC was applied to study possible changes from the perspective of a patient. A total of 88.6% of the intervention group reported improvements in PGIC, and although the control group also scored improvements, the between-group differences were significant, in favor of the intervention group. Physical activity has been found to have a positive impact on the experience of health (42), and increased physical activity and fitness improve health status (43). We believe that improved physical fitness, demonstrated by the performance-based tests, conveyed to the patients a sense of improved health.

The self-reported hours of exercise at a moderate-to-intense level increased by >2 hours per week in the intervention group,

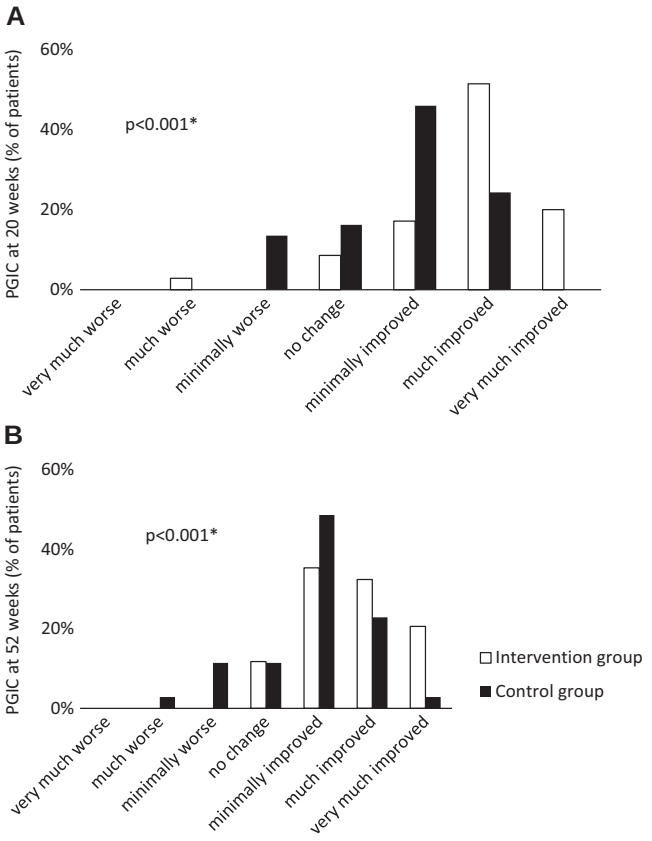

Figure 3. Rating of Patient's Global Impression of Change (PGIC) after (**A**) 20 weeks, and (**B**) 52 weeks. * = significant difference between groups.

and the intensity of the performed exercise program appears to be crucial for achieving the effect of the exercise (44). Only a few drawbacks or adverse events were observed, leading to a minor, temporary modification of the protocol. This study showed that exercise with person-centered guidance and a moderate-to-high intensity is possible for older adults with RA with a low-to-moderate disease activity. To be able to perform exercise at a moderate-to-high intensity at an older age is important to improve health outcomes and reduce mortality (45). A person-centered approach, implying that the patients were actively involved in the tailoring of their own exercise (46), promoting empowerment (47) and the ability to manage symptoms while exercising, through individualization of load and progression, was assumed to have been a contributing factor for success. Personal goals were included in the individual exercise plans, which may also have contributed to the adherence over time (48). The adherence of the control group, which performed exercise at the level recommended as the minimum to obtain health benefits (11), was also good.

At the 12-month follow-up, there were no significant differences between groups on HAQ DI score or on most of the performance-based tests. However, the endurance test was significantly improved in the intervention group compared to the control group, and leg-muscle strength, assessed by the STS test, improved in both groups. In order to maintain positive outcomes of exercise, the intensity of the exercise must be maintained (49), and the diminishing results at the 12-month follow-up are assumed to be related to the reduction of total exercise in the group, commonly referred to as de-training (50) and which occurs independently of exercise intensity (51). In the current study, approximately 50% of the patients in the intervention group at 12 months still reported exercising at an intensity in accordance with the intervention, which can be regarded as a high percentage when compared to a general Swedish RA population (13). Maintenance of exercise is a commonly known difficulty in patients with RA, who need to overcome several barriers, both general and diagnosis-specific (52). In the current study, a contributing reason for the ability to continue exercising at a moderate-to-high–intensity level despite barriers might be found in the support from the physiotherapist on how to remain physically active (52). Barriers and facilitators will be further studied in a subsequent qualitative interview study.

A limitation to consider in this study is that as part of the screening and inclusion process, several potential participants were not included due to having a heart condition. This exclusion was a safety measure, because the exercise was performed outside the health care setting. A number of potential participants declined to participate due to reasons that were not always explicitly described but were possibly associated with health status. However, 46% of the patients had concomitant diseases or previous cancer, and 23% had prostheses and comorbidities that are negatively associated with physical functioning (53). An alternative for HAQ DI, showing floor effects in the current study, should be considered in future studies. Additionally, improvement of physical function in upper extremities appears to require changes in the exercise program or in an instrument to assess it.

Moderate-to-high intensity exercise with person-centered guidance was found to effectively improve physical fitness in terms of aerobic capacity, endurance, strength, and dynamic balance in older adults with RA. The participants also rated their experienced health as improved. After 12 months, the positive effects of physical fitness partially persisted. The supervised exercise intervention is recommended for older adults with RA with a low disease activity.

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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. Mrs. Lange 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. Svensson, Gjertsson, Mannerkorpi.
Acquisition of data. Lange, Kucharski, Svedlund, Svensson, Bertholds, Gjertsson, Mannerkorpi.
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Tofacitinib in Rheumatoid Arthritis: Lack of Early Change in Disease Activity and the Probability of Achieving Low Disease Activity at Month 6

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Objective. Optimal targeted treatment in rheumatoid arthritis requires early identification of failure to respond. This post hoc analysis explored the relationship between early disease activity changes and the achievement of low disease activity (LDA) and remission targets with tofacitinib.

Methods. Data were from 2 randomized, double-blind, phase III studies. In the ORAL Start trial, methotrexate (MTX)–naive patients received tofacitinib 5 or 10 mg twice daily, or MTX, for 24 months. In the placebo-controlled ORAL Standard trial, MTX inadequate responder patients received tofacitinib 5 or 10 mg twice daily or adalimumab 40 mg every 2 weeks, with MTX, for 12 months. Probabilities of achieving LDA (using a Clinical Disease Activity Index [CDAI] score ≤10 or the 4-component Disease Activity Score in 28 joints using the erythrocyte sedimentation rate [DAS28-ESR] ≤3.2) at months 6 and 12 were calculated, given failure to achieve threshold improvement from baseline (change in CDAI ≥6 or DAS28-ESR ≥1.2) at month 1 or 3.

Results. In ORAL Start, 7.2% and 5.4% of patients receiving tofacitinib 5 and 10 mg twice daily, respectively, failed to show improvement in the CDAI ≥6 at month 3; of those who failed, 3.8% and 28.6%, respectively, achieved month 6 CDAI-defined LDA. In ORAL Standard, 18.8% and 17.5% of patients receiving tofacitinib 5 and 10 mg twice daily, respectively, failed to improve CDAI ≥6 at month 3; of those who failed, 0% and 2.9%, respectively, achieved month 6 CDAI-defined LDA. Findings were similar when considering improvements at month 1 or DAS28-ESR thresholds.

Conclusion. In patients with an inadequate response to MTX, lack of response to tofacitinib after 1 or 3 months predicted a low probability of achieving LDA at month 6. Lack of an early response may be considered when deciding whether to continue treatment with tofacitinib.

INTRODUCTION

Using the treat-to-target (or targeted treatment) approach in patients with rheumatoid arthritis (RA) requires regular assessments of disease activity and adjustment of therapy associated with an inadequate response (1,2). Thus, clinical guidelines recommend frequent follow-up for patients with active disease to closely monitor disease activity and adjust treatment accordingly (3,4). European League Against Rheumatism (EULAR) guidelines specify follow-up every 1–3 months, with more frequent monitoring for patients with high disease activity; in addition, they suggest that if no improvement is seen within 3 months or if the treatment target is not reached within 6 months, treatment should be changed (4). To optimize this therapeutic strategy, an understanding of the relationship between short- and longer-term responses is needed for each antirheumatic therapy.

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SIGNIFICANCE & INNOVATIONS

- We conducted a post hoc analysis of 2 randomized, double-blind phase III studies of tofacitinib (ORAL Start and ORAL Standard), to explore the relationship between early disease activity changes and achievement of low disease activity (LDA) and remission targets.
- Failure to achieve early improvements in disease activity (improvement from baseline using the Clinical Disease Activity Index score ≥6 or the 4-component Disease Activity Score in 28 joints using the erythrocyte sedimentation rate ≥1.2) was predictive of low probabilities of achieving LDA and remission at months 6 and 12.
- Lack of early response may be considered when deciding whether to continue treatment with tofacitinib.

While the therapeutic response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) is usually observed after 6 to 12 weeks of treatment (5), biologic DMARDs (bDMARDs) (6) and targeted synthetic DMARDs (tsDMARDs) (7,8) are often more rapidly effective. However, for all drug classes, the response to therapy is unpredictable (9,10), and whether patients who fail to show an initial response to tsDMARDs might still respond later in the course of treatment is unclear.

There is evidence that early response to RA treatment predicts the probability of achieving the treatment target over time. Response at 4 weeks has been shown to be predictive of later response to csDMARDs (11) and to the JAK inhibitor baricitinib (12). Furthermore, the predictive value of failing to achieve an early response to a desired treatment target (negative predictive value [NPV]) may be greater than the predictive value of achievement of an early response (positive predictive value [PPV]). Both the Rheumatoid Arthritis Prevention of Structural Damage (RAPID 1) study (13) and the PREMIER study (14) showed that failure to achieve early improvements in disease activity with a combination of a bDMARD and methotrexate (MTX) was predictive of a low probability of achieving a longer-term clinical response.

Tofacitinib is an oral JAK inhibitor for the treatment of RA. The efficacy and safety of tofacitinib 5 and 10 mg twice daily, administered as monotherapy or in combination with csDMARDs, mainly MTX, in patients with moderately to severely active RA, have been demonstrated in phase II (15–19) and phase III (7,20–24) studies of up to 24 months' duration and in long-term extension studies with up to 114 months of observation (25–27).

The aim of the current study was to understand the relationship between timing and magnitude of early changes in disease activity (at months 1 and 3) and the probability of achieving low disease activity (LDA) or remission at months 6 and 12 in 2 different patient populations treated with tofacitinib from phase III studies: patients with an inadequate response to MTX (MTX-IR) receiving tofacitinib plus MTX in ORAL Standard, and MTX-naive patients receiving tofacitinib monotherapy in ORAL Start.

PATIENTS AND METHODS

Study design. This was a post hoc analysis of data from 2 randomized, double-blind, phase III studies of tofacitinib. ORAL Start was a 24-month study in MTX-naive patients with RA. Patients were randomized 2:2:1 to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, or MTX at a starting dosage of 10 mg per week, with increments of 5 mg per week every 4 weeks to 20 mg per week by week 8 (22).

ORAL Standard was a 12-month study in MTX-IR patients with RA. Patients were randomized 4:4:4:1:1 to receive tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab (ADA) 40 mg administered subcutaneously once every 2 weeks, placebo changing to tofacitinib 5 mg twice daily, or placebo changing to tofacitinib 10 mg twice daily, all with MTX (24). Patients in the placebo group advanced to tofacitinib 5 or 10 mg twice daily at month 3 if they were nonresponders (<20% reduction from baseline in both swollen and tender joint counts) or at month 6. Both studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines and were approved by the institutional review boards and/or independent ethics committees at each investigational center. All patients provided written informed consent.

Patient inclusion. Inclusion and exclusion criteria for both studies have been reported previously (22,24). Briefly, eligible patients were age ≥18 years, with a diagnosis of RA based on the American College of Rheumatology 1987 revised criteria (28), with active RA, defined as ≥6 tender/painful joints (68-joint count) and ≥6 swollen joints (66-joint count), and with either an erythrocyte sedimentation rate (ESR) >28 mm/hour or a C-reactive protein (CRP) level >7 mg/liter.

Assessments. The Clinical Disease Activity Index (CDAI), as the primary analysis, and the 4-component Disease Activity Score in 28 joints using the ESR (DAS28-ESR) were assessed at baseline (prior to the first study dose), and at months 1, 3, 6, 9, and 12 (or at the end-of-study visit). LDA and remission criteria, respectively, were defined as CDAI score of ≤10 and ≤2.8 and as DAS28-ESR of ≤3.2 and <2.6 (29). The proportion of patients who failed to achieve a number of different thresholds of improvement in disease activity was assessed. Improvement thresholds were a decrease from baseline in CDAI of ≥3, ≥6, ≥9, and ≥12, and a decrease from baseline in DAS28-ESR of ≥0.3, ≥0.6, ≥0.9, ≥1.2, ≥1.5, and ≥1.8 (12). An improvement of ≥6 in

CDAI after 4 weeks of treatment with baricitinib was found to be the minimum level predictive of a response at later time points (12), and an improvement of ≥1.2 in DAS28-ESR and a baseline value of >5.1 are deemed a moderate response in patients with RA (30). These values were therefore considered as the key thresholds for improvement at months 1 and 3.

Statistical analysis. Data from the full analysis set, comprising all randomized patients who received ≥1 dose of study drug and had ≥1 post-baseline value, were included. Both studies were analyzed separately due to differences in study design and patient populations. One-year data were used, and nonresponder imputation was applied

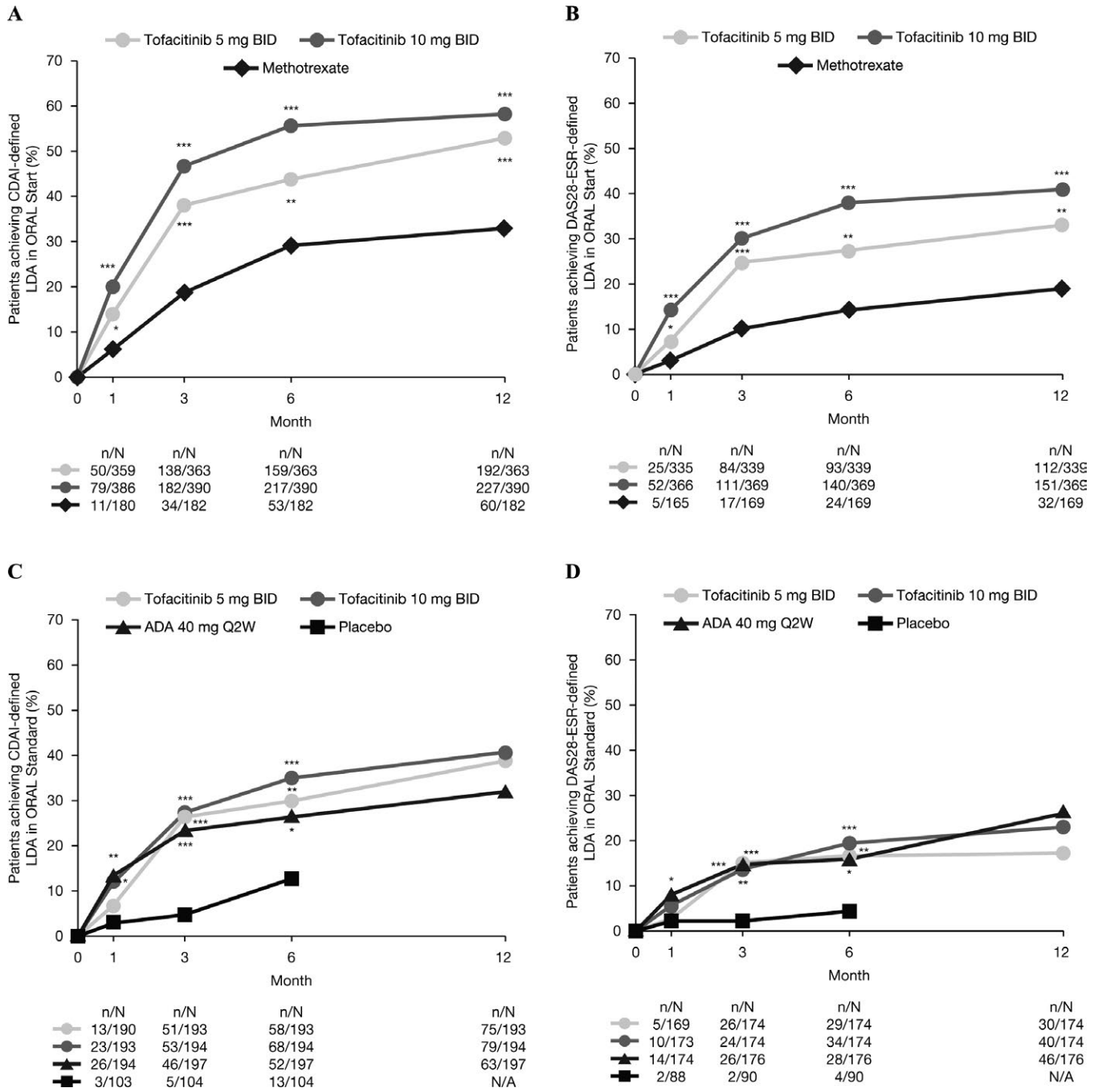

Figure 1. Proportions of patients achieving (**A**) Clinical Disease Activity Index (CDAI)–defined low disease activity (LDA) in ORAL Start, (**B**) 4-component Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR)–defined LDA in ORAL Start, (**C**) CDAI-defined LDA in ORAL Standard, and (**D**) DAS28-ESR–defined LDA in ORAL Standard (full analysis set, nonresponder imputation). Low disease activity was defined as CDAI ≤10 or DAS28-ESR ≤3.2. Because nonresponders receiving placebo in ORAL Standard moved to active treatment at month 3, patients randomized to receive placebo in this study were also excluded from the analysis. BID = twice a day; ADA = adalimumab; Q2W = every 2 weeks; N/A = not applicable; * = $P < 0.05$; ** = $P < 0.001$; *** = $P < 0.0001$.

for missing values of the binary end points for all patients post-baseline.

The probability that a patient achieved CDAI- or DAS28-ESR–defined LDA or remission at month 6 or month 12 was calculated for each tofacitinib treatment group, given the failure to achieve improvement from baseline in disease activity at month 1 or month 3. For each patient, improvements from baseline were assessed across the prespecified range of thresholds, and the probability of achieving LDA and remission was estimated. Patients were categorized by whether they had achieved or failed to achieve improvement from baseline at the month 1 or month 3 visit. The number of patients who achieved LDA or remission at month 6 or month 12 was calculated, and the probability of achieving LDA or remission was estimated as a relative frequency. PPV (defined as the probability that patients who achieve LDA [CDAI ≤10 or DAS28-ESR ≤2.3] or remission [CDAI ≤2.8 or DAS28-ESR <2.6] at month 1 or month 3 will achieve LDA or remission at month 6 or month 12) and NPV (defined as the probability that patients who do not achieve LDA or remission at month 1 or month 3 will not achieve LDA or remission at month 6 or month 12) were calculated for the probabilities associated with each outcome.

Because this analysis is focused on the response to tofacitinib, data for the relationship between early changes in disease activity and the probability of achieving LDA or remission at month 6 and month 12 in patients randomized to receive MTX in ORAL Start or ADA in ORAL Standard are shown in Supplementary Appendix A and Supplementary Tables 1–7, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract. Also, because nonresponders receiving placebo in ORAL Standard moved to active treatment at month 3, patients randomized to receive placebo in this study were excluded from the analysis. Data on achievement of remission in both studies are fully reported in Supplementary Appendix A and Supplementary Tables 1–7, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract.

RESULTS

Patients. Overall, 948 patients from ORAL Start (tofacitinib 5 mg twice daily [n = 370], tofacitinib 10 mg twice daily [n = 394], MTX [n = 184]) and 717 patients from ORAL Standard (tofacitinib 5 mg twice daily [n = 204], tofacitinib 10 mg twice daily [n = 201], ADA [n = 204], placebo changing to tofacitinib 5 mg twice daily [n = 56], placebo changing to tofacitinib 10 mg twice daily [n = 52]) were randomized to study treatment. Patient demographics and baseline disease characteristics within each study were generally similar across treatment groups (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract). Patients in ORAL Start were younger than those in ORAL Standard (mean ages 48.8–50.3 versus 52.5–53.8 years), with a shorter duration of RA (mean 2.7–3.4 versus 7.4–8.1 years), and a higher mean CRP level at baseline (20.2–26.1 versus 14.6–17.4 mg/liter).

Proportion of patients achieving LDA and remission. In both studies, a significantly greater proportion of patients achieved CDAI- and DAS28-ESR–defined LDA with tofacitinib compared with MTX (ORAL Start) or placebo (ORAL Standard) at month 6 (Figure 1). In addition, a significantly greater proportion of patients achieved CDAI-defined remission (tofacitinib 10 mg twice daily) and DAS28-ESR–defined remission (both tofacitinib doses) versus MTX or placebo at month 6 (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract). In ORAL Standard, the proportions of patients achieving CDAI- and DAS28-ESR–defined LDA and remission at month 6 were numerically similar for those patients receiving tofacitinib and those receiving ADA (Figures 1C and D and Supplementary Figures 1C and D, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract).

Table 1. Probabilities of achieving low disease activity (LDA) at month 6 or month 12 given failure to achieve improvement in Clinical Disease Activity Index (CDAI)–defined disease activity at month 1 or month 3 with tofacitinib in ORAL Start (full analysis set, nonresponder imputation)*

	Probabilities of achieving LDA (CDAI ≤10)		NPV, %		PPV, %	
Achievement of LDA given failure to improve CDAI ≥6	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
Month 6						
Failure to improve at month 1	15/84 (17.9)	22/65 (33.8)	82.1	66.2	51.1	60.1
Failure to improve at month 3	1/26 (3.8)	6/21 (28.6)	96.2	71.4	46.3	57.1
Month 12						
Failure to improve at month 1	30/84 (35.7)	31/65 (47.7)	64.3	52.3	58.4	60.8
Failure to improve at month 3	3/26 (11.5)	4/21 (19.0)	88.5	81.0	56.2	60.7

* Unless indicated otherwise, values are the number of patients who failed to meet the improvement threshold/the number who also achieved LDA (defined as CDAI ≤10) (%). BID = twice daily; NPV = negative predictive value (defined as the probability that patients who do not achieve LDA at month 1 or month 3 will not achieve LDA at month 6 or month 12); PPV = positive predictive value (defined as the probability that patients who achieve LDA at month 1 or month 3 will achieve LDA at month 6 or month 12).

Relationship between early changes in disease activity and rates of LDA at months 6 and 12 in ORAL Start (MTX-naive). At month 3, 7.2% of patients (26 of 359) receiving tofacitinib 5 mg twice daily and 5.4% of patients (21 of 387) receiving tofacitinib 10 mg twice daily failed to achieve CDAI-defined improvement from baseline ≥6. Of these patients, 3.8–11.5% with tofacitinib 5 mg twice daily and 19.0–28.6% with tofacitinib 10 mg twice daily went on to achieve CDAI-defined LDA at months 6 and 12 (Table 1 and Supplementary Figures 2A and B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract). The NPV for CDAI-defined LDA at month 6 associated with failure to achieve CDAI improvement at month 3 was 96% for tofacitinib 5 mg twice daily and 71% for 10 mg twice daily, and was >80% at month 12 (Table 1 and Supplementary Figures 2A and B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract). Among patients receiving MTX, 16.1% of those who failed to achieve CDAI improvement from baseline ≥6 at month 3 achieved CDAI-defined LDA at month 6, with an associated NPV of 84% (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract).

Similarly, at month 3, 21.8% of patients (74 of 339) receiving tofacitinib 5 mg twice daily and 14.4% of patients (53 of 369) receiving tofacitinib 10 mg twice daily failed to achieve DAS28-ESR–defined improvement from baseline ≥1.2. Of these patients, 6.8–14.9% with tofacitinib 5 mg twice daily and 11.3–22.6% with tofacitinib 10 mg twice daily achieved DAS28-ESR–defined LDA at months 6 and 12 (Table 2 and Supplementary Figures 2C and D, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract). The NPV for DAS28-ESR–defined LDA at month 6 associated with failure to achieve DAS28-ESR–defined improvement at month 3 was 93% and 89% for tofacitinib 5 and 10 mg twice daily, respectively, and 85% and 77% at month 12 for tofacitinib 5 and 10 mg twice daily, respectively (Table 2 and Supplementary Figures 2C and D, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract). For patients receiving MTX, 6.2% of those who failed to achieve DAS28-ESR–defined improvement from baseline ≥1.2 at month 3 achieved DAS28-ESR–defined LDA at month 6, with an associated NPV of 94% (see Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract). The relationship between early changes in disease activity using different thresholds and rates of LDA at months 6 and 12 are shown in Supplementary Figure 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract.

ORAL Standard (MTX-IR). At month 3, 18.8% of patients (36 of 191) receiving tofacitinib 5 mg twice daily and 17.5% of patients (34 of 194) receiving tofacitinib 10 mg twice daily failed to achieve CDAI improvement from baseline ≥6. Of these patients, 0–2.8% treated with tofacitinib 5 mg twice daily and 2.9–8.8% treated with tofacitinib 10 mg twice daily achieved CDAI-defined LDA at months 6 and 12 (Table 3 and Supplementary Figures 3A and B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract). The NPV for CDAI-defined LDA at month 6 or month 12 associated with failure to achieve CDAI improvement from baseline ≥6 at month 3 was >90% for tofacitinib 5 and 10 mg twice daily (Table 3 and Supplementary Figures 3A and B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract). Among patients receiving ADA, 6.1% of those who failed to achieve CDAI-defined improvement from baseline ≥6 at month 3 achieved CDAI-defined LDA at month 6, with an associated NPV of 94% (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract).

Table 2. Probabilities of achieving low disease activity (LDA) at month 6 or month 12 given failure to achieve improvement in DAS28-ESR–defined disease activity at month 1 or month 3 with tofacitinib in ORAL Start (full analysis set, nonresponder imputation)*

	Probabilities of achieving LDA (DAS28-ESR ≤3.2)		NPV, %		PPV, %	
Achievement of LDA given failure to improve DAS28-ESR ≥1.2	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
Month 6						
Failure to improve at month 1	22/150 (14.7)	23/118 (19.5)	85.3	80.5	37.8	46.8
Failure to improve at month 3	5/74 (6.8)	6/53 (11.3)	93.2	88.7	33.2	42.4
Month 12						
Failure to improve at month 1	37/150 (24.7)	31/118 (26.3)	75.3	73.7	40.0	47.6
Failure to improve at month 3	11/74 (14.9)	12/53 (22.6)	85.1	77.4	38.1	44.0

* Unless indicated otherwise, values are the number of patients who failed to meet the improvement threshold/the number who also achieved LDA (defined as DAS28-ESR ≤3.2) (%). DAS28-ESR = 4-component Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; BID = twice daily; NPV = negative predictive value (defined as the probability that patients who do not achieve LDA at month 1 or month 3 will not achieve LDA at month 6 or month 12); PPV = positive predictive value (defined as the probability that patients who achieve LDA at month 1 or month 3 will achieve LDA at month 6 or month 12).

Table 3. Probabilities of achieving low disease activity (LDA) at month 6 or month 12 given failure to achieve improvement in Clinical Disease Activity Index (CDAI)–defined disease activity at month 1 or month 3 with tofacitinib in ORAL Standard (full analysis set, nonresponder imputation)*

	Probabilities of achieving LDA (CDAI ≤10)		NPV, %		PPV, %	
Achievement of LDA given failure to improve CDAI ≥6	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
Month 6						
Failure to improve at month 1	5/51 (9.8)	9/48 (18.8)	90.2	81.3	38.4	40.0
Failure to improve at month 3	0/36 (0)	1/34 (2.9)	100.0	97.1	37.4	41.9
Month 12						
Failure to improve at month 1	9/51 (17.6)	10/48 (20.8)	82.4	79.2	47.1	47.6
Failure to improve at month 3	1/36 (2.8)	3/34 (8.8)	97.2	91.2	47.7	47.5

* Unless indicated otherwise, values are the number of patients who failed to meet the improvement threshold/the number who also achieved LDA (defined as CDAI ≤10) (%). BID = twice daily; NPV = negative predictive value (defined as the probability that patients who do not achieve LDA at month 1 or month 3 will not achieve LDA at month 6 or month 12); PPV = positive predictive value (defined as the probability that patients who achieve LDA at month 1 or month 3 will achieve LDA at month 6 or month 12).

At month 3, 31.6% of patients (55 of 174) receiving tofacitinib 5 mg twice daily and 36.2% of patients (63 of 174) receiving tofacitinib 10 mg twice daily failed to achieve DAS28-ESR improvement from baseline ≥1.2. Of these patients, none with tofacitinib 5 mg twice daily and 3.2–7.9% with tofacitinib 10 mg twice daily achieved DAS28-ESR–defined LDA at months 6 and 12 (Table 4 and Supplementary Figures 3C and D, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract). The NPV for DAS28-ESR–defined LDA at month 6 or month 12 associated with failure to achieve DAS28-ESR–defined improvement from baseline ≥1.2 at month 3 was >90% for tofacitinib 5 mg and 10 mg twice daily (Table 4 and Supplementary Figures 3C and D, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract). Among patients receiving ADA, 5.5% of those who failed to achieve DAS28-ESR–defined improvement from baseline ≥1.2 at month 3 achieved DAS28-ESR–defined LDA at month 6, with an associated NPV of 95% (see Supplementary Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract).

Relationship between early changes in disease activity and rates of remission at months 6 and 12. In both ORAL Start and ORAL Standard and across treatment groups (tofacitinib, MTX, and ADA), failure to achieve improvement thresholds (decrease from baseline of CDAI ≥6 and DAS28-ESR ≥1.2) at months 1 and 3 was predictive of low probabilities of remission at months 6 and 12 (see Supplementary Tables 4–7, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract).

Relationship between timing and magnitude of early changes in disease activity and rates of LDA. In both ORAL Start and ORAL Standard, failure to achieve improvement thresholds at month 1, whether defined by CDAI or DAS28-ESR,

Table 4. Probabilities of achieving low disease activity (LDA) at month 6 or month 12 given failure to achieve improvement in DAS28-ESR–defined disease activity at month 1 or month 3 with tofacitinib in ORAL Standard (full analysis set, nonresponder imputation)*

	Probabilities of achieving LDA (DAS28-ESR ≤3.2)		NPV, %		PPV, %	
Achievement of LDA given failure to improve DAS28-ESR ≥1.2	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
Month 6						
Failure to improve at month 1	7/85 (8.2)	11/87 (12.6)	91.8	87.4	26.2	25.6
Failure to improve at month 3	0/55 (0)	2/63 (3.2)	100.0	96.8	24.4	28.8
Month 12						
Failure to improve at month 1	10/85 (11.8)	9/87 (10.3)	88.2	89.7	22.6	34.9
Failure to improve at month 3	0/55 (0)	5/63 (7.9)	100.0	92.1	25.2	31.5

* Unless indicated otherwise, values are the number of patients who failed to meet the improvement threshold/the number who also achieved LDA (defined as DAS28-ESR ≤3.2) (%). DAS28-ESR = 4-component Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; BID = twice daily; NPV = negative predictive value (defined as the probability that patients who do not achieve LDA at month 1 or month 3 will not achieve LDA at month 6 or month 12); PPV = positive predictive value (defined as the probability that patients who achieve LDA at month 1 or month 3 will achieve LDA at month 6 or month 12).

was less strongly predictive of achievement of LDA at month 6 or month 12 than failure to achieve improvement thresholds at month 3 (Tables 1–4) for patients receiving tofacitinib. Indeed, the NPVs for LDA at month 6 associated with failure to achieve threshold improvement from baseline at month 1 were lower than those associated with failure to achieve threshold improvement from baseline at month 3 for all treatments in both studies (Tables 1–4). A similar pattern in NPVs was observed for patients receiving MTX (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract) and ADA (see Supplementary Table 3, at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract).

In both ORAL Start and ORAL Standard, for both tofacitinib groups, failure to achieve greater improvement thresholds in disease activity at month 3 was generally associated with an increasing proportion of patients achieving LDA at months 6 and 12, compared with failure to achieve lower improvement thresholds (see Supplementary Figures 2 and 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23585/abstract). Data are not reported for patients receiving MTX or ADA.

DISCUSSION

This was a post hoc analysis of data from 2 phase III randomized controlled trials (RCTs), undertaken to explore the relationship between early changes in disease activity and the probability of achieving LDA or remission at month 6 and month 12 in MTX-IR (ORAL Standard) or MTX-naive (ORAL Start) patients with RA who were treated with tofacitinib, with the aim of improving patient management. Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily who were MTX-naive achieved LDA and remission compared with patients who were MTX-IR.

Across both studies, failure to achieve early improvements in disease activity (improvement from baseline of CDAI ≥6 or DAS28-ESR ≥1.2) was predictive of low probabilities of achieving LDA and remission at months 6 and 12 with tofacitinib, MTX, and ADA. In this analysis, disease activity as assessed by the CDAI was considered the primary analysis; however, findings using DAS28-ESR thresholds and DAS28-ESR–defined LDA were supportive. Findings were similar when considering early improvements in disease activity at month 3 or month 1, and when taking achievement of LDA at month 6 or month 12 as targets.

In this analysis, higher values were reported for NPV than PPV for the achievement of longer-term LDA based on early changes in disease activity. The consistently higher values for NPV versus PPV indicate that, although improvement at early time points is not necessarily predictive of achievement of treatment targets, failure to see early improvements predicts that such targets will not be reached. The NPV for LDA at month 6 associated with a failure to achieve CDAI improvement ≥6 and DAS28-ESR improvement ≥1.2 at month 3 generally exceeded 90% for tofacitinib in ORAL Standard and 70% in ORAL Start (corresponding data for ADA in ORAL Standard exceeded 90%, and those for MTX in ORAL Start exceeded 80%), providing robust evidence that failure to achieve these improvement thresholds at month 3 was strongly predictive of failure to achieve LDA at month 6.

These findings are consistent with those from other RA studies reporting early treatment response as predictive of longer-term outcomes. In prior analyses of ORAL Standard, few patients who failed to achieve improvement in disease activity (decrease in DAS28-ESR ≥0.6) after 1 month with tofacitinib and background MTX then achieved LDA at 12 months (31). An analysis of an observational cohort of patients with RA (<12 months' symptom duration) receiving csDMARDs reported that DAS28-ESR scores at 4 weeks predicted scores at 28 and 52 weeks (11). Analysis of 2 phase III RCTs of baricitinib demonstrated that failure to achieve a decrease in DAS28-ESR ≥0.6 or CDAI ≥6 after 4 weeks of treatment was associated with low rates of LDA or remission at 12 or 24 weeks (12). High NPVs were also reported in the RAPID 1 trial, in which failure to achieve improvement in DAS28-ESR within the first 12 weeks of treatment with certolizumab pegol and MTX was predictive of a low probability of achieving LDA at 1 year, with the accuracy of the prediction strongly dependent on the degree and timing of the lack of the response (13). Similarly, the PREMIER study reported that patients receiving MTX who did not show a clinical response at 3 months demonstrated worse long-term clinical, functional, and radiographic outcomes (14). This information supports current recommendations for targeted treatment, specifically EULAR guidelines, suggesting that if no improvement is seen within 3 months, or if the treatment target is not reached within 6 months, treatment should be changed (4).

A number of limitations in this analysis should be considered. This was a post hoc analysis, and the studies were not designed to consider the relationship between changes in disease activity at months 1 and 3 and the achievement of LDA or remission at month 6 and 12. Joint structure preservation was not considered in this analysis; however, disease activity measures may not always correlate with radiographic outcomes (32), and further research into this correlation is ongoing. Due to differing study designs and the inclusion of different patient populations, data from the studies could not be pooled for analysis. Patient numbers were relatively low in some groups, resulting in the need to interpret findings with caution. Finally, this analysis did not explore the association of baseline characteristics with outcomes; this question will be addressed in a separate analysis exploring predicted treatment outcome based on several baseline clinical and sociodemographic characteristics.

In conclusion, this analysis of data from ORAL Start and ORAL Standard shows that failure to achieve improvements in disease activity at months 1 and 3 is predictive of a low probability of achieving LDA and remission at months 6 and 12. Given that lack of early improvement may be predictive of a low probability of achieving stringent disease activity targets, decisions on the continuation of tofacitinib treatment in patients with moderately to severely active RA may benefit from consideration of early assessment of response.

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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. Keystone 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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Perspectives of Rheumatoid Arthritis Patients on Electronic Communication and Patient-Reported Outcome Data Collection: A Qualitative Study

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Objective. To identify the perspectives of patients with rheumatoid arthritis (RA) on electronic recording of between-visit disease activity and other patient-reported outcomes (PROs) and on sharing this information with health care providers or peers.

Methods. Patients with RA were recruited to participate in focus groups from December 2014 to April 2015. The topic guide and analysis were based on the Andersen–Newman framework. Sessions were audiorecorded, transcribed, independently coded, and analyzed for themes.

Results. Thirty-one patients participated in 7 focus groups. Their mean ± SD age was 51 ± 13.1 years, 94% were women, 52% were African American, 11% were Hispanic, and 37% were white. Three themes emerged: provider communication, information-seeking about RA, and social and peer support. Participants expressed a willingness to track disease activity data to share with health care providers electronically if providers would act on the information. Participants envisioned symptom tracking and information sharing as a mechanism to relay and obtain reliable information about RA. Participants were also interested in electronic communication between visits if it facilitated learning about symptom management and enhanced opportunities for social support among patients with RA.

Conclusion. Patients with RA may be amenable to electronic collection and sharing of PRO-type data between clinical encounters if it facilitates communication with health care providers and provides access to reliable information about RA. Providing patients with social support was important for enhancing PROs collection by helping them overcome barriers by using electronic devices and overcome reservations about the value of these data.

INTRODUCTION

Evidence-based guidelines recommend that patients with rheumatoid arthritis (RA) be treated with the goal of attaining clinical remission or low disease activity as measured by validated patient- and/or rheumatologist-assessed disease activity measures (1). Strong evidence has shown that many patient-reported outcomes (PRO scores), including health-related quality of life, pain, physical function, fatigue, sleep, work, and home productivity, improve with use of disease-modifying antirheumatic drugs for RA (2–7). Indeed, some evidence suggests that patient self-assessments of RA are less subject to the placebo response than are some commonly accepted measures of inflammation, such as erythrocyte sedimentation rate and C-reactive protein level (4).

A growing body of literature suggests that rheumatologists may not have placed enough emphasis on patient perspectives on RA symptoms and functioning, which may lead patients to decline treatment escalation recommended by their rheumatologists (8,9). Patients view disease activity based on criteria such as arthritis-related symptoms, functional impairment, and other disturbances to the quality of life, some of which may have

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SIGNIFICANCE & INNOVATIONS

- The major motivation for patients with rheumatoid arthritis (RA) to complete questionnaires at home was that their treating rheumatologists would pay attention to and act upon this information.
- Participants were eager to have a platform, preferably endorsed by their treating rheumatologist, with reliable information about RA, side effects of RA medications, diet, and exercise. Combining a learning experience about these aspects with completion of questionnaires at home would motivate them because they would not only provide but also obtain information.
- Providing patients with social support by peers appeared to be a reasonable approach to enhance the collection of patient-reported outcomes by helping them overcome barriers with the use of electronic devices and patients' reservations about the value of collecting these data for their provider.

been additionally influenced by concurrent conditions such as fibromyalgia or depression. Perhaps in part for this reason, recent analyses have shown that >50% of patients do not undergo escalation of RA therapies despite not having achieved low disease activity (10–13). RA disease activity likely influences several domains, including physical function, social and work-related duties, fatigue, and depression. Presenting information about their disease activity to patients can show the interplay of these domains and changes over time with RA treatment (i.e., changes in PRO scores). This information can deepen patients' understanding of the way that RA treatment affects their lives as well as improve the shared decision-making process.

Collection of PRO scores typically occurs only every 2–3 months during follow-up visits, if at all, despite the importance of PRO data in clinical decision-making. During the interval between visits, patients may experience worsening joint pain, swelling, and flares that resolve and are not reported or documented at the subsequent encounter. Moreover, several studies have shown that PRO scores are inconsistently collected at the point of care due to time constraints, system-related errors, and communication lapses (14,15). Results from 1 investigation suggested that integrating self-reported patient data collected outside of clinical settings could allow for more comprehensive symptom reporting and could enhance fidelity and consistency of patient data (14). Those investigators proposed that by incorporating more frequent patient self-reporting, the patient–physician interaction could shift from symptom recall to addressing symptom severity and causality (14). However, to date, a structured investigation of barriers to and facilitators of communication and symptom reporting between provider visits has not been conducted among patients with RA. This reporting is particularly important among patients with RA because they experience a variety of symptoms that inform treatment recommendations. Still, accurate assessment or measurement of each symptom may not occur in clinical encounters that happen only once every 2–3 months or even less frequently.

The collection of patient-reported measures of disease activity between scheduled physician encounters (recorded at home by the patient) can provide a more frequent, accurate, and quantifiable representation of RA disease activity that can be incorporated into treatment decisions as part of routine clinical care. However, how willing patients are to collect such data or communicate between office encounters is not clear. A deeper understanding of RA patients' motivations, interests, and expectations related to collecting PRO-type data between visits is needed to inform the design and utility of tools to engage patients in PRO recording outside of the clinical setting. This study's objectives were to elicit perspectives of patients with RA regarding perceived barriers to and facilitators of collecting data electronically to monitor disease activity and to assess patients' willingness to share data with others, including their health care providers (rheumatologist or primary care provider), staff (nurse, infusion nurse, pharmacist, or triage personnel), and other patients with RA. We wanted to examine whether sharing information with other patients with RA will help overcome barriers to electronic data collection at home.

PATIENTS AND METHODS

Study design and protocol. We collected data in focus groups, using a topic guide based on a specific theoretical framework. This guide was reviewed for content in several iterations by a multidisciplinary team with expertise in rheumatology, preventive medicine, and health behavior, as well as by patients with RA participating in the Patient Powered Research Network ArthritisPower, funded by the Patient-Centered Outcomes Research Institute. The guide was developed with an emphasis on addressing the 3 main domains of the Andersen–Newman framework that consist of predisposing, enabling, or illness-level factors that may affect use of RA clinical and ancillary services (Figure 1) (16). Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23580/abstract, contains a summary of the topic guide for this project. Briefly, we asked participants to share their perspectives about their health, finding health information, and seeking support from family, friends, peers, nonphysician medical professionals, or their current physician (predisposing factors). Other points of discussion were access to RA providers, treatment, and communication tools (enabling factors) and access to mechanisms for tracking RA symptoms (illness-level factors). Finally, we inquired about RA symptom management, tracking, and reporting, including how symptoms inform decisions regarding follow-up and sharing of

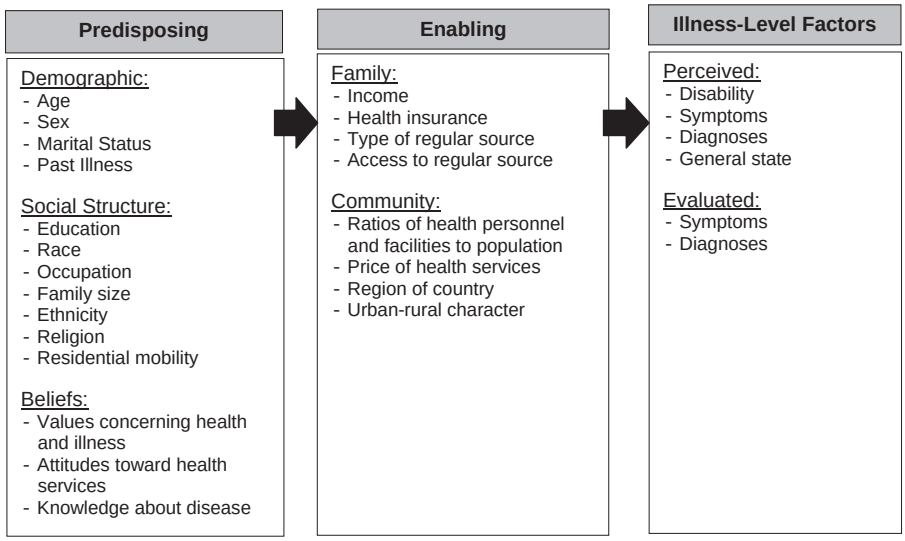

Figure 1. Individual determination of health service utilization (the Andersen–Newman framework).

health information with providers, family, and other patients with RA. We also elicited information on factors that influenced a willingness to track and share individual-level symptom information over time in face-to-face or online formats (e.g., online forums, journaling or blogs, or using apps to track symptoms) with the patient's health care team and others (e.g., relatives, friends, and other patients with RA).

To describe the sample, we gathered demographic information as well as each participant's experience with RA, recent medication adherence (the last 30 days), and comfort level with and likelihood of sharing RA and overall health data with a health care team as well as with family, friends, and other patients with RA (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23580/abstract). We obtained written informed consent from participants prior to each session. The University of Alabama at Birmingham (UAB) Institutional Review Board approved study procedures.

Participant recruitment and eligibility. Participants were adult volunteers with RA (ages ≥19 years) recruited from the UAB rheumatology clinic from December 2014 to April 2015. Recruitment relied on provider-initiated referrals during regularly scheduled rheumatology clinic visits and study flyers posted in the rheumatology clinic. We aimed to recruit participants who reflected the demographics and disease duration observed in the clinic's RA population. Eligibility criteria included a diagnosis of RA and willingness to participate in an audiorecorded focus group session.

Data collection. Trained research staff cofacilitated each focus group using the structured moderator guide. Groups met 1 time for 90 minutes each and were conducted in a private meeting space in the medical center. Sessions were audiorecorded. After each session, each participant individually completed a brief paper questionnaire. The first 3 focus groups had a high no-show rate (2–3 participants per group); thus, we conducted additional groups with 5–8 participants in each subsequent group for a total of 7 focus groups before reaching thematic saturation. Digital audio recordings from each session were securely uploaded into our server at UAB and transcribed verbatim by a medical transcription service. Transcriptions were uploaded into NVivo software, version 10 (QSR International) for analysis.

Analysis. Transcripts were reviewed and coded by 2 independent trained staff members (AZ and SS) for comparison prior to analysis, with an initial coding outline structured according to the predisposing, enabling, and illness-level domains described in the Andersen–Newman framework, as related to RA management, information seeking, symptom tracking, and use of RA services. We generated the initial set of codes, which were then grouped into subthemes and subsequently themes. We deduced novel domains and associated themes during initial coding and generation of thematic summaries, and these domains and themes were combined with framework domains to produce an initial codebook. The panel of rheumatology providers who assisted with the development of the topic guide was consulted for coding discrepancies. Post–focus group questionnaire responses were analyzed using descriptive statistics to characterize the focus group cohort.

RESULTS

A total of 31 patients with RA participated in the focus groups. The mean ± SD age of participants was 51 ± 13.1 years (range 25–84 years), 94% of participants were women, 52%

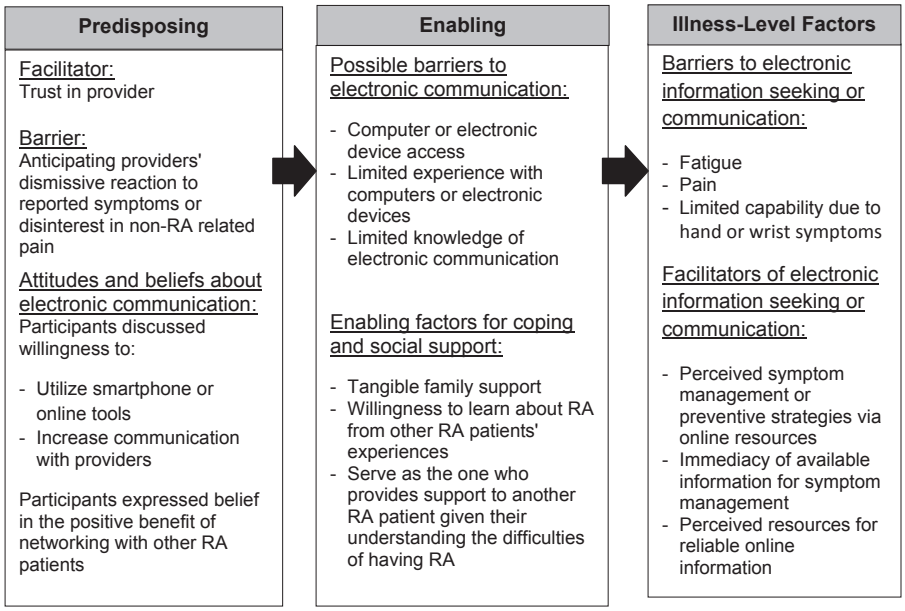

Figure 2. Summary of barriers to and facilitators of electronic data collection among patients with rheumatoid arthritis (RA).

were African American, and 37% were white, with 11% identifying as Hispanic ethnicity, and the mean ± SD disease duration was 10 ± 9.4 years. Among this group of patients, 18 participants (58%) were very or extremely likely to use electronic/online tools for keeping track of their RA (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23580/abstract).

Themes/meaning units. Figure 2 shows a summary of several points that emerged during these focus groups that correspond to the main 3 domains of the Andersen–Newman framework. The 3 major themes and supporting quotes are shown in Table 1.

Theme 1: provider communication. Participants expressed a great deal of interest in augmented communication with RA health care providers in real time or soon after symptoms arise. Most participants preferred phone or email communication, with few reporting use of a patient portal or electronic medical record messaging. Common reasons for reaching out to providers were flare symptoms, medication refills, questions about medication, or requesting an earlier appointment. Participants expressed the idea that their provider was a crucial source of support and trust for information, recommendations, and treatment decisions. However, participants were less interested in communicating with their physicians between visits if they perceived that they were doing well. Groups listed common perceived barriers to and facilitators of electronic communication with providers as well as to completing questionnaires electronically (Figure 2).

Barriers to electronic data collection at home. Barriers were illness-level factors, attitudes about care, and low awareness of a platform for collecting PRO scores. Many participants expressed their inability to type on a computer keyboard or phone keypad during symptoms of fatigue or hand pain. Other barriers were not having access to a computer or unfamiliarity with this technology. Participants were interested in providing data to physicians, but they also expressed discouragement when physicians did not attend to the information they provided at the point of care. Participants emphasized that if they shared information with the provider, whether at home or at the point of care, they wanted physicians to act on this information. If physicians did not incorporate the provided data, patients were far less interested in completing questionnaires at home.

Facilitators for electronic data collection at home. Facilitators were largely enabling factors, including access to a computer, internet service, and familiarity with computers or smartphones. Those who expressed difficulty with technology indicated that having formal instruction or someone to assist or engage them in the electronic communication could empower them to consider this avenue. Some participants were already journaling or recording symptoms at home, and many indicated a willingness to share additional data if their treating rheumatologist requested it. At the same time, they expressed motivation to collect data if the data were used to manage symptoms or obtain support from their physician (themes 1, 2, and 3 and Figure 2). Participants also expressed interest in the data collection platform allowing them to learn about RA and RA medications, including side effects (themes 2 and 3), and learn about nonmedical (i.e., self-management) options for treating RA.

Theme 2: information-seeking and strategies for symptom management. Nearly all participants expressed the belief that their health care provider was their most trusted source of health information and treatment recommendations (theme 1),

Table 1. Themes with respective quotes that emerged as part of the focus groups conducted to interpret patients' perspectives about tracking symptoms electronically at home

Theme	Quote
Theme 1: provider communication	"This app would give me a reminder time when to take my medications, it would give me a way to communicate with my doctor via email, it would be a tool that if I am going through something I can talk into the phone and store this information and go back at a later date and review it."
	"I want to be able to communicate with him but not just drive him crazy…I am going to tell him the most important things and give him time to make the arrangements to try and help me because I'm not the only patient."
	"I guess a lot of it is whatever is affecting me that day. And I might not even think about what to ask, but I need to be proactive and writing down things because of this. Even 3 months, you know even 4, even month-to-month you might think of something. If I don't write it down I'm going to forget. If it doesn't affect me between then and when I go back, it's gone."
	"I had an app that you have to keep up with when you're trying to get pregnant. You could also go to a chat room from the app, and you could track your symptoms and stuff like that. It was really nice to have. I'm sure they're out there for rheumatoid arthritis, but I haven't even bothered to look yet."
Theme 2: information-seeking and strategies for symptom management	"A place where questions could be asked about that to a doctor that, you know, is well read that can get that information back to us. Because, you know, the media is killing us."
	"I try to avoid the internet for any questions. I just prefer to go ahead, to go to the sources and just go to my medical doctor and be like, 'Look, I have this question, I'm having these symptoms, I feel like this. What should I do?'"
	"The internet…you know, you can ask the internet anything. Now just because it's on there doesn't mean it's true…I look to sources like WebMD, MD Anderson, or Johns Hopkins."
Theme 3: social and peer support	"If we had, like, a central, you know, where people from Birmingham could talk about rheumatoid arthritis, and people from the Southeast could talk about rheumatoid arthritis, you could have, like, some sort of a website where you list all of your symptoms and keep an eye on them for yourself. And you can send that to your provider, or you could talk to somebody about a certain joint disease, all in 1 webpage or app for those of us who like our iPhones a lot."
	"'We show you, you know, how to access it through your email,' or we take your phone and say, 'This is how you find this app. This is how you do it.' Have someone, whether it's a receptionist, or a nurse, or somebody from the IT department, say, 'Okay, this is the person who's going to help the people who aren't tech savvy access this stuff.'"
	"I have family support."
	"I'm all about apps and stuff like that. But for people who aren't, have someone in the office to show them, walk them through it step by step and make sure that they're okay with it before they leave."
	"Well I have adult children and they taught me the art of communication through text messaging, 'If you want to ask me a question text me,' and I did."
	"I think it's great because you get to see other people and talk to them and hear how they dealt with theirs and…for instance, me, a year and a half I've had it and known about it. And I don't really have anybody to talk to. So I don't know what they're doing and what they have done. I know of a few people that have it, and when I first was diagnosed I did call one girl that I know, but I don't see her regularly and interact with her."

and they preferred to learn about RA from their provider. Few were certain about the trustworthiness of electronic resources. Many participants described frustrations with illness-level factors, including pain, the effects of RA on the body, and interference with daily activity, particularly near the time of diagnosis. They expressed interest in accessing educational resources for medical and nonmedical symptom management. Several participants were interested in learning from others with RA about available online resources, how to better use electronic or online resources available for patients with RA, and the best ways to communicate with their doctors. However, very few participants were aware of existing platforms for PRO-type data collection that they can use to track their symptoms and share the information with their provider or even another patient with RA.

Barriers to obtaining information about symptom management. Several participants identified a need for resources for accurate and tailored medication information, provided in lay terms, that include evidence of long-term effects of RA medication and potential drug interactions (e.g., thyroid medication and antibiotics). Many participants were unsure of how to retrieve dependable information online or in real time. For some participants, actual and anticipated side effects were barriers to therapeutic management of symptoms, and persons who reported using electronic or online resources expressed concerns regarding understandability and credibility of online sources.

Facilitators for obtaining information about symptom management. Participants expressed interest in learning about symptom and medication management through platforms similar to those with which they communicated data to their providers. They expressed the idea that having this information would be a motivator for them to enter responses to electronic questionnaires through platforms, moreso if their provider also requested that they complete the questionnaires. Still, as mentioned in theme 1, participants emphasized that providers should use this information to keep the patient motivated to continue tracking their symptoms (via PROs).

Theme 3: social and peer support. Participants agreed that having some form of social support was vital to wellness and coping. This social support included supportive communication, electronic or in person, with their health care team, receiving support from partners and family members, and supportive communication (giving or receiving) with other patients with RA.

Barriers to social and peer support. Few participants had made social connections with other patients with RA. Most received a significant amount of support from local family members for coping and health management. However, many participants expressed feelings of isolation at the time of diagnosis and were unsure of how to establish supportive connections with peers with RA, online or in person.

Facilitators for social and peer support. Participants expressed eagerness to communicate with other patients with RA to establish expectations of treatment and obtain information about flares and symptom management. They expressed interest in a platform for connecting with others with RA as a way of learning about RA and coping, particularly for reducing isolation. They wanted to learn what to expect from their treating rheumatologist, how best to communicate with providers, and what to expect from RA and the medications used to treat it. Participants expressed the idea that these resources can help them overcome their feelings of isolation, which at the same time could serve as a motivation for them to engage in electronic data collection as well. They noted that working with another patient with RA could help overcome their lack of familiarity with computers and electronic devices and assist in completing questionnaires about disease activity online (barriers theme 1and enabling domain in Figure 2).

Participants expressed the desire to have an initial interaction in a structured, facilitated meeting or face-to-face group to establish trust before engaging in online communication with peers. Participants further expressed the idea that initiating social connections in person could help overcome reservations for sharing RA data electronically, the process of sharing symptoms, and entering disease activity data in a PRO or electronic format.

DISCUSSION

The results of this study demonstrate that these patients with RA were interested in frequent, positive communication with a trusted provider, as well as interested in reliable, tailored information for symptom management in therapeutic and nonmedical approaches (i.e., self-management), and in supportive connections, including those with other patients with RA. Many participants expressed willingness to find and share data regarding RA disease activity for improved symptom management and social support, but most were unfamiliar with electronic or PRO platforms. Focus group participants expressed interest in tracking and sharing symptoms between visits, which may include PRO platforms, as part of their clinical care, if their treating rheumatologist would use the information to treat their disease. Other aspects of great importance as motivators to electronic data collection were a desire to learn about expectations for short- and long-term disease management, information on symptoms and medication side effects, and seeking support from physicians, family, and other patients with RA. However, our findings indicated that asking patients to collect and share data electronically is not enough to engage them. Disease monitoring through electronic tracking of symptoms or PRO platform use should be aligned with social and/or provider support, adequate instruction on electronic device use (e.g., smartphones and computers), tailored information on managing symptoms and side effects, and lifestyle programs for patients with RA. Meeting these needs may provide necessary motivation among patients with RA to electronically track and report data between doctor visits, especially if the purpose of the data collection is clearly explained.

Because many participants were unfamiliar with electronic PRO platforms, they did not mention how information provided through PRO platforms is helpful to them personally, how it could reflect the status of their disease, and how it could allow comparison of their disease status with other patients with RA. A possible explanation is that they did not understand that PRO platforms can provide individual and population-based information about RA longitudinally. Giving patients a general understanding about PRO platforms and their clinical utility could serve as another motivation for patients to collect these data. Since patients indicated difficulty typing on electronic devices due to disease activity, another technology for consideration is passive data collection (e.g., body sensors of gait, texting speed, or pedometers).

Participants valued positive communication with trusted providers and information about what to expect of medications. These findings suggest that coupling PRO scores collection at home with education on medications and side effects may be a reasonable strategy for collecting this information between visits. These findings are consistent with published benefits of PRO platform use in clinical practice, including improvement in patient–physician communication, self-efficacy, and treatment plan adherence, as well as greater satisfaction with care and more efficient use of resources (17). Additionally, compared with simply asking patients to complete PRO questionnaires, collection of PRO data paired with a learning experience for the patient

was shown to be more successful in engaging patients to use self-tracking technologies (18).

It was important to patients that their providers use the disease information they shared. Compared with standard paper forms or unstructured self-report at the visit, an electronic tool may allow easier data entry for patients and simpler interpretation for providers. A recent study showed that young patients with RA prioritize function, while older patients with RA want to avoid fatigue (19). Therefore, systematic symptom and disease activity data collection by patients may enhance interpretability so physicians can better address patient priorities.

Importantly, participants showed great interest in obtaining information for RA management. Providing patients with appropriate guidance and encouraging them to use a PRO platform may enable useful insights into the significance and trends of their individual data and into how these measures can be used to improve RA care and support. These data can also facilitate discussion with providers at or between visits about aspects of health that matter most to patients. This study serves as a foundation for follow-up studies to evaluate the use of PRO platforms for improved patient satisfaction and outcomes in RA.

Our study has several strengths. It is a qualitative investigation guided by a conceptual framework of factors influencing health care utilization, which provided a consistent structure from conception (research question and topic guide) through analysis (coding and theme structure). The topic guide used for the focus groups was extensively vetted by patients and investigators with different backgrounds and expertise, resulting in the incorporation of a variety of perspectives. This study achieved theme saturation and engaged a relatively large sample size for a qualitative study. Additionally, the final sample included a large number of women and African Americans, groups traditionally underrepresented in RA research.

Several limitations to our study are also worth considering. The participants were from a single center, and not all scheduled participants took part. However, the sample allowed us to recognize patients' perspectives, attitudes, and opinions and met the goal of hypothesis generation. We also obtained the patient perspective only, and subsequent investigation into rheumatologists' perspectives on the use of PRO platforms to inform RA treatment is warranted.

In conclusion, patients may be willing to use questionnaires to collect PRO scores between office visits, and many are amenable to electronic data capture. An electronic data capture tool may be useful in providing quantifiable information to RA health care providers to complement signs and symptoms described during office encounters. Patients may be more willing to engage with such a tool if it also provides reliable educational information about RA and its treatments, preferably delivered or at least recommended by their doctor. These patients valued the receipt of information regarding symptom management and support, as well as communication with trusted providers, at and between scheduled clinic visits. Electronic tracking of PRO data may be an important communication mechanism for patients with RA and their health care team. Self-tracking technologies may be more attractive to patients with RA if coupled with opportunities to learn about RA-specific issues, including symptom management, medications and side effects, and opportunities to obtain social support.

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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. Navarro-Millán 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. Navarro-Millán, Zinski, Willig, Curtis, Safford.

Acquisition of data. Navarro-Millán, Zinski, Shurbaji, Curtis, Safford.

Analysis and interpretation of data. Navarro-Millán, Zinski, Johnson, Fraenkel, Danila, Yun, Curtis, Safford.

ROLE OF THE STUDY SPONSOR

Pfizer had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Pfizer.

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BRIEF REPORT

Safety and Immunogenicity of Rituximab Biosimilar GP2013 After Switch From Reference Rituximab in Patients With Active Rheumatoid Arthritis

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Objective. Comparable clinical efficacy of the rituximab (RTX) biosimilar GP2013 and reference RTX has been established in blinded randomized trials. However, when switching from a reference biologic to a biosimilar, potential safety implications are often an important consideration. Therefore, the aim of this study was to evaluate the safety of switching from reference RTX to RTX biosimilar GP2013 compared with treatment continuation with reference RTX in patients with rheumatoid arthritis (RA).

Methods. In this multinational, randomized, double-blind, parallel-group safety study, 107 patients with RA who had previously received treatment (of any duration) with reference RTX as part of routine practice and who required continuation of treatment were randomized to receive either GP2013 or to continue treatment with reference RTX. All patients received a stable dosage of methotrexate and folic acid during the study. Study assessments included the incidence of hypersensitivity, infusion-related and anaphylactic reactions, immunogenicity (antidrug antibodies), and general safety.

Results. Regardless of whether patients switched to GP2013 or continued treatment with reference RTX, the incidences of hypersensitivity (9.4% and 11.1%, respectively) and infusion-related reactions (11.3% and 18.5%, respectively) were similarly low. Only 1 patient (in the reference RTX group) developed antidrug antibodies to RTX after starting study treatment. No neutralizing antidrug antibodies were observed. Antidrug antibodies were not associated with adverse events (AEs). No clinically meaningful differences in the rate of AEs were observed between treatment groups.

Conclusion. No safety risks were detected when patients switched from reference RTX to GP2013. The safety profiles of patients in both treatment groups were similar, although the study was not powered for statistical testing of equivalence in safety.

INTRODUCTION

Biosimilars are biologic agents that match reference biologics in terms of structure, efficacy, and safety and are expected to increase patient access as well as provide savings to health care systems (1). The rituximab (RTX) biosimilar GP2013 has been developed using a stepwise approach comprising extensive physicochemical and functional characterization followed by in vitro bioassays as well as in vivo preclinical studies (2). Equivalence of pharmacokinetics and pharmacodynamics as well as similar efficacy, safety, and immunogenicity between GP2013

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SIGNIFICANCE & INNOVATIONS

- Comparable clinical efficacy of the rituximab (RTX) biosimilar GP2013 and reference RTX has previously been demonstrated in randomized, controlled, double-blind studies. However, clinicians may be uncertain about switching from a reference biologic to an approved biosimilar, predominantly related to safety and immunogenicity.
- In this international, multicenter, randomized, controlled study in patients with rheumatoid arthritis, the safety and immunogenicity of switching from RTX to the rituximab biosimilar GP2013 was comparable with continuation of reference RTX.
- Using 3 separate instruments, a comparable incidence of specific adverse events, which could be associated with a potential immunologic response, was observed following the switch from reference RTX to the biosimilar.
- Immunogenicity of the switch was thoroughly monitored using a multi-tiered approach comprising a 3-step analysis of binding anti-RTX antibodies followed by a cell-based assay of the neutralizing capacity of anti-RTX antibodies.

and reference RTX have been demonstrated in 2 randomized, double-blind, controlled trials in patients with rheumatoid arthritis (RA) (3) and non-Hodgkin's lymphoma (follicular lymphoma) (4).

When considering a treatment switch from a reference biologic to a biosimilar, the safety profile in terms of the type, frequency, and severity of adverse events (AEs), as well as immunogenicity, are of particular interest for prescribing physicians. The potential safety implications of such a switch are currently under debate, with some regional differences in perceptions (5,6). Existing data on switching for selected biosimilar molecules have been generated from observations in open-label studies (7), extensions of approval studies (8), and from national studies performed after switches to biosimilars were mandated by decisions of local health care authorities (9,10). To date, none of the data for switching for approved biosimilars have indicated any significant concerns with respect to efficacy or safety.

The current study presents an additional step of biosimilarity assessment, providing a comparison with regard to safety and immunogenicity between either continuation of reference RTX or a switch from reference RTX to GP2013 in patients with RA.

PATIENTS AND METHODS

Patients. The study population consisted of adult patients with RA who had previously received RTX as part of routine practice and who required continuation of RTX treatment according to the judgment of the consulting rheumatologist. There was no limitation regarding the duration of previous RTX treatment. The key inclusion and exclusion criteria are shown in Supplementary Section 1 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr23771./abstract). The study was approved by competent authorities and ethics committees at each center. All participants provided written informed consent.

Study design and treatment. This randomized, double-blind, controlled study was conducted at 54 centers across 4 countries (US, Germany, Poland, and Hungary). After a screening period of 4–6 weeks and an evaluation of RTX antidrug antibody status at screening, eligible patients were randomized 1:1 via a central Interactive Response Technology system to receive two 1,000-mg intravenous infusions of either GP2013 or reference RTX (sourced from either the European Union or the US; as received prior to study enrollment). Randomization was stratified by region (US, European Union), antidrug antibody status at screening, and number of previous RTX treatment courses. Patients, study investigators, and other study personnel assessing outcomes and analyzing data were blinded to treatment allocation. Two intravenous infusions of study medication were administered at investigational sites on 2 consecutive visits 2 weeks apart, with intravenous methylprednisolone, antipyretic, and antihistamine premedication given prior to each infusion. All patients received a stable dosage of methotrexate (7.5–25 mg/week) and folic acid during the study.

Outcomes and data collection. Key safety end points were incidences of infusion-related reactions, anaphylactic reactions, and hypersensitivity, as well as the incidence of antidrug antibodies. Safety follow-up took place at study visits at week 2 (second infusion visit), week 12, and week 24 (end of study visits). In addition, patients were contacted remotely within the 24-hour period after each infusion to assess potential reactions to the study drug. AEs were assessed by non-directive questioning of the patient during each contact. RA disease activity was assessed according to the local routine, but data were not collected for study evaluation. However, investigators were instructed to report any lack of efficacy as an AE.

Hypersensitivity reactions were identified from the study AEs database by a Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) (11). Infusion-related reactions were identified by an SMQ of AEs occurring either on the day of or the day after GP2013/RTX infusions. Anaphylactic reactions were defined according to National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria (12), requiring the occurrence of any 2 of the following symptoms within 24 hours of the start of infusion: respiratory symptoms (e.g., dyspnea, wheeze–bronchospasm, stridor); skin/mucosal symptoms (e.g., generalized hives, itch–flush, swollen lips–tongue–uvula, throat irritation); systolic blood pressure <90 mm Hg or a decrease of >30%, or associated symptoms of reduced blood pressure; and; gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).

If a patient had previously experienced an infusion-related reaction, systolic blood pressure <90 mm Hg or a decrease of >30%, or associated symptoms, would be sufficient to define an anaphylactic reaction.

Immunogenicity assessment. Blood sampling for assessing routine safety parameters and determining the presence of antidrug antibodies was performed at each study visit. Antidrug antibody sampling was also performed when any AE was considered by the investigator to be immune-related. A validated affinity capture elution enzyme-linked immunosorbent assay (ELISA) was used for the determination of antidrug antibodies, using a multitiered approach comprising screening, confirmation, and titration of binding RTX antidrug antibodies. Antidrug antibody–positive samples were further analyzed in a cell-based assay to assess the neutralizing capacity of the antidrug antibodies. Further methodology details are shown in Supplementary Section 2 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23771/abstract).

Statistical analysis. Due to the known low incidence of investigated key safety end points after RTX treatment in patients with RA, a prohibitively large sample size would be required to perform fully powered hypothesis testing for equivalence. Therefore, the sample size in this study was not based on statistical considerations. Descriptive statistics were used for all safety end points; point estimates and 95% confidence intervals (95% CIs) were calculated for differences in the incidence rates of key safety end points between treatment arms. Given the small sample size and low event rate observed in this study, the 95% CIs were estimated using the most conservative approach, based on the exact unconditional method (for details, see Supplementary Section 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23771/abstract). With a

Table 1. Demographics and baseline disease characteristics (safety analysis set)*

Characteristic	GP2013 (switch) (n = 53)	Reference RTX (n = 54)	Total (n = 107)
Age at screening, years	56.8 ± 9.9	57.1 ± 12.1	57.0 ± 11.0
Age group, no. (%)			
18 to <45 years	6 (11.3)	9 (16.7)	15 (14.0)
45 to <65 years	38 (71.7)	30 (55.6)	68 (63.6)
≥65 years	9 (17.0)	15 (27.8)	24 (22.4)
Female sex, no. (%)	46 (86.8)	39 (72.2)	85 (79.4)
Male sex, no. (%)	7 (13.2)	15 (27.8)	22 (20.6)
Weight, kg	80.12 ± 20.2	81.62 ± 20.5	80.88 ± 20.3
BMI, kg/m^2	29.58 ± 7.4	29.19 ± 7.6	29.38 ± 7.5
Region, no. (%)			
US	17 (32.1)	18 (33.3)	35 (32.7)
European Union	36 (67.9)	36 (66.7)	72 (67.3)
Duration of RA, years	13.5 ± 9.4	14.0 ± 8.5	13.7 ± 8.9
No. of prior biologics other than RTX	1.2 ± 1.0	1.4 ± 1.0	1.3 ± 1.0
No. of previous treatment courses with RTX	4.1 ± 3.3	5.0 ± 3.8	4.6 ± 3.6
Previous treatment courses with RTX, no. (%)			
1 course of treatment	13 (24.5)	13 (24.1)	26 (24.3)
>1 course of treatment	40 (75.5)	41 (75.9)	81 (75.7)
Time since last RTX treatment, weeks	35.8 ± 13.2	39.85 ± 15.0	37.9 ± 14.2
MTX dosage, mg/week	14.5 ± 6.2	15.5 ± 5.1	15.0 ± 5.7
Receiving steroids, no. (%)	23 (43.4)	26 (48.1)	49 (45.8)
Prednisone equivalent, mg/day†	5.4 ± 1.8	4.6 ± 2.4	5.0 ± 2.1
CRP, mg/liter (ref. range ≤5 mg/liter)	9.7 ± 24.2	11.6 ± 23.6	10.7 ± 23.8
Serum IgG, gm/liter (ref. range 6.9–14.0 gm/liter)	10.1 ± 2.1	10.2 ± 2.3	10.4 ± 2.2
Serum IgM, gm/liter (ref. range 0.34–2.4 gm/liter)	0.9 ± 0.5	0.8 ± 0.5	0.9 ± 0.5
Serum IgA, gm/liter (ref. range 0.7–4.10 gm/liter)	2.4 ± 1.1	2.6 ± 1.5	2.5 ± 1.3
Anti-RTX antibody–positive at screening	1 (1.9)	1 (1.9)	2 (1.9)

* The safety analysis set consists of all patients who received the study drug at least once (all study patients). Except where indicated otherwise, values are the mean ± SD. RTX = rituximab; BMI = body mass index; MTX = methotrexate; CRP = C-reactive protein.
† Calculated based only on patients treated with glucocorticoids.

Table 2. Key safety assessments and immunogenicity (safety analysis set)*

	GP2013 (switch) (n = 53)	Reference rituximab (n = 54)	Difference, %	95% CI for difference
Hypersensitivity reactions†				
After first and before second infusion	3/53 (5.7)	4/54 (7.4)	−1.7	−20.6, 16.9
After second infusion up to end of study	2/51 (3.9)	3/54 (5.6)	−1.6	−20.9, 17.3
Overall from first infusion up to end of study‡	5/53 (9.4)	6/54 (11.1)	−1.7	−20.6, 16.9
Severe	1/53 (1.9)§	0		
Anaphylactic reactions¶				
Within 24 hours of either infusion	0	1/54 (1.9)	−1.9	−20.6, 16.9
Infusion-related reactions#				
First infusion	4/53 (7.5)	7/54 (13.0)	−5.4	−24.2, 13.3
Second infusion	2/51 (3.9)	5/54 (9.3)	−5.3	−24.5, 13.6
Overall‡	6/53 (11.3)	10/54 (18.5)	−7.2	−26.0, 11.4
Severe	1/53 (1.9)§	0		
Antidrug antibodies**				
Antidrug antibody positivity post-treatment	0	1/53 (1.9)	−1.9	−21.2, 17.6

* The safety analysis set consists of all patients who received the study drug at least once (all study patients). Values are the number of patients/number of patients assessed (%). 95% CI = confidence interval.
† Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query was used to identify hypersensitivity reactions in the database of adverse events.
‡ Patients with reactions after both infusions are counted only once in this category.
§ One patient with fatigue, fever, and muscle pains reported as being serum sickness was withdrawn after the first infusion. This patient is listed under both hypersensitivity and infusion-related reactions based on study methodology.
¶ 2006 National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria were used to define anaphylactic reactions within 24 hours of the start of GP2013/ritixumab infusions.
# MedDRA Query was used to identify infusion-related reactions in the database of adverse events occurring on the day of or day after GP2013/RTX infusions.
** Patients with negative results of antidrug antibody testing at screening and at least an evaluable post-randomization antidrug assessment were included in the analysis.

sample size of 100 patients (50 patients per treatment group), the expected upper limits of the 95% CIs for the incidence differences between treatment groups were 10.3% for hypersensitivity, 3.9% for anaphylaxis, 17.0% for infusion-related reactions, and 11.2% for the incidence of antidrug antibodies. In the safety analysis, any difference between treatment groups that exceeded the respective upper limit value would be considered a statistically significant signal of potential difference in the specific end point. Calculations were based on the assumption that no difference would be observed between treatment groups, and based on the incidences of safety end points as observed both in previous literature or in prior studies of GP2013: hypersensitivity, 7.5%; anaphylaxis, 1%; infusion-related reactions, 17.0%; and immunogenicity, 9%.

RESULTS

Patient disposition and baseline characteristics. A total of 107 patients (85 female and 22 male) were randomized to either switching to GP2013 (n = 53) or continuing reference RTX (n = 54). All randomized patients received the first infusion, but in the switch group, 2 patients withdrew before the second infusion (1 experienced a hypersensitivity reaction, and 1 withdrew informed consent).

The demographics and baseline clinical characteristics were comparable between the treatment groups (Table 1). Patient disposition and recruitment by region are shown in Supplementary Figure 1 and Supplementary Table 1, respectively (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23771/abstract).

Key safety assessments. The incidences of 3 types of reaction were used in the study to thoroughly assess the incidence of AEs that might be associated with the switch from reference RTX to the biosimilar RTX GP2013: anaphylactic reactions at any study time point; hypersensitivity reactions at any study time point; and infusion-related reactions, occurring either on the day of or day after each infusion. A degree of redundancy was observed between these 3 safety instruments, which therefore represent a conservative approach to identify any potential safety risks.

Only 1 patient in the RTX group experienced a combination of AEs fulfilling the criteria for anaphylaxis (mild throat irritation as-

sociated with a decrease in systolic blood pressure and mild vomiting). The incidence of hypersensitivity reactions was similarly low in both treatment groups (Table 2) and was slightly lower after the second infusion. Overall, the majority of hypersensitivity events were mild. Serum sickness with symptoms of fatigue, fever, and muscle pain—the only event that defined severe hypersensitivity—occurred in 1 patient from the switch group, leading to study drug discontinuation. All hypersensitivity reactions are shown in Supplementary Table 2 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23771/abstract). The incidence of infusion-related reactions was higher in the RTX group (Table 2). The severity of most events was mild, and no cluster of particular AEs was observed. All infusion-related reactions are shown in Supplementary Table 3 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23771/abstract).

Immunogenicity. In total, antidrug antibody samples were missing for only 2 patients (at 1 visit each), meaning that 99.5% of planned antidrug antibody samples were collected and analyzed. The 2 patients who tested antidrug antibody–positive at screening (1 in each group) were antidrug antibody–negative at all post-screening visits, whereas 1 patient in the RTX group who was antidrug antibody–negative at screening was antidrug antibody–positive at all visits after the start of treatment. No AEs were reported for this patient throughout the study. All antidrug antibodies were non-neutralizing. The only patient with severe hypersensitivity (serum sickness) in the switch group was antidrug antibody–negative at all visits. The patient in the RTX group who had an anaphylactic reaction during the first infusion was antidrug antibody–positive at screening but antidrug antibody–negative at all subsequent visits.

Standard safety assessments. There was a low incidence of serious AEs (SAEs), all of which occurred only in the RTX group. One patient died in the RTX group due to cardiopulmonary failure, which was not suspected to be related to the study drug. AEs were reported in more patients in the switch group, while more patients in the RTX group experienced severe AEs. In all system organ classes with numerical imbalances in incidence between treatment groups, no cluster of specific events could be observed (Figure 1). Arthralgias, reported only in the switch group, involved large joints in 2 of 3 patients, both of whom presented with osteoarthritis at study initiation. None of the infections was reported as serious or severe, and no opportunistic infections occurred. Only 1 patient withdrew due to safety reasons (Figure 1).

DISCUSSION

In this study, we evaluated the safety of switching from reference RTX to the biosimilar RTX GP2013. To our knowledge, this is the only randomized switching study to date enrolling patients who were treated with RTX as part of routine practice or within clinical studies, without any limitation to previous treatment duration.

The key safety end points of this study (anaphylaxis, hypersensitivity, infusion-related reactions, and immunogenicity) were chosen to assess a potential immunologic response following a switch from reference RTX to the biosimilar. The end points selected assessed this potential response from different perspectives and with a certain degree of redundancy. The results for the key safety end points did not show any clinically meaningful differences between treatment groups, and the incidences were similarly low. The reason for the low incidence of infusion-related reactions in this study could be attributed to the high number of RTX treatment courses previously administered to patients. According to the literature, most serious infusion-related reactions occur during the first infusion of RTX (13). Patients in this study had, on average, 4–5 courses of RTX treatment before the start of the study. There were very few SAEs in the study, and none were observed in the switch group. The differences in the incidence of AEs in individual categories could not be attributed to a cluster of specific events, while certain imbalances were already observed among comorbidities at the time of study initiation.

Immunogenicity was rigorously monitored during the study, because an almost complete set of serum samples was obtained from all patients at all visits. Only 1 patient in the RTX group developed antidrug antibodies after the start of treatment, which is less than the known incidence of antidrug antibodies in patients receiving RTX treatment. However, the literature indicates that the occurrence of antidrug antibodies to RTX decreases with repeated treatments (14,15). In the current study, post-treatment antidrug antibodies were not linked to any AEs. In particular, patients experiencing serum sickness and anaphylaxis were antidrug antibody–negative post-treatment. Furthermore, no antidrug antibodies were detected in any patient in the switch group, suggesting that the switch from reference RTX to the biosimilar is not associated with increased immunogenicity.

It is known that results of biosimilar switching studies depend to a certain extent on the study design. Although some open-label studies have shown an increased number of withdrawals or AEs following a switch (7,10), these effects were less frequently observed in randomized studies (8,9), suggesting the potential occurrence of a “nocebo” effect resulting from negative expectations toward the biosimilar (10).

The small sample size is another known factor that potentially contributes to imbalances in the baseline characteristics of patients, which might consequently lead to imbalances in AEs related to comorbidities. However, to adequately power a comparison of safety end points that have a very low incidence (e.g., anaphylaxis ≥1/1,000 to <1/100) would have required enrollment of a prohibitively high number of patients. Definition of equivalence margins for major safety events is also challenging, resulting in descriptive analyses of safety end points

Number of patients with	GP2013 (switch) N = 53 n (%)	Reference RTX N = 54 n (%)
Any adverse events	37 (69.8)	28 (51.9)
Severe adverse events*	1 (1.9)	3 (5.6)
Related adverse events**	6 (11.3)	11 (20.4)
Serious adverse events*	0	3 (5.6)
Adverse events leading to discontinuation	1 (1.9)	0
Deaths	0	1 (1.9)
Adverse Events reported at a ≥ 2% incidence		
Musculoskeletal and connective tissue disorders[#]	11 (20.8)	4 (7.4)
Arthralgia[§]	3 (5.7)	0
Osteoarthritis	2 (3.8)	0
Infections and infestations	10 (18.9)	13 (24.1)
Bronchitis	1 (1.9)	3 (5.6)
Upper respiratory tract infection	1 (1.9)	3 (5.6)
Sinusitis	2 (3.8)	1 (1.9)
Injury, poisoning and procedural complications	4 (7.5)	2 (3.7)
Fall	3 (5.7)	0
Skin and subcutaneous tissue disorders	4 (7.5)	3 (5.6)
General disorders and administration site conditions	3 (5.7)	1 (1.9)
Investigations	3 (5.7)	3 (5.6)
Nervous system disorders	3 (5.7)	5 (9.3)
Headache	2 (3.8)	2 (3.7)
Gastrointestinal disorders	2 (3.8)	10 (18.5)
Nausea	1 (1.9)	2 (3.7)
Vomiting	0	3 (5.6)
Respiratory, thoracic and mediastinal disorders	1 (1.9)	5 (9.3)
Vascular disorders	1 (1.9)	3 (5.6)

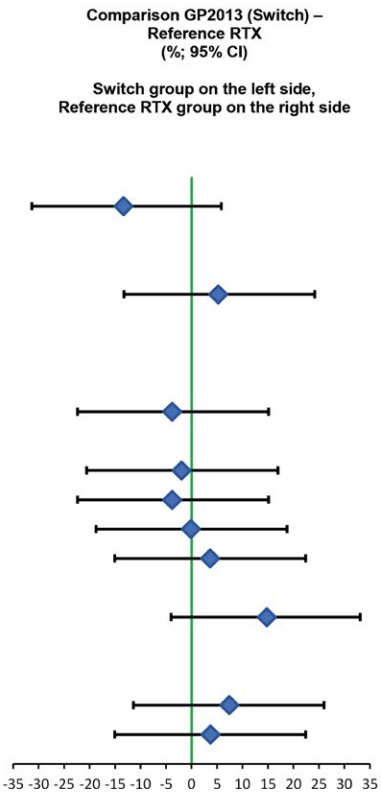

Figure 1. Summary of adverse events (safety analysis set),* The severity of adverse events was assessed by study investigators according to the study protocol. An adverse event was considered severe if it prevented the patient's normal activities. ICH GCP definition of seriousness of adverse event criteria was applicable. **As suspected by the study investigator. [#]MedDRA system organ classes (SOC). [§]MedDRA Preferred terms (PT). CI = confidence interval; GCP = Good clinical practice; ICH = International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with an adverse events after the infusion; N = total number of patients who received the respective infusion; RTX = rituximab. Safety analysis set consists of all patients who received study drug at least once (all study patients).

generally being used in biosimilar trials, including other trials investigating treatment switches from a reference biologic to a biosimilar (8–10). Introduction of a certain level of redundancy by evaluating different immunologic end points after the switch, as done in this study, increases the robustness of the safety assessment.

Stratification by region, antidrug antibody status at screening, and number of prior RTX treatment courses was used to improve balance of these important factors across treatment groups, but given the small sample size, this may have compromised balance in other factors. Furthermore, although the study was performed at multiple centers and across several countries, a low number of patients were included at each site, which might have led to selection bias. Nonetheless, the fact that the inclusion/exclusion criteria were consistent with RTX label recommendations supports the notion that this study adequately represents a real-world scenario of patients transitioning to a biosimilar, as would be performed by health care professionals.

In summary, the results of this study demonstrate that treatment switch from reference RTX to the biosimilar GP2013 in RA patients previously treated with RTX as part of routine practice has a safety profile comparable to continuation of reference RTX. No additional safety risks were detected in patients who switched from reference RTX to GP2013.

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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. Dr. Tony 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. Tony, Kollins.
Acquisition of data. Krüger, Schulze-Koops, Kivitz, Jeka, Vereckei.
Analysis and interpretation of data. Krüger, Cohen, Schulze-Koops, Kivitz, Jeka, Vereckei, Cen, Kring, Kollins.

ROLE OF THE STUDY SPONSOR

Sandoz facilitated the study design, provided writing assistance for the manuscript, and reviewed and approved the manuscript prior to submission. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication. Editorial assistance was provided by Ben Caldwell (Spirit, Manchester, UK) and funded by Hexal AG, a Sandoz company. Publication of this article was not contingent upon approval by Sandoz.

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Racial Disparities in the Incidence of Primary Chronic Cutaneous Lupus Erythematosus in the Southeastern US: The Georgia Lupus Registry

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Objective. Relative to studies of systemic lupus erythematosus (SLE), epidemiologic studies of chronic cutaneous lupus erythematosus (CCLE) are rare and are limited to populations with no racial diversity. We sought to provide minimum estimates of the incidence of primary CCLE (CCLE in the absence of SLE) in a population comprised predominantly of white individuals and black individuals in the southeastern region of the US.

Methods. The Georgia Lupus Registry allowed for the use of multiple sources for case-finding, including dermatology and rheumatology practices, multispecialty health care facilities, and dermatopathology reports. Cases with a clinical or clinical/histologic diagnosis of CCLE were classified as definite. Cases ascertained exclusively from dermatopathology reports were categorized as probable. Age-standardized incidence rates stratified by sex and race were calculated for discoid lupus erythematosus (DLE) in particular and for CCLE in general.

Results. The overall age-adjusted estimates for combined (definite and probable) CCLE were 3.9 per 100,000 person-years (95% confidence interval [95% CI] 3.4–4.5). The overall age-adjusted incidences of definite and combined DLE were 2.9 (95% CI 2.4–3.4) and 3.7 (95% CI 3.2–4.3) per 100,000 person-years, respectively. When capture–recapture methods were used, the age-adjusted incidence of definite DLE increased to 4.0 (95% CI 3.2–4.3). The black:white and female:male incidence ratios for definite DLE were 5.4 and 3.1, respectively.

Conclusion. Our findings underscore the striking racial disparities in susceptibility to primary CCLE, with black individuals having a 3-fold to 5-fold increased incidence of CCLE in general, and DLE in particular, compared with white individuals. The observed sex differences were consistent with those reported previously, with a 3 times higher risk of DLE in women compared with men.

INTRODUCTION

Cutaneous lupus erythematosus (CLE) comprises multiple dermatologic disorders, which can be limited to the skin or associated with underlying systemic lupus erythematosus (SLE). CLE has distinctive clinical and histopathologic features, which are categorized as acute (ACLE), subacute (SCLE), or chronic (CCLE) (1,2). CCLE comprises discoid lupus erythematosus (DLE), lupus erythematosus profundus (LEP), lupus erythematous tumidus (LET), and chilblain lupus erythematosus. CCLE subtypes are less likely to overlap with or progress to SLE compared with other CLE types (2–4); however, these subtypes pose a significant burden on individuals and the health care system. For instance, DLE, the hallmark of CCLE, represents 80% of the CLE cases seen by dermatologists (5–7). DLE is characterized by erythematous indurated plaques with adherent scales primarily on the scalp, face, and ears. Older lesions are hyperpigmented, particularly on the edge of the plaques, and often show central hypopigmentation and atrophy (8). Because DLE can cause scarring alopecia and facial disfigurement (2,5,6,9), its impact on an individual's quality of life may be substantial (10,11).

DLE has a relatively characteristic clinicopathologic description and has been recognized in individuals of all races (12–15). Although DLE is less likely to be associated with SLE (2) than with

The findings and conclusions reported herein are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

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SIGNIFICANCE & INNOVATIONS

- There are no studies that directly compare racial differences in the incidence of chronic cutaneous lupus erythematosus (CCLE) in a single population.
- The incidence of CCLE in general and discoid lupus erythematosus in particular in a large population comprised predominantly of black individuals and white individuals in the southeastern region of the US is 3-fold to 5-fold in blacks compared with whites.
- The disparities in the Georgia Lupus Registry between black individuals and white individuals in the incidence of CCLE are analogous to those described for SLE in the same geographic area, suggesting that these 2 extremes in the lupus spectrum may share common biologic and environmental pathways that contribute to the higher risk in black individuals.
- Whether black populations are also disproportionally affected by more severe CCLE phenotypes and poorer outcomes, as has been described in SLE, and whether black individuals with CCLE are at higher risk of progression from cutaneous to systemic lupus phenotypes, are questions that warrant further research.

other CLE subtypes, only a few population-based studies have estimated the incidence of DLE in the absence of SLE ("primary" DLE) (4,15–17). Early reports suggest that, similar to SLE, DLE might be more frequent among black persons compared with white persons (18). However, recent incidence estimates were higher (3.6 per 100,000 per year) in a predominantly white population of the US than in the population of persons of African descent in French Guiana, South America (nearly 2.6 per 100,000 per year) (16,17). Methodologic differences limit the comparability of both studies, and to our knowledge, no epidemiologic studies have targeted populations comprised of black individuals and white individuals to assess racial disparities in susceptibility to CCLE. We sought to determine minimum estimates for the incidence of CCLE in general, and of DLE in particular, in a population of black individuals and white individuals in the southeastern region of the US.

PATIENTS AND METHODS

Georgia Lupus Registry (GLR) data were examined to assess CCLE and DLE in the absence of SLE. The GLR is a population-based registry designed to better estimate the incidence and prevalence of SLE in a large population with a high proportion of high-risk black individuals. The GLR methodology has been described extensively (19,20). Briefly, GLR is 1 of 5 lupus registries funded by the Centers for Disease Control and Prevention (21) to conduct more reliable surveillance of lupus in the US. The GLR catchment area, Fulton and DeKalb counties in Atlanta, encompassed a population of 1.5 million people with a nearly even representation of white individuals and black individuals. The Georgia Department of Public Health (DPH) allowed Emory University to collect private health information and review medical records without patient consent, using the health surveillance exemption to the Health Insurance Portability and Accountability Act privacy rules (45 CFR parts 160 and 164), a key authorization to ascertain and validate cases on a population level. The project was approved by the Institutional Review Boards of Emory University and the Georgia DPH.

Study population and period. The study population consisted of all residents of Fulton and DeKalb counties, which are the largest counties in the Atlanta metropolitan area. The Bureau of the Census population estimate for the 2 counties in 2002 was 1,552,970, with 51.1% women, 49.3% black persons, and 46.4% white persons (21). Incidence rates for a diagnosis from January 1, 2002 through December 31, 2004 were estimated in a catchment area population of 4,742,264 person-years.

Ascertainment and validation of CCLE and DLE. Although the GLR was designed primarily to ascertain the full spectrum of SLE, registry efforts also entailed identifying and validating patients with a variety of lupus-related conditions, including primary CCLE (20). The GLR used multiple sources in the pluralistic US health care system to identify potential cases. The primary sources included hospitals as well as rheumatology, nephrology, and dermatology practices in and around the catchment area. As described elsewhere, 18 of 25 dermatology groups in the target area contributed, along with the other sources, to identifying CCLE cases (20). With the exception of 1 high-yield practice, dermatology groups that declined to contribute to the registry efforts were either cosmetically oriented practices or self-reported serve a low number of patients with CCLE. Administrative databases were queried for International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic code 695.4 (discoid lupus), in addition to code 710.0 (SLE), code 710.8 (other specified connective tissue disease), and code 710.9 (unspecified connective tissue disease). Secondary sources for ascertainment of cases of CCLE included the 2 largest dermatopathology laboratories in the target area, which were queried for ICD-9 code 695.4 or for a wide range of key words in skin pathology reports (e.g., CLE, lupus, discoid, DLE, LE, tumidus, chilblain, panniculitis, lupus profundus).

After screening for residence in the catchment counties during the target period was performed, medical records and pathology reports for an extended period of time (e.g., 2001–2005) were requested, allowing for more complete capture of clinical information. Capturing private health information was required in

order to avoid counting the same case multiple times. All available medical records for each case were fully abstracted for >200 data elements, 36 of which corresponded to cutaneous manifestations (see Manual of Standards for the Georgia Lupus Registry, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23578/abstract). Abstractors also recorded the final diagnosis stated by the attending physician, type of physician (dermatologist, rheumatologist, nephrologist, other), the earliest date of diagnosis (CCLE, SLE), fulfillment of the American College of Rheumatology (ACR) criteria for SLE (22), and the earliest date of fulfillment of each ACR criterion and occurrence of each skin manifestation. Demographic information, including race, was gathered from medical records. Detailed definitions for each data element were shown in a data dictionary. Abstractors were thoroughly trained and tested before entering the field and continued to undergo periodic quality assessments.

Case definitions. The accepted diagnosis of CCLE is based on a characteristic clinical presentation with supporting histologic features (2,8). This standard may not be achieved in every case, because a biopsy may be unnecessary, particularly when lesions are classic in appearance or are present on cosmetically sensitive areas. In such cases, the diagnosis is based solely on clinical evaluation. Therefore, the requirement for histologic confirmation of the case definition in epidemiologic studies may lead to an underestimation of the population burden posed by CCLE.

Using the classification system described by Gilliam and Sontheimer (23), we included any of the following for the definition of CCLE: DLE, lupus panniculitis, lupus profundus, lupus tumidus or chilblain lupus, or a combination of any of those conditions. Definitions of CCLE subtypes and keywords used to guide medical data abstraction are shown in Supplementary Table 1 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23578/abstract). In order to estimate the incidence of primary CCLE, we excluded patients in whom SLE was diagnosed by the treating dermatologist, rheumatologist, and/or nephrologist or fulfilled the ACR classification criteria for SLE (22) within 2 months of the initial CCLE diagnosis. Two months was chosen as an appropriate time frame for conducting clinical evaluation for possible systemic manifestations that may have occurred in association with the onset of CCLE.

CCLE cases were classified as DLE or other CCLE subtypes and subdivided into either definite or probable categories. Patients for whom a clinicopathologic or clinical diagnosis of a specific CCLE subtype was documented in the medical records were considered to have definite CCLE. Probable cases of CCLE were ascertained through a dermatopathology report, in which both the presumed clinical diagnosis by the attending dermatologists and the histopathology findings were highly suggestive of either DLE, LEP, or LET, but the original medical records from the attending dermatologist who ordered the biopsy were unavailable. Cases were preclassified as probable DLE if they were either 1) submitted by the attending dermatologist to rule out DLE and had a histologic description consistent with CLE or 2) submitted to rule out CLE, lupus, or a similar condition and had a histologic description consistent with a discoid pattern of CLE (interface dermatitis at the dermal–epidermal junction, superficial and deep dermal perivascular and periadnexal lymphocytic infiltrate, with or without increased dermal mucin, and follicular hyperkeratosis) (24). Similarly, cases with both a clinical assessment of probable CLE and a histologic description suggestive of lupus erythematosus panniculitis (lobular lymphocytic panniculitis, paraseptal lymphoid follicles, hyaline degeneration of the fat, mucin deposition, with or without overlying features of DLE) or lupus erythematosus tumidus (interstitial mucin deposition, superficial and deep dermal lymphocytic perivascular, and periadnexal infiltrate, with relative sparing of the dermal–epidermal junction) were preclassified as probable LEP or LET, respectively (24,25). Next, 2 of the authors (both dermatologists) with extensive experience in CLE (SP and LDA) reviewed the dermatopathology reports for final case validation. Incidence estimates were reported for 3 case definition categories: 1) definite DLE, 2) "combined" definite and probable DLE, and 3) "combined" definite and probable CCLE, which included definite and probable cases of all CCLE subtypes.

Statistical analysis. Crude incidence rates and 95% confidence intervals (95% CIs) as well as race- and sex-stratified incidence rates were estimated using methods based on Poisson distribution (26). The numerator consisted of patients with a first diagnosis between 2002 and 2004. Denominator data for DeKalb and Fulton counties were obtained from the postcensal population estimates for the years 2002–2004 (27). Age-adjusted estimates and 95% CIs were calculated using the standard 2000 projected age distribution by direct standardization, which calculates age-standardized rates and "exact" confidence intervals based on the gamma distribution (28). To estimate underascertainment of definite DLE cases, we conducted capture–recapture analysis accounting for the degree of overlap among multiple case-finding sources (29). Community dermatologists, community rheumatologists and other specialists, and multispecialty health care facilities (e.g., community hospitals, Emory University Health System, Grady Health System, and Kaiser Permanente) were chosen to be the primary sources of cases. Log-linear modeling was performed to estimate the number of cases with definite DLE that were missed in the registry. The best-fitting model was determined by goodness-of-fit statistics and the parsimony principle. Capture–recapture methods were implemented using the SAS GENMOD procedure.

RESULTS

Of 231 patients in whom CCLE was newly diagnosed between 2002 and 2004, 41 (17.5%) were excluded because they

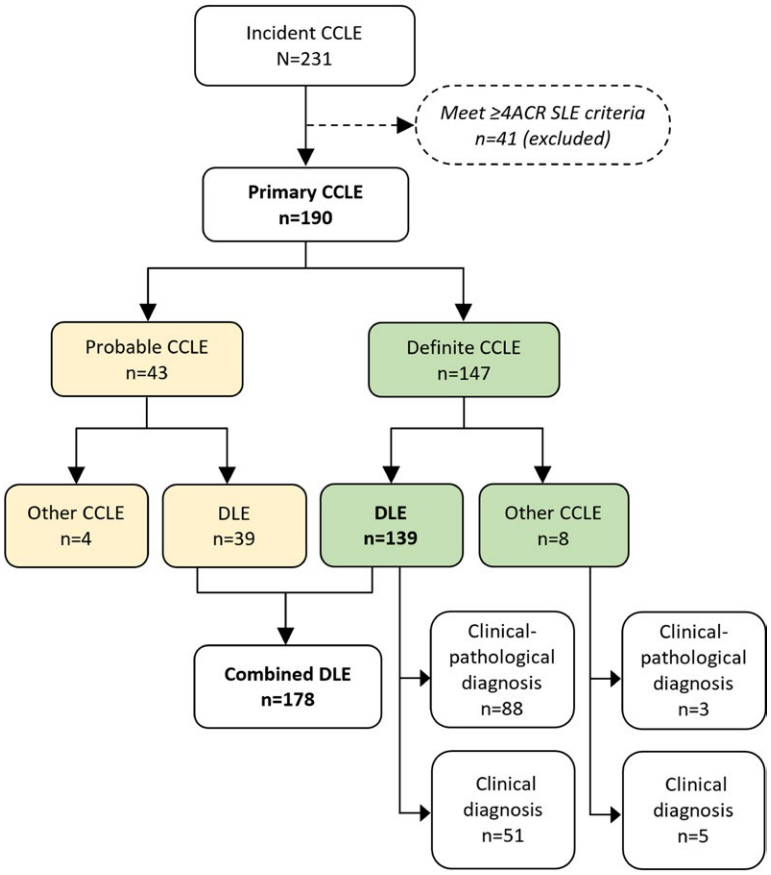

Figure 1. Flow chart showing the procedure for ascertaining and defining cases. CCLE = chronic cutaneous lupus erythematosus; ACR = American College of Rheumatology; SLE = systemic lupus erythematosus; DLE = discoid lupus erythematosus.

fulfilled ≥4 ACR criteria for SLE, and the remaining 190 patients had primary CCLE. Among these 190 patients, 147 with either a clinicopathologic or clinical diagnosis of CCLE were classified as having definite CCLE, and 43 patients in whom the diagnosis was ascertained through a pathology report were classified as having probable CCLE (Figure 1). The overlap of cases ascertained by the sources is shown in Figure 2.

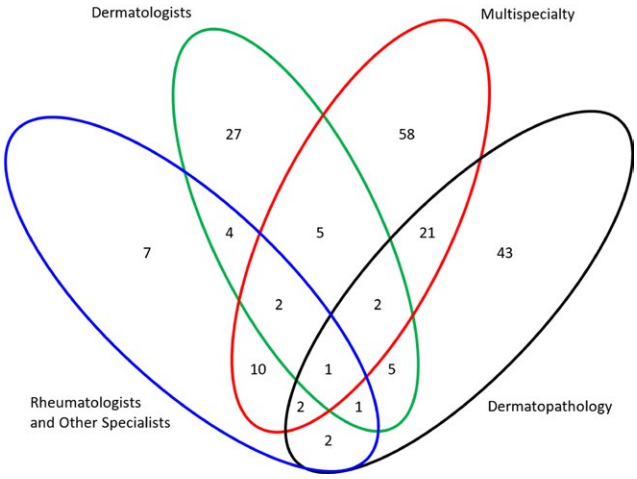

Figure 2. Venn diagram showing overlap of sources used to ascertain cases of chronic cutaneous lupus erythematosus.

Description of CCLE subtypes. *DLE*. A total of 139 patients had definite DLE, among whom 88 (63.3%) had a clinicopathologic diagnosis of DLE by a dermatologist (Figure 1). Among the other 51 patients, a clinical diagnosis of DLE was given by a dermatologist in 30 patients (21.6%), a rheumatologist in 10 patients (7.2%), and other physicians in 11 patients (7.9%). Among 43 patients with probable CCLE, 39 were classified as having DLE (Figure 1), among whom 32 (78.6%) had a clinical diagnosis of DLE by a dermatologist and a histologic description consistent with DLE (n = 31) or CLE (n = 1) (24). Among the 7 remaining patients, 5 had a clinical diagnosis of CLE. The histopathologic description was consistent with the discoid pattern of CLE as described in Patients and Methods, in all 7 patients. Overall, 178 patients had combined DLE (definite or probable).

Other CCLE subtypes. Eight patients had definite CCLE that was different from DLE: 4 had LEP (1 with skin biopsy findings consistent with LEP), 3 had LET (1 with biopsy findings consistent with LET), and 1 had a clinicopathologic diagnosis of LEP and LET. Four cases ascertained through dermatopatholo-

Table 1. Incidence rates of DLE and CCLE in Fulton County and DeKalb County, Georgia, January 1, 2002 through December 31, 2004*

		Definite DLE			Combined (definite and probable) DLE			Combined (definite and probable) CCLE		
Race/sex	Catchment area population (person-years)	No. of cases	Crude rate (95% CI)	Age-adjusted rate (95% CI)	No. of cases	Crude rate (95% CI)	Age-adjusted rate (95% CI)	No. of cases	Crude rate (95% CI)	Age-adjusted rate (95% CI)
Overall	4,742,264	139	2.9 (2.5–3.5)	2.9 (2.4–3.4)	178	3.8 (3.2–4.3)	3.7 (3.2–4.3)	190	4.0 (3.5–4.6)	3.9 (3.4–4.5)
Women	2,424,592	105	4.3 (3.6–5.2)	4.3 (3.5–5.2)	131	5.4 (4.6–6.4)	5.3 (4.5–6.3)	137	5.7 (4.8–6.7)	5.6 (4.7–6.6)
Men	2,317,672	34	1.5 (1.0–2.0)	1.4 (1.0–2.0)	47	2.0 (1.5–2.7)	1.9 (1.4–2.6)	53	2.3 (1.7–3)	2.2 (1.7–2.9)
Black	2,321,302	113	4.9 (4.0–5.9)	4.9 (4.1–5.9)	135	5.8 (4.9–6.9)	5.8 (4.9–6.9)	143	6.2 (5.2–7.3)	6.2 (5.3–7.3)
Women	1,239,819	83	6.7 (5.4–8.3)	6.6 (5.3–8.2)	100	8.1 (6.6–9.8)	7.9 (6.5–9.6)	104	8.4 (6.9–10.2)	8.3 (6.8–10)
Men	1,081,483	30	2.8 (1.9–4.0)	2.8 (1.9–4.0)	35	3.2 (2.3–4.5)	3.3 (2.4–4.5)	39	3.6 (2.6–4.9)	3.7 (2.7–5)
White	2,210,389	20	0.9 (0.6–1.4)	0.9 (0.6–1.4)	33	1.5 (1.1–2.1)	1.4 (1–2)	37	1.7 (1.2–2.3)	1.6 (1.2–2.3)
Women	1,082,131	17	1.6 (1.0–2.5)	1.6 (1–2.5)	24	2.2 (1.5–3.3)	2.2 (1.5–3.3)	26	2.4 (1.6–3.5)	2.4 (1.6–3.5)
Men	1,128,258	3	0.3 (0.1–0.8)	0.2 (0.1–0.7)	9	0.8 (0.4–1.5)	0.7 (0.4–1.4)	11	1.0 (0.5–1.7)	0.9 (0.5–1.6)

* Age-adjusted rates were determined using the projected 2000 US population. Patients with a clinical or clinicopathologic diagnosis of discoid lupus erythematosus (DLE) were considered to have definite DLE. The combined definition for DLE included cases validated as definite and those ascertained through pathology reports (probable). Combined chronic cutaneous lupus (CCLE) included either definite or probable cases with all types of CCLE, including DLE. Three cases in individuals of Asian race and 7 cases in individuals of unknown race were not included in the estimates by race.

Table 2. Incidence rates of DLE in Fulton and DeKalb counties, Georgia, January 1, 2002 through December 31, adjusted by capture–recapture methods

Race	Catchment area population (person-years)	No. of cases	Crude rate (95% CI)	Age-adjusted rate (95% CI)	Capture–recapture*	
					No. of cases missed (95% CI)	Capture–recapture–adjusted rate (95% CI)
Total	4,742,264	139	2.9 (2.5–3.5)	2.9 (2.4–3.4)	53 (23–119)	4.0 (3.5–4.7)
Black	2,321,302	113	4.9 (4–5.9)	4.9 (4.1–5.9)	35 (12–100)	6.4 (5.4–7.5)
White	2,210,389	20	0.9 (0.6–1.4)	0.9 (0.6–1.4)	6 (1–36)	1.2 (0.8–1.7)

* Values are the estimated number of definite cases of discoid lupus erythematosus (DLE) that were missed and the capture–recapture–adjusted incidence rate. 95%CI = 95% confidence interval.

gy reports were classified as probable CCLE (1 with LEP and 3 with LET). In these 4 patients, biopsies were requested in order to rule out CLE, and the histologic description and pathologist assessment were consistent with LEP and LET, as described in the Patients and Methods.

Incidence of DLE. Crude and age-adjusted incidence rates of DLE were similar, overall and across demographic categories. The age-adjusted incidence rate was 2.9 (95% CI 2.4–3.4) per 100,000 person-years for definite DLE and 3.7 (95% CI 3.2–4.3) per 100,000 person-years for combined (definite and probable) DLE (Table 1). The highest age-adjusted incidence rates for definite and combined DLE were observed among black women (for definite DLE, 6.6 [95% CI 5.3–8.2] per 100,000 person-years; for combined DLE, 7.9 [95% CI 6.5–9.6] per 100,000 person-years). The female:male ratio was 3.1 for definite DLE and 2.8 for combined DLE. The incidence of DLE was also higher among black persons, with black:white ratios of 5.4 for definite DLE and 4.1 for combined DLE. The lowest incidence rates for all categories were in white men (0.2 [95% CI 0.1–0.7] and 0.7 [95% CI 0.4–1.4] per 100,000 person-years, for definite and combined DLE, respectively). Data on race were not available in 7 individuals, who were not included in the estimates by race.

When capture–recapture methods were used, 53 additional cases of definite DLE were ascertained, rendering the age-adjusted incidence for definite DLE to 4.0 (95% CI 3.5–4.7) (Table 2). Thirty-five and 6 cases of definite DLE were missed among black persons and white persons, respectively. Capture–recapture analyses yielded incidence estimates per 100,000 person-years of 6.4 (95% CI 5.4–7.5) and 1.2 (95% CI 0.8–1.7) for black individuals and white individuals, respectively, with a black:white ratio of 5.3.

Incidence of CCLE and progression to SLE. Crude and age-adjusted incidence rates for all CCLE subtypes, including patients with definite CCLE and those with probable CCLE, were 4.0 (95% CI 3.5–4.6) and 3.9 (95% CI 3.4–4.5) per 100,000 person-years, respectively. Crude and age-adjusted rates were similar across demographic categories. The highest age-adjusted incidence rates were observed among black women (8.3 [95% CI 6.8–10] per 100,000 person-years) and the lowest rates were observed among white men (0.9 [95% CI 0.5–1.6] per 100,000 person-years). The female:male and black:white ratios were 2.5 and 3.9, respectively. In black persons, CCLE was diagnosed nearly 4 years earlier, on average, compared with white persons (P = 0.11). The mean ages of the patients at the time of onset of CCLE and DLE are shown in Table 3.

The age-specific incidence rates of combined DLE were significantly higher among black individuals ages 30–59 years compared with their white counterparts (Figure 3). Although the incidence peak in black persons was 13.7 per 100,000 person-years at ages 40–49 years, 2 incident peaks of 3.2 and 2.9 per 100,000 person-years at ages 40–49 years and ≥60 years, respectively, were observed in white persons. Moreover, age-specific incidence rates reached 10.3 per 100,000 person-years at ages 40–49 years in black women, as opposed to 2.6 and 2.5 per 100,000 person-years, at age 40–49 years and >60 years, respectively, in white women (data not shown). The incidence of DLE peaked at ages 40–49 years and 50–59 years (3.4 and 3.6

Table 3. Age at diagnosis in patients with incident DLE or CCLE, according to race*

Case definition	Black	White	P
Combined DLE			
No. of patients	135	33	
Age, mean ± SD years	43.6 ± 13.1	47.5 ± 14.2	0.13
Median (IQR)	43.6 (36.0–51.1)	44.3 (37.7–60.5)	
Range	(9.4–83.5)	(20.5–76.5)	
Combined CCLE			
No. of patients	143	37	
Age, mean ± SD years	43.9 ± 13.2	47.2 ± 14.9	0.19
Median (IQR)	43.6 (36.0–52.3)	44.3 (37.7–60.5)	
Range	(9.4–83.5)	(15.9–76.5)	

* DLE = discoid lupus erythematosus; CCLE = chronic cutaneous lupus erythematosus.

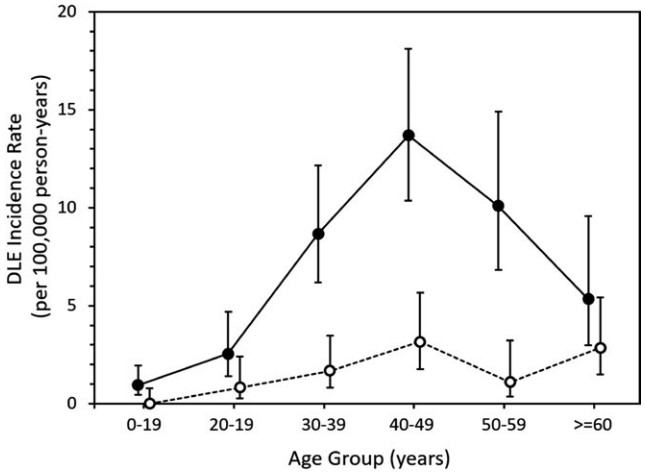

Figure 3. Incidence of discoid lupus erythematosus (DLE) according to age in black individuals (solid line) and white individuals (broken line). Circles represent the mean, the bars represent the 95% confidence intervals.

per 100,000 person-years, respectively) in black men, in contrast to ~0.5 per 100,000 person-years in all white men older than 20 years (data not shown).

Progression to SLE. Nine cases and 16 cases progressed to SLE at 1 year and 3 years since diagnosis, respectively. The progression rates were 5.3% (95% CI 2.8–10.0) and 12.3% (95% CI 7.5–20.1) at 1 year and 3 years, respectively.

DISCUSSION

This study leveraged the population-based GLR in order to provide minimum incidence estimates of CCLE in a population comprised predominantly of black individuals and white individuals in the southeastern region of the US. The overall incidence rates of definite DLE, combined DLE (definite and probable), and combined CCLE (all CCLE disorders, including definite and probable) were 2.9, 3.7, and 3.9 per 100,000 person-years, respectively. When we performed capture–recapture analysis, we observed that the number of new cases of definite DLE increased from 139 to 192, rendering an age-adjusted incidence of 4.0 per 100,000 person-years. Substantial racial disparities in susceptibility to CCLE in general, and DLE in particular, were uncovered. The black:white ratios were 3.4, 3.9, and 5.4 for combined CCLE, combined DLE, and definite DLE, respectively. Interestingly, the black:white ratio for primary CCLE reported in this study is similar to the ratio for SLE reported by our group in the same geographic area (20).

Prior population-based studies of the incidence of CCLE were conducted in 2 predominantly white populations in the US (Olmsted County, Minnesota) and Sweden, as well as in an African-descendant population in French Guiana, South America (4,16,17). The annual incidence of DLE of 1.4 per 100,000 among white individuals in our catchment area is lower than previous estimates in Sweden (3.2 per 100,000) and Olmsted County (3.6 per 100,000) (4,16). Operational differences may account for our lower estimates in white individuals. For instance, the DLE definition in the Swedish study was based on ICD Tenth Revision codes, which could lead to an overestimation of the incidence (4). In contrast, nearly 80% of DLE cases in our study were validated through medical records review. Moreover, because we targeted CCLE without coexisting SLE, we excluded cases that fulfilled the ACR criteria for the classification of SLE close to the time of the diagnosis of DLE. Such an approach differs from that used in the Swedish study, in which 24% of DLE patients had coexisting SLE (4). In contrast, data from the Rochester Epidemiology Project were used in the US study, which allows for more efficient retrieval of medical information from multiple sources for Olmsted County residents (16). Moreover, Olmsted County residents face fewer health care access barriers compared with residents of the southern states in the US. Consequently, we cannot exclude underascertainment associated with underdiagnosis as a potential explanation for the lower incidence of CCLE among white persons in our study. Additionally, variability in biologic factors (e.g., DNA methylation) and environmental factors (e.g., sun exposure, early diagnosis/treatment) between populations and geographic areas can account for differences in estimates of the incidence of DLE (30). Notably, the incidence of CCLE in the black population in Atlanta was 6.2, as opposed to an incidence of 2.6 in French Guiana, where 90% of the population are of African descent (17). However, methodologic differences limit the comparability of these studies, and whether socioenvironmental factors play a role in the higher risk of CCLE in black persons from the southeast region of the US deserve further research.

Our findings suggest that disparities between black individuals and white individuals may also occur in relation to age at diagnosis, with black persons tending to develop CCLE at an earlier age compared with white persons, as noted with SLE in the same population (20). The incidence rates of combined DLE in black individuals ages 30–59 years were significantly higher than those in their white counterparts. However, the difference in the mean age at the time of DLE diagnosis according to race (43.6 years and 47.5 years for black individuals and white individuals, respectively) was not statistically significant, which can be potentially explained by the small number of white persons in our registry. The mean ages at DLE diagnosis were 48.5 years and 53 years in the predominantly white populations of Olmstead County and Sweden, respectively (4,16) and 32 years in the population of persons of African descent in French Guiana (17). These findings support racial differences in the natural history of primary CCLE, which are analogous to the differences in SLE.

The overall incidence rates of CCLE in general, and DLE in particular, are relatively lower than the rates that we recently reported for SLE in the same catchment area (20). Although the GLR overall age-adjusted incidence rate for SLE was 5.6 per

100,000 person-years, the rates for DLE and CCLE were 3.7 and 3.9 per 100,000 person-years, respectively. Our findings differ from those observed in the largely white population in Olmsted County, where the incidence of CLE and SLE were similar (15). However, in addition to CCLE, the study in Olmsted County targeted bullous lupus erythematosus and SCLE, both of which are conditions linked to the HLA–B8;DR3 haplotype, which in turn disproportionately affects white individuals (31).

Other factors can potentially explain the relatively lower incidence of primary CCLE compared with SLE in the GLR catchment area. First, socioenvironmental factors might increase the risk of coexisting SLE and CCLE or progression from primarily cutaneous to systemic phenotypes (30). GLR data support a higher rate of progression from primary CCLE to SLE in our catchment area compared with Olmsted County (16,32). While the 5-year cumulative incidence of SLE among patients with primary CLE in Olmsted County was 5% (31), we reported 5% and 12% SLE progression at 1 and 3 years, respectively. Additionally, 15% of patients with incident SLE ascertained in our catchment area had coexisting DLE, as opposed to only 7% in Olmsted Country (16,20). Second, disproportionately greater underascertainment may have occurred for CCLE/DLE than SLE in our study. Although the majority of collaborating facilities focused on medical dermatology, cosmetic practices were not included as sources for case finding, potentially leading to missed cases. Underascertainment may also have occurred because dermatology offices were contacted for case finding between 4 years and 6 years after the surveillance dates of interest. This time discrepancy may have resulted in underreporting of CCLE cases due to limited accessibility of records. To overcome this limitation, we conducted capture–recapture analysis. This method rendered an overall age-adjusted incidence of definite DLE of 4.0 per 100,000 person-years. The numbers of cases missed were estimated to be 35 and 6 among black persons and white persons, respectively, which increases the incidence of definite DLE from 4.0 to 6.5 and from 0.9 to 1.2 among black individuals and white individuals, respectively. The black:white ratio after adjustment remained >5, which stresses the greater predisposition for this condition among black persons.

Third, because GLR data were collected from medical records, we cannot exclude the possibility that some patients with overlapping CCLE and SLE may have been misclassified as having primary CCLE. However, data abstraction entailed periodic audits to ensure consistency and accuracy in abstracting ACR criteria and other clinical data. Additionally, almost all rheumatology practices in the catchment area served as sources of cases, and all available medical records for each incident case were fully abstracted. As a result, the number of underreported cases of incident SLE rendered by capture–recapture methods was very low (n = 31), suggesting that the majority of cases of overlapping SLE and CCLE were captured by GLR methods (20).

Fourth, because our case definition relied on medical records review, and we assumed that attending physicians knew how to differentiate CCLE/DLE from other major forms of CLE and other autoimmune conditions, we cannot exclude the possibility that CCLE cases were misclassified. However, these are limitations of population-based studies in general, in which assessment by individual study physicians is not feasible (13,15–17,33). Additionally, although clinical or clinical/histologic documentation of the diagnosis of CCLE was obtained in nearly 80% of our patients, medical records were unavailable for 43 patients who were further classified and analyzed separately as having probable CCLE based on data from dermatopathologist reports. Fifth, patients with SCLE were not included, because only 8 patients with a dermatologist-confirmed diagnosis of primary SCLE were identified. Sixth, it is possible that DLE in white individuals may have been underdiagnosed by physicians, which is a diagnostic challenge faced by many clinicians. Additionally, we cannot exclude underascertainment of white persons with CCLE due to lower participation of dermatology practices located in areas with higher concentration of white persons. Finally, the results of this study are best generalized to white individuals and black individuals in the southeastern region of the US. Because race was assigned based primarily on the physician's assessment documented in the medical record, it may not reflect the patient's true self-identity, particularly among multiracial individuals.

Our study has several strengths. First, this is the first report of the incidence of primary CCLE and the DLE subtype in a large population of black individuals and white individuals from the same geographic area. With the exception of a study in French Guiana (17), prior epidemiologic studies have focused on overall CLE and targeted primarily populations of white individuals. Furthermore, the GLR allowed for acquisition of clinical data (including the earliest date of fulfillment of each ACR criteria) from medical records across multiple facilities, reducing misclassification of incident cases of SLE as primary CCLE and vice versa. Moreover, most facilities provided medical records for an extended period (i.e., 2001–2005), and all available medical charts from multiple sources were fully abstracted. Thus, our efforts entailed the collection of comprehensive clinical information from the time of disease onset through December 31, 2004, potentially reducing loss to follow-up. The GLR also cross-references records from multiple sources, avoiding double counting of cases.

In conclusion, this is the first epidemiologic study of primary CCLE in a population comprised predominantly of black individuals and white individuals and shows that CCLE disproportionately affects black individuals, paralleling the disparities observed in SLE in this region (20) and other US populations (30,34).

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. Drenkard 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. Drenkard, Parker, Aspey, Lim.

Acquisition of data. Drenkard, Parker, Aspey, Gordon, Helmick, Bao, Lim.
Analysis and interpretation of data. Drenkard, Parker, Aspey, Gordon, Helmick, Bao, Lim.

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Lipid Testing and Statin Prescriptions Among Medicaid Recipients With Systemic Lupus Erythematosus or Diabetes Mellitus and the General Medicaid Population

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Objective. Cardiovascular disease (CVD) risks in systemic lupus erythematosus (SLE) are similar to those in diabetes mellitus (DM). We investigated whether the numbers of lipid tests and statin prescriptions in patients with SLE are comparable with those in patients with DM and those in individuals without either disease.

Methods. Using Analytic eXtract files from 29 states for 2007–2010, we identified a cohort of US Medicaid beneficiaries, ages 18–65 years, with prevalent SLE. Each SLE patient was matched for age and sex with 2 patients with DM and 4 individuals in the general Medicaid population who did not have either SLE or DM. We compared the proportions of patients in each cohort who received ≥1 lipid test and ≥1 statin prescription during 1-year follow-up. We used multivariable logistic regression to calculate the odds of lipid testing and receiving prescriptions for statins and conditional logistic regression to compare the matched cohorts.

Results. We identified 3 Medicaid cohorts: 25,950 patients with SLE, 51,900 patients with DM, and 103,800 Medicaid recipients without either condition. In these cohorts, lipid testing was performed in 24% of patients in the SLE group, 43% of patients in the DM group, and 16% of individuals in the group with neither condition, and statin prescriptions were dispensed in 11%, 33%, and 7% of these groups, respectively. SLE patients were 66% less likely (odds ratio [OR] 0.34, 95% confidence interval [95% CI] 0.34–0.35) to have lipid tests and 82% less likely (OR 0.18, 95% CI 0.18–0.18) to fill a statin prescription compared with DM patients. SLE patients were also less likely (OR 0.89, 95% CI 0.84–0.94) to fill a statin prescription compared with individuals in the general Medicaid population.

Conclusion. Despite having an elevated risk of CVD, SLE patients received less lipid testing and received fewer statin prescriptions compared with age- and sex-matched DM patients and individuals in the general Medicaid population; this gap should be a target for improvement.

INTRODUCTION

Systemic lupus erythematosus (SLE), a multisystem autoimmune disease that affects young individuals (the vast majority of whom are women), is associated with high rates of atherosclerotic cardiovascular disease (CVD). In multiple previous epidemiologic studies, the estimated risks of myocardial infarction and stroke were 2–3-fold higher in patients with SLE compared with the risks in the general population (1). SLE patients were recently shown to have a higher risk of CVD compared with age- and sex-matched patients with diabetes mellitus (DM), which is a population with a very high risk of CVD (2,3). Given the greatly increased CVD risk in DM patients, DM is considered to be an independent CVD risk factor, and aggressive risk assessment with annual lipid screening and hydroxymethylglutaryl-coenzyme A reductase inhibitor ("statin") prescription has led to improvements in CVD morbidity and mortality (4,5). The proportion of DM patients receiving recommended lipid testing has been reported to be as high as 87% among patients seen in academic centers from 2000 to 2002 (6).

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SIGNIFICANCE & INNOVATIONS

- The risk of cardiovascular disease (CVD) in patients with systemic lupus erythematosus (SLE) is similar to that in age- and sex-matched patients with diabetes mellitus, but whether CVD risk assessment and management are performed in SLE patients is unknown.
- In this large cohort study, only 24% of US Medicaid recipients with SLE received lipid testing over a 1-year follow-up period.
- SLE patients were 66% less likely to have lipid testing and 82% less likely to fill a statin prescription compared with age- and sex-matched patients with diabetes mellitus.
- Our study results demonstrate that despite expert opinion–based recommendations for annual assessment for the risk of CVD, the rates of preventive care among Medicaid recipients with SLE was low.

Aggressive management of traditional CVD risk factors in patients with SLE has been widely advocated, but it is not known how well this guidance has been accepted (7,8). In a 2009 expert opinion–based quality indicator set for SLE management, annual assessments of CVD risk factors, including annual lipid measurements, were recommended (8). Previous studies showed that provision of care based on these recommendations was suboptimal in academic centers (9–11). Use of statins has been strongly advocated and has been shown to be safe in SLE patients who are not pregnant (12). Statins have both lipid-lowering and antiinflammatory effects and are likely to be beneficial for CVD prevention in SLE, although the evidence from randomized trials is still not decisive (13).

The aim of the current study was to examine whether the rates of lipid testing and dispensing of prescriptions for statins in SLE patients were comparable with those in age- and sex-matched patients with DM and in Medicaid recipients who did not have SLE or DM. Medicaid is the US health insurance program for individuals with low income and resources and provides coverage for medical expenses and prescription drugs. We hypothesized that despite the greatly increased risk of CVD in SLE patients, the rates of lipid testing and dispensing of prescriptions for statins would be lower than those in age- and sex-matched patients with DM, revealing poor acceptance of and adherence to expert opinion–based recommendations.

PATIENTS AND METHODS

Study population and cohort assembly. Within Medicaid Analytic eXtract (MAX), a database that includes billing claims, demographic information, and data regarding medication dispensing, we identified adults ages 18–65 years from the 29 most populated states in the US who were enrolled in Medicaid for ≥18 months between January 1, 2007 and December 31, 2010.

Prevalent SLE cohort. Individuals were classified as having prevalent SLE if they had ≥3 visits ≥30 days apart with an International Classification of Diseases, Ninth Revision (ICD-9) code for SLE (710.0) from hospital discharge diagnoses or physician visit claims, as in prior studies (14,15). In the current study, a 6-month period of continuous enrollment was required for collection of baseline covariable data prior to the index date (date on which the criteria for SLE were met) as well as ≥12 months of continuous follow-up for assessment of outcomes after the index date. In the event that the date of the third ICD-9 code occurred before the 6-month baseline period could be established, the next SLE-related claim that would allow for a 6-month baseline period was used to define the index date. Patients with ICD-9 codes for pregnancy during the follow-up period were excluded, because statins are contraindicated in during pregnancy. Among patients with SLE, those with lupus nephritis were identified by the presence of ≥2 ICD-9 hospital discharge diagnoses or physician billing claims for nephritis, proteinuria, and/or renal failure, occurring ≥30 days apart, on or after the SLE criteria were met (16,17).

Age- and sex-matched prevalent DM cohort and general Medicaid population cohort. We identified patients with prevalent DM (type 1 or type 2) as those having ≥3 ICD-9 codes for DM (249.XX, 250.XX, 357.2, 362.01–362.06, 366.41) from hospital discharge diagnoses or physician visit claims, each separated by ≥30 days, without any claims for SLE (18,19). We required 6 months of continuous enrollment prior to the index date, which was defined as the baseline period. The index date was the date of the third ICD-9 code, or in the event that the date of the third ICD-9 coding occurred before the 6-month baseline period could be established, the next DM-related claim thereafter that would allow for a 6-month baseline period was used to define the index date. Among the DM patients, those with diabetic nephropathy were defined as having ≥2 ICD-9 hospital discharge or physician billing codes for nephritis, proteinuria, and/or renal failure ≥30 days apart on or after the criteria for DM were met (20).

We also identified age- and sex-matched individuals in the general Medicaid population who had ICD-9 codes for any non-SLE or non-DM diagnoses from hospital discharge diagnoses or physician visit claims on the same index date as that for each SLE patient, with 6 months of continuous enrollment prior to the index date defined as the baseline period. Patients with ICD-9 codes for either SLE or DM during the baseline period were excluded from this cohort.

We required that all individuals were continuously enrolled in Medicaid for ≥12 months prior to the index date. Patients with

ICD-9 codes for pregnancy during the follow-up period were excluded. We then used a greedy algorithm to match each SLE patient, according to age at the index date and sex, with 2 DM patients and 4 patients in the general Medicaid population (21).

Data collection. Characteristics of the patients in all cohorts were collected during the baseline period: age, sex, self-reported race/ethnicity, US region of residence, and zip code–level socioeconomic status in quartiles, using median household income from 2007 to 2010 US Census data as a proxy. Using ICD-9 codes, diagnosis-related group codes, and/or Current Procedural Terminology (CPT) codes, we collected covariables during the baseline period, including the number of outpatient physician visits, smoking, obesity, and hypertension. Hyperlipidemia was defined by ICD-9 codes, without accounting for lipid-lowering medication (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23584/abstract). CVD at baseline was defined as the presence of any of the following covariables during the baseline period: acute myocardial infarction (MI), old MI, angina, percutaneous coronary intervention, coronary atherosclerosis, coronary artery bypass graft, cerebrovascular accident, peripheral vascular disease, carotid artery stenosis, and heart failure (see Supplementary Table 1).

We calculated a Charlson comorbidity index for all patients and an SLE-specific risk adjustment index for SLE patients (22). We identified filled prescriptions using National Drug Codes (NDCs) and summed the number of unique medication prescriptions filled per subject during the baseline period. For SLE patients, we assessed baseline prescriptions for glucocorticoids (prednisone, methylprednisolone, dexamethasone, hydrocortisone, prednisolone, and cortisone, which are defined as prednisone equivalents), hydroxychloroquine, and immunosuppressive drugs (mycophenolate mofetil, mycophenolic acid, cyclophosphamide, azathioprine, cyclosporine, methotrexate, leflunomide, rituximab, and tacrolimus). We assessed the number of insulin prescriptions that were filled during the baseline period. We used NDCs to assess the use of statins at baseline, which may alter the frequency of lipid testing. We used CPT codes to identify lipid testing in billing claims and NDCs to identify dispensing of statin prescriptions at both baseline and during follow-up in all subjects (23).

Statistical analysis. We examined the sociodemographic and clinical characteristics of patients in each cohort and compared these using descriptive statistics. We calculated the proportion of patients in each cohort who received ≥1 lipid test and for whom ≥1 statin prescription was dispensed during the 12-month follow-up period, and compared these proportions using chi-square tests. In the SLE cohort, we examined the odds ratios (ORs) for lipid testing and dispensing of statin prescriptions, using multivariable logistic regression analysis, with adjustment for age, sex, race/ethnicity, US region of residence, socioeconomic status, number of medications, number of outpatient visits, glucocorticoid use, SLE risk adjustment index (22), baseline CVD, and lupus nephritis. We conducted similar logistic regression analyses in the DM cohort, with adjustment for age, sex, race/ethnicity, US region of residence, socioeconomic status, number of medications, number of outpatient visits, insulin use, Charlson comorbidity index, baseline CVD, and diabetic nephropathy. Similar logistic regression analyses were conducted in the general Medicaid population cohort, with adjustment for the same factors except insulin use and nephropathy.

In analyses comparing lipid testing and statin prescription fill rates in age- and sex-matched SLE, DM, and general Medicaid population cohorts, conditional logistic regression analyses were used to preserve the matching. Sensitivity analyses were performed in separate logistic regression analyses, with adjustment for the matching factors and including only patients with CVD at baseline, or excluding patients with CVD, those who had lipid testing, and those who received statin prescriptions at baseline.

All analyses were conducted using SAS version 9.4. Data were obtained from the Centers for Medicare and Medicaid Services (CMS) through an approved data use agreement; cell sizes <11 were suppressed, in accordance with CMS policies. The Partners' Healthcare Institutional Review Board approved this study.

RESULTS

Cohort sociodemographic and clinical characteristics. The SLE cohort included 25,950 patients, 92% of whom were female, with a mean ± SD age of 41.4 ± 11.9 years (Table 1). The age- and sex-matched DM cohort was comprised of 51,900 patients, and the matched general Medicaid population cohort was comprised of 103,800 individuals. During the cohort selection process, 5,580 patients fulfilled the criteria for both the SLE and DM cohorts and were not included in either cohort. The SLE cohort included a higher proportion of African American patients compared with the DM and general Medicaid population cohorts. The geographic distribution was similar in the SLE and DM cohorts, but the general Medicaid population cohort included more patients in the West and fewer patients in the South.

The prevalence of CVD at baseline was 14% in the SLE cohort, 13% in the DM cohort, and was lowest in the general Medicaid population (4%) ($P < 0.001$). A higher proportion of patients in the SLE cohort had renal involvement: 21% of the SLE patients had lupus nephritis, and 7% of the DM patients had diabetic nephropathy according to our definitions ($P < 0.001$). Hypertension was prevalent in both the SLE and DM cohorts (35% and 41%, respectively; $P < 0.001$), and obesity and hyperlipidemia as identified by ICD-9 codes were more prevalent in the DM cohort and less prevalent in the general Medicaid population (Table 1).

Lipid testing and statin prescriptions in each cohort. Overall, 24% of the patients in the SLE cohort, 43% of patients in the DM cohort, and 16% of the age- and sex-matched individuals

Table 1. Baseline characteristics of patients with SLE, age- and sex-matched patients with DM, and age- and sex-matched general Medicaid cohorts*

	SLE (n = 25,950)	DM (n = 51,900)	General Medicaid (n = 103,800)
Female sex	23,903 (92)	47,806 (92)	95,612 (92)
Age, mean ± SD years	41.4 ± 11.9	41.4 (+11.9)	41.4 (11.9)
Age range			
18–39 years	11,674 (45.0)	23,295 (45)	46,646 (45)
40–49 years	7,305 (28)	14,636 (28)	29,259 (28)
50–65 years	6,971 (27)	13,969 (27)	27,895 (27)
No. of outpatient visits, mean ± SD	4.5 ± 4.6	3.5 ± 3.9	1.8 ± 2 .9
US region of residence			
West	5,352 (21)	10,023 (19)	28,888 (28)
Northeast	5,567 (21)	10,657 (21)	22,162 (21)
South	9,975 (38)	19,789 (38)	30,810 (30)
Midwest	5,056 (19)	11,431 (22)	21,940 (21)
Race/ethnicity			
White	8,944 (35)	24,001 (46)	49,855 (48)
African American	11,108 (43)	15,835 (31)	23,430 (23)
Hispanic	4,072 (16)	8,311 (16)	23,640 (23)
Asian	805 (3)	1,554 (3)	3,061 (3)
American Indian/Alaska Native	262 (1)	638 (1)	985 (1)
Lupus nephritis/diabetic nephropathy	5,333 (21)	3,606 (7)	
Baseline comorbidities			
Hypertension	8,978 (35)	21,018 (41)	13,686 (13)
Obesity	924 (4)	5,650 (11)	2,445 (2)
Hyperlipidemia	2,532 (10)	12,624 (24)	6,524 (6)
Smoking	1,564 (6)	2,855 (6)	4,229 (4)
Presence of CVD†	3,729 (14)	6,628 (13)	4,541 (4)
Total no. of medications, mean ± SD	10.1 ± 9.4	10.6 ± 9.7	3.6 ± 5.6
Hydroxychloroquine	9,795 (38)	130 (<1)	173 (<1)
Immunosuppressant agent‡	5,580 (22)	516 (1)	517 (1)
Glucocorticoid ≥10 mg/day ever	10,071 (39)	3,603 (7)	4,400 (4)
Insulin	117 (1)	13,405 (26)	
Risk adjustment index for SLE, mean ± SD	1.0 ± 1.9		
Charlson Comorbidity Index, mean ± SD	1.8 ± 1.3	1.7 ± 1.3	0.4 ± 1.2
Baseline lipid testing	4,590 (18)	18,294 (35)	10,082 (10)
Baseline statin prescription	2,204 (9)	13,605 (26)	4,457 (4)

* The baseline period was defined as 6 months of continuous Medicaid enrollment prior to the index date. For patients with systemic lupus erythematosus (SLE) and patients with diabetes mellitus (DM), the index date was defined as the date on which the International Classification of Diseases, Ninth Revision (ICD-9) criteria for either SLE or DM were met (3 codes, each ≥30 days apart). For the general Medicaid cohort, the index date was defined as the date of any ICD-9 code for non-SLE and non-DM diagnoses on same index date as each age- and sex-matched SLE patient. Except where indicated otherwise, values are the number (%).

† Baseline presence of any cardiovascular disease (CVD) according to ICD-9 codes for angina, myocardial infarction (MI), old MI, percutaneous coronary intervention, atherosclerosis, cardiovascular accident, coronary artery bypass graft, peripheral vascular disease, carotid stenosis, or heart failure.

‡ Including mycophenolate mofetil, mycophenolic acid, cyclophosphamide, azathioprine, cyclosporine, methotrexate, leflunomide, rituximab, and tacrolimus.

Table 2. Proportions of patients in all cohorts who had ≥1 lipid test during the 1-year observation period, overall and stratified by baseline covariables*

	SLE (n = 25,950)	DM (n = 51,900)	General Medicaid (n = 103,800)
Overall, no. (%)	6,310 (24)	22,389 (43)	16,454 (16)
Sex			
Female	24	43	16
Male	23	41	16
Age range			
18–39 years	22	42	10
40–49 years	25	45	19
50–65 years	28	44	22
Outpatient visits†			
High	32	54	20
Low	14	25	10
Race/ethnicity			
White	23	41	16
African American	22	39	16
Hispanic	29	52	14
Asian	37	63	26
American Indian/Alaska Native	19	35	13
US region of residence			
West	29	52	13
Northeast	25	44	19
South	25	43	18
Midwest	20	35	14
Socioeconomic status			
Quartile 1	23	43	18
Quartile 2	24	42	16
Quartile 3	25	44	16
Quartile 4	25	44	14
Lupus nephritis/diabetic nephropathy	27	38	
Cardiovascular disease			
Present	28	45	33
Not present	24	43	15
No. of medications†			
High	35	57	24
Low	14	31	9
Charlson comorbidity index†			
High	27	43	24
Low	23	43	14
Glucocorticoid use ≥10 mg/day ever			
Yes	31	54	27
No	20	42	15

* Proportion is defined as the percentage of patients in the cohort who received lipid testing during 1-year follow-up from index date (e.g., 24% of female patients in the systemic lupus erythematosus [SLE] cohort received lipid testing during 1-year follow-up from the index date). DM = diabetes mellitus.
† High = greater than or equal to the median; low = lower than the median.

Table 3. Proportion of patients who received ≥1 statin prescription during the 1-year observation period in all cohorts, overall and stratified by covariables*

	SLE (n = 25,950)	DM (n = 51,900)	General Medicaid (n = 103,800)
Overall, no. (%)	2,777 (11)	17,045 (33)	6,926 (7)
Sex			
Female	11	33	7
Male	12	31	7
Age range			
18–39 years	7	24	1
40–49 years	10	38	7
50–65 years	17	43	15
Outpatient visits†			
High	14	39	8
Low	7	23	4
Race/ethnicity			
White	11	31	7
African American	10	29	7
Hispanic	11	40	4
Asian	16	51	9
American Indian/Alaska Native	6	29	5
US region of residence			
West	11	37	4
Northeast	12	38	8
South	10	29	8
Midwest	12	31	8
Socioeconomic status			
Quartile 1	11	33	8
Quartile 2	10	32	7
Quartile 3	11	33	6
Quartile 4	11	34	6
Lupus nephritis/diabetic nephropathy	17	35	
Cardiovascular disease			
Present	22	44	30
Not present	9	31	6
No. of medications†			
High	18	49	12
Low	4	19	2
Charlson comorbidity index†			
High	14	34	14
Low	8	32	5
Glucocorticoid use ≥10 mg/day ever			
Yes	15	42	15
No	8	32	6

* Proportion is defined as the percentage of patients in the cohort who received a statin prescription during 1-year follow-up from the index date (e.g., 11% of female patients in the systemic lupus erythematosus [SLE] cohort received a statin prescription during 1-year follow-up from the index date). DM = diabetes mellitus.
† High = greater than or equal to the median; low = less than the median.

in the general Medicaid population cohort had received ≥1 lipid test during the 1-year observation period (Table 2). In all age categories, more DM patients than SLE patients received lipid testing ($P < 0.001$). The proportion of SLE patients who underwent lipid testing increased with increasing age, whereas the proportion of patients in the DM cohort who had ≥1 lipid test did not. The proportion of SLE patients for whom ≥1 statin prescription was dispensed during the 1-year observation period was 11% compared with 33% of the DM patients ($P < 0.001$) (Table 3). Among individuals in the general Medicaid population, 7% had ≥1 statin prescription dispensed. In all age categories, a higher proportion of DM patients compared with SLE patients received prescriptions for statins ($P < 0.001$). A higher proportion of patients with renal involvement had ≥1 statin prescription: 17% of those with lupus nephritis compared with 11% of those with SLE ($P < 0.001$) and 35% of those with diabetic nephropathy (compared with 33% of those with DM; $P = 0.001$).

Among patients in the SLE cohort, increased odds of having lipid testing were associated with older age, more outpatient visits and number of medications, glucocorticoid use, and presence of lupus nephritis (Table 4). The odds of undergoing lipid testing were higher in Asian (OR 1.86, 95% CI 1.58–2.19), Hispanic (OR

Table 4. Multivariable logistic regression analyses for the odds of lipid testing and receipt of statin prescriptions in the SLE cohorts*

	Lipid testing			Statin prescription		
	Overall SLE cohort (n = 25,950)†	Patients with baseline CVD excluded (n = 22,221)‡	Patients with baseline CVD (n = 3,729)‡	Overall SLE cohort (n = 25,950)†	Patients with baseline CVD excluded (n = 22,221)‡	Patients with baseline CVD (n = 3,729)‡
Age group						
18–39 years	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
40–49 years	1.28 (1.19–1.38)	1.27 (1.17–1.37)	1.38 (1.23–1.69)	1.71 (1.53–1.91)	1.71 (1.51–1.95)	1.68 (1.33–2.12)
50–65 years	1.57 (1.46–1.69)	1.57 (1.45–1.71)	1.58 (1.30–1.92)	3.15 (2.83–3.50)	3.42 (3.03–3.86)	2.41 (1.93–3.01)
Sex						
Female	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Male	1.04 (0.93–1.17)	1.02 (0.90–1.16)	1.12 (0.88–1.44)	1.23 (1.06–1.43)	1.23 (1.03–1.47)	1.20 (0.91–1.57)
Race/ethnicity						
White	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
African American	1.09 (1.01–1.18)	1.10 (1.02–1.19)	1.04 (0.87–1.26)	0.87 (0.79–0.97)	0.90 (0.79–1.01)	0.81 (0.66–0.99)
Hispanic	1.37 (1.25–1.50)	1.37 (1.24–1.52)	1.34 (1.05–1.72)	1.06 (0.93–1.21)	1.11 (0.95–1.29)	0.93 (0.71–1.23)
Asian	1.86 (1.58–2.19)	1.85 (1.56–2.20)	1.88 (1.15–3.06)	1.56 (1.25–1.95)	1.68 (1.32–2.14)	1.08 (0.62–1.87)
American Indian/ Alaskan Native	0.74 (0.54–1.03)	0.80 (0.57–1.12)	0.35 (0.10–1.25)	0.57 (0.34–0.96)	0.58 (0.33–1.03)	0.51 (0.14–1.81)
No. of outpatient visits	1.06 (1.05–1.07)	1.06 (1.05–1.07)	1.06 (1.05–1.08)	1.00 (0.99–1.01)	0.99 (0.98–1.00)	1.02 (1.00–1.03)
No. of medications	1.04 (1.04–1.05)	1.04 (1.04–1.05)	1.05 (1.04–1.06)	1.07 (1.06–1.07)	1.07 (1.06–1.07)	1.06 (1.05–1.07)
Glucocorticoid use ≥10 mg/ day ever	1.07 (1.00–1.15)	1.09 (1.01–1.17)	1.01 (0.84–1.20)	1.22 (1.11–1.34)	1.21 (1.08–1.35)	1.24 (1.02–1.50)
SLE risk adjustment index	0.98 (0.96–1.00)	0.98 (0.95–1.00)	0.98 (0.95–1.01)	0.98 (0.96–1.01)	1.00 (0.97–1.04)	0.98 (0.95–1.01)
Presence of CVD	1.06 (0.97–1.17)	–	–	2.04 (1.82–2.29)	–	–
Presence of LN	1.39 (1.29–1.51)	1.44 (1.32–1.57)	1.22 (1.02–1.47)	2.39 (2.16–2.65)	2.88 (2.55–3.24)	1.44 (1.18–1.75)

* Values are the odds ratio (95% confidence interval).
† Multivariable logistic regression analysis adjusted for age, sex, race, US region of residence, socioeconomic status, number of outpatient visits, number of medications, glucocorticoid use, systemic lupus erythematosus (SLE) risk adjustment index, presence of cardiovascular disease (CVD), and presence of lupus nephritis (LN).
‡ Multivariable logistic regression model adjusted for the same covariables as the overall cohort except for the presence of CVD.

Table 5. Odds of lipid testing in patients with in SLE patients with DM compared with the odds in the general Medicaid population, overall and stratified according to age and baseline CVD status*

	No. of patients	General Medicaid, ref.	SLE, OR (95% CI)	DM, OR (95% CI)
Overall	181,650	1.0	0.96 (0.92–1.00)	2.79 (2.71–2.87)
Age group				
Ages 18–39 years	81,615	1.0	1.31 (1.23–1.40)	4.22 (4.02–4.44)
Ages 40–49 years	51,200	1.0	0.83 (0.78–0.89)	2.39 (2.26–2.51)
Ages 50–65 years	48,835	1.0	0.77 (0.71–0.82)	1.89 (1.80–2.00)
Excluding baseline CVD	166,752	1.0	0.98 (0.94–1.03)	2.98 (2.89–3.07)
With baseline CVD	14,898	1.0	0.55 (0.49–0.61)	1.26 (1.15–1.38)

* Conditional multivariable logistic regressions with all 3 cohorts (systemic lupus erythematosus [SLE], diabetes mellitus [DM], and general Medicaid population) combined, adjusted for age, sex, race, US. Region of residence, socioeconomic status, number of outpatient visits, number of medications, Charlson comorbidity index, presence of cardiovascular disease (CVD), lupus nephritis/diabetic nephropathy overall and stratified according to age group and by baseline CVD status (without adjustment for the presence of CVD when stratified according to baseline CVD status). OR = odds ratio; 95% CI = 95% confidence interval.

1.37, 95% CI 1.25–1.50), and African American (OR 1.09, 95% CI 1.01–1.18) patients compared with white patients. Older age, Asian race, a greater number of medications, glucocorticoid use, and lupus nephritis were associated with increased odds of receiving a statin prescription, as was baseline CVD (Table 4). In multivariable models within the SLE cohort, lupus nephritis was associated with a higher odds of lipid testing (OR 1.39, 95% CI 1.29–1.51) and receipt of a statin prescription (OR 2.39, 95% CI 2.16–2.65), and within the DM cohort, diabetic nephropathy was associated with a slight increase in lipid testing (OR 1.09, 95% CI 1.01–1.18) and receipt of a statin prescription (OR 1.15, 95% CI 1.06–1.25) (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23584/abstract). Factors associated with lipid testing and statin prescription in the DM and general Medicaid population cohorts are shown in Supplementary Tables 2 and 3 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23584/abstract). The associations were similar in sensitivity analyses that excluded patients with baseline CVD (Table 4), baseline lipid testing, or baseline statin use, in separate models.

Lipid testing and statin use across cohorts. In multivariable conditional logistic regression analyses, compared with age- and sex-matched DM patients, SLE patients were 66% less likely to have lipid testing (OR 0.34, 95% CI 0.34–0.35), and 82% were less likely to have a statin prescription dispensed during the 12-month period (OR 0.18, 95% CI 0.18–0.18). The results remained similar in sensitivity analyses excluding patients with baseline CVD, baseline lipid testing, and baseline statin use in separate models. Compared with the general Medicaid population, SLE patients had similar odds of lipid testing but were less likely to have a statin prescription dispensed during the 12-month period (OR 0.89, 95% CI 0.84–0.94). On the contrary, compared with the general Medicaid population, DM patients had 2.79 increased odds of having lipid tests (95% CI 2.71–2.87) and 4.93 increased odds of having a statin prescription dispensed (95% CI 4.75–5.11). In examinations of age-stratified groups, both

Table 6. Odds of receiving a statin prescription in patients with DM, patients with SLE, and individuals in the general Medicaid population, overall and stratified according to age group and baseline CVD status*

	No. of patients	General Medicaid, ref.	SLE, OR (95% CI)	DM, OR (95% CI)
Overall	181,650	1.0	0.89 (0.84–0.94)	4.93 (4.75–5.11)
Age group				
18–39 years	81,615	1.0	2.52 (2.23–2.84)	13.66 (12.46–14.97)
40–49 years	51,200	1.0	0.87 (0.79–0.96)	5.60 (5.24–5.97)
50–65 years	48,835	1.0	0.58 (0.53–0.63)	2.83 (2.67–2.99)
Excluding baseline CVD	166,752	1.0	0.91 (0.86–0.97)	5.83 (5.60–6.07)
With baseline CVD	14,898	1.0	0.52 (0.47–0.59)	1.49 (1.36–1.63)

* Conditional multivariable logistic regressions with all 3 cohorts (systemic lupus erythematosus [SLE], diabetes mellitus [DM], and general Medicaid population) combined, adjusted for age, sex, race, US region of residence, socioeconomic status, number of outpatient visits, number of medications, Charlson comorbidity index, presence of cardiovascular disease (CVD), lupus nephritis/diabetic nephropathy overall and stratified according to age group and by baseline CVD status (without adjustment for the presence of CVD when stratified according to baseline CVD status). OR = odds ratio; 95% CI = 95% confidence interval.

patients with SLE and patients with DM ages 18–39 years had increased odds of lipid testing and receipt of a statin prescription compared with the general Medicaid population (Tables 5 and 6). However, within the age groups 40–49 and 50–65 years, patients with SLE had lower odds of lipid testing and receipt of statin prescriptions compared with the general Medicaid population, whereas the odds remained greater for patients with DM compared with the general Medicaid population across all age groups. In sensitivity analyses, the lower odds among SLE patients compared with the general population were most pronounced in patients with baseline CVD for both lipid testing and statin prescription.

DISCUSSION

In this large cohort study within US Medicaid, patients with SLE had more prevalent CVD at baseline compared with age- and sex-matched patients with DM but were 66% less likely to have lipid testing and 82% less likely to have a statin prescription dispensed during 1-year follow-up. The proportion of patients who received lipid testing increased with increasing age in the SLE cohort but remained well below the proportion observed in the DM cohort. In contrast, the rate of testing in the DM cohort was high across the age ranges, suggesting that DM patients receive more consistent and frequent lipid testing regardless of age. These findings are consistent with those from of a previous population-based cohort study of mortality and CVD in patients with SLE in Wisconsin in which low proportions of lipid testing and statin prescription among those in whom hyperlipidemia was diagnosed were reported (24). In that study, lipid tests were performed in only 66% of patients with SLE during a mean follow-up of 7.7 years, and <20% of patients with hyperlipidemia diagnosis were prescribed a statin.

Because our primary analyses did not distinguish between primary and secondary prevention in comparisons of lipid testing and statin prescriptions in each cohort, we performed sensitivity analyses excluding patients with a history of CVD during the baseline period and observed similar results in each cohort. Of note, although baseline CVD was associated with statin prescriptions in all cohorts, the presence of CVD in patients with SLE and those with DM was not associated with increased lipid testing, as it was in the general Medicaid population. In fact, the presence of baseline CVD was associated with lower odds of lipid testing in DM patients, suggesting that, for secondary prevention, DM patients may be prescribed statins without repeat lipid testing. For SLE patients, no association between baseline CVD and lipid testing was observed, and this finding remained the same in sensitivity analysis in which those with baseline statin use were excluded. In sensitivity analyses across cohorts, excluding patients with baseline CVD, the odds of both lipid testing and receipt of statin prescriptions were more similar to general Medicaid patients for SLE, while the odds became slightly higher for patients with DM compared with the odds in the general Medicaid population. In contrast, when only patients with baseline CVD were included, the odds of lipid testing and dispensing of statin prescriptions decreased even further in patients with SLE compared with subjects in the general Medicaid population and remained elevated in patients with DM, although to a lesser extent.

Among the patients who were excluded from our study because they fulfilled criteria for both SLE and DM, the rate of lipid testing was 40%, and the rate of receipt of statin prescriptions was 29%. Both of these rates were higher than those among SLE patients but were slightly lower than those among DM patients, as expected. Both lupus nephritis and diabetic nephropathy have been associated with a higher risk of CVD compared with SLE or DM patients without renal involvement (25,26). We observed that both lupus nephritis and diabetic nephropathy were associated with higher odds of lipid testing and dispensing of statin prescriptions compared with those without renal involvement in the SLE cohort and DM cohort, respectively. However, the presence of lupus nephritis increased the odds of lipid testing and dispensing of statin prescriptions by higher ratios in SLE patients compared with the increased odds associated with diabetic nephropathy in DM patients. This suggests that renal involvement may lead to more awareness and confers more aggressive CVD risk prevention in both cohorts, although to a lesser extent in DM patients. Additionally, polypharmacy was associated with higher ORs for lipid testing and dispensing of statin prescriptions in all cohorts. These higher ORs may represent a provider effect, in that health care providers who prescribe more medications may also provide more testing and statin prescriptions. It is also possible that these patients are more willing to have testing and to take medications, or that they have more comorbidities, putting them at higher risk for CVD.

In this study assessing CVD risk management in patients with SLE, we identified a comparison cohort of age- and sex-matched patients with DM (a condition that is considered to be a CVD risk equivalent) in which aggressive CVD risk management efforts, including annual lipid testing (27–30), have led to decreased mortality (5). SLE has not been similarly established as a recognized independent risk factor for CVD, although CVD risks are greatly elevated and even higher than those in age- and sex-matched DM patients and individuals in the general Medicaid population (1–3,31). The 2009 SLE expert opinion–based recommendation for annual lipid testing for CVD risk assessment is based on expert consensus rather than clinical trial evidence, because the benefits and cost-effectiveness of yearly lipid testing compared with less frequent laboratory screening have not been demonstrated (8). In our sensitivity analyses, when patients who received baseline lipid testing were excluded, the proportion of SLE patients who received lipid testing during follow-up decreased from 24% to 18%, demonstrating that 25% of the patients who received lipid testing during follow-up had received lipid testing during the baseline period as well.

Statins decrease the risk of CVD in the general population and in patients with DM (5,32,33). SLE patients tolerate statins well, experience lipid-lowering effects similar to those in subjects in the general population, and were shown to have significant mortality benefit in a retrospective study in Taiwanese SLE patients with hyperlipidemia (12,34). It has been postulated that SLE patients may additionally benefit from the antiinflammatory effect of statins for CVD risk modification; however, this hypothesis has not been proven. No study of statins in patients with SLE had yet examined the hard outcomes of CVD, because enrollment in prevention trials has proven challenging in this population (35). Previous studies investigating the effects of atorvastatin on coronary artery calcium scores as a surrogate for CVD outcome have not been conclusive. Furthermore, changes in coronary artery calcium may not be appropriate surrogates for statin efficacy, because statins have a well-established track record in reducing major CV events in patients with and those without established CVD and yet have been shown to increase the coronary artery calcium score (36–38). One possible explanation for this observation is that statins may increase coronary artery calcium content, because they stabilize plaques and decrease the number of CVD events.

In a previous study in 60 SLE patients randomized to receive atorvastatin 40 mg daily or placebo, coronary artery calcium deposition increased in the placebo group but not in the intervention group after 1 year of treatment (39). Another trial involving 200 SLE patients randomized to receive atorvastatin 40 mg daily or placebo showed no significant difference in the coronary artery calcium score or SLE disease activity after 2 years of follow-up (40). However, in a post hoc analysis, fewer SLE patients randomized to atorvastatin had progression of carotid intimal media thickness (CIMT)/plaque compared with those who received placebo (40). Among pediatric SLE patients randomized to atorvastatin or placebo, a nonsignificantly reduced progression of CIMT in the atorvastatin group was observed (41). Additionally, subgroup analysis revealed that patients with higher baseline high-sensitivity C-reactive protein levels had slower progression of CIMT during atorvastatin treatment (42). However, a meta-analysis of 3 statin trials including 493 SLE patients demonstrated no statistically significant improvement in CIMT, although use of this surrogate for CVD is controversial (43). Unfortunately, because previous trials have been limited and inconclusive, there are no current, clear guidelines for statin therapy to prevent CVD in patients with SLE, which may be reflected in the low rates of lipid testing and statin use observed in this high-risk population.

Our study has a number of strengths and limitations that merit discussion. First, the MAX database includes a very large racially and ethnically diverse population. However, generalizability of our findings to populations of individuals with a higher socioeconomic status and private medical insurance is not known. Although we used published methods to identify SLE (16,44–46) and DM (18), the possibility of misclassification exists. There may also be possible misclassification of covariables, in particular obesity and smoking, using ICD-9 codes (47,48), as well as a possibility of incompletely capturing baseline covariates such as CVD within a 6-month period during which covariates were assessed. Disease duration may influence the rates of lipid testing and dispensing of statin prescriptions, but we were not able to assess for this effect in these prevalent cohorts. Claims data lack information about results of lipid tests, which would have allowed evaluation of whether patients are receiving appropriate statin therapy based on traditional risk factors. Additionally, because our data extend only through 2010, we were unable to assess uptake of the 2009 quality indicator recommendations for SLE and the effect of these recommendations on CVD outcomes (8).

Our study demonstrates that despite recommendations for annual CVD risk assessment, only 24% of these Medicaid beneficiaries with SLE received lipid testing during 1-year follow-up. Additionally, despite our observation that the prevalence of CVD at baseline in SLE patients was higher than that in age- and sex-matched patients with DM, SLE patients received significantly fewer lipid tests and filled fewer statin prescriptions. Care for the prevention of CVD in SLE patients receiving Medicaid is not consistently provided, and efforts should be made to establish and disseminate clear evidence-based guidelines to improve care and outcomes in this high-risk population.

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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. Dr. Chen 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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Patients With Systemic Lupus Erythematosus Show an Increased Arterial Stiffness That is Predicted by IgM Anti–β_2-Glycoprotein I and Small Dense High-Density Lipoprotein Particles

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Objective. To investigate the metabolic and immunologic factors associated with the presence of central arterial stiffness as measured by the augmentation index (AIx).

Methods. We conducted a cross-sectional study of 69 female patients with systemic lupus erythematosus (SLE) compared with a control group of 34 healthy women. The anthropometrical variables, the vascular studies, and the analytic data were obtained the same day. The AIx was assessed by peripheral arterial tonometry. The analysis of lipoprotein populations was performed using nuclear magnetic resonance (NMR) spectroscopy.

Results. Arterial stiffness was increased in patients with SLE compared with control subjects (mean ± SD 20.30 ± 21.54% versus 10.84 ± 11.51%; $P = 0.0021$). Values for the AIx were correlated with the Framingham risk score (r = 0.481, $P < 0.001$), carotid intima-media thickness (r = 0.503, $P < 0.001$), systolic blood pressure (r = 0.270, $P < 0.001$), and age (r = 0.365, $P < 0.001$). Patients receiving antimalarial drugs had a lower AIx (mean ± SD 11.74 ± 11.28% versus 24.97 ± 20.63%; $P = 0.024$). The AIx was correlated with the atherogenic lipoproteins analyzed by NMR. The immunologic variables associated with the AIx were C4 (r = 0.259, $P = 0.046$) and IgM anti–β_2-glycoprotein I (IgM anti-β_2GPI) (r = 0.284, $P = 0.284$). In the multivariate analysis, age ($\beta = 0.347$, 95% confidence interval [95% CI] 0.020–0.669, $P = 0.035$), IgM β_2GPI ($\beta = 0.321$, 95% CI 0.024–0.618, $P = 0.035$) and small dense high-density lipoprotein (HDL) particles ($\beta = 1.288$, 95% CI 0.246–2.329, $P = 0.017$) predicted the AIx.

Conclusion. SLE patients had increased arterial stiffness compared with healthy control subjects. Arterial stiffness was decreased in patients treated with antimalarial drugs. Age, IgM β_2GPI, and the number of small dense HDL particles predicted the AIx.

INTRODUCTION

Patients affected by systemic lupus erythematous (SLE) have increased cardiovascular morbidity and mortality despite improvements in the control of disease activity and its complications (1–4). The accelerated atherosclerosis observed in patients with SLE cannot be entirely explained by the traditional cardiovascular risk factors. Other non-classic cardiovascular risk factors related to inflammation have been associated with this accelerated atherosclerosis process (5–8).

The cardiovascular risk scales used in the general population underestimate the risk of cardiovascular events in SLE patients, because the other non-classic cardiovascular risk factors associated with SLE disease are not considered (9). These data are supported by the results of several studies showing a higher prevalence of subclinical atherosclerosis in this young population of patients with SLE, as measured by carotid intima-media thickness (IMT), stiffness, and endothelial dysfunction (10–14). Thus, in SLE patients, the study of the arterial wall structure and its function is of particular interest in order to improve the evaluation and optimization of the individual cardiovascular risk in each patient (15,16).

Endothelial dysfunction is considered to be the earliest alteration in the arteries that leads to atherosclerosis. Another vascular alteration that precedes atherosclerosis is increased rigidity of the arterial wall (14). Several indices have been developed to assess arterial stiffness, including aortic pulse wave velocity (PWV) and the augmentation index (AIx) (17). The AIx is defined as an increase in

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SIGNIFICANCE & INNOVATIONS

- The augmentation index (AIx) is a noninvasive method used to evaluate arterial stiffness in patients with systemic lupus erythematosus (SLE); it is well correlated with other surrogate markers of atherosclerosis such as carotid intima-media thickness.
- SLE patients had increased arterial stiffness compared with healthy controls, although there were no differences with respect to the classic cardiovascular risk factors.
- Patients treated with antimalarials had significantly decreased AIx levels, similar to those in the control group.
- Age, antiphospholipid antibodies, IgM anti–β_2-glycoprotein I, and proinflammatory small high-density lipoprotein particles were the variables that predicted the AIx levels.

pressure after the first systolic shoulder to the peak of aortic pressure and is expressed as a percentage of the aortic pulse pressure. The AIx is associated with several cardiovascular risk factors, including age, hypertension, diabetes mellitus, hyperhomocysteinemia, and cigarette smoking. In the Framingham Heart Study cohort, arterial stiffness was shown to be associated with an increased risk of developing a first cardiovascular event, thus improving prediction of classic risk factors (18,19). It has been demonstrated in several studies that SLE patients show impaired arterial stiffness as measured by the AIx, which has been associated with inflammatory factors and SLE disease activity and duration (20–26).

Our group has focused on research regarding surrogate markers of subclinical atherosclerosis in SLE patients and a more detailed method to analyze the lipid profile by nuclear magnetic resonance (NMR), because standard laboratory methods did not reflect the real atherogenic lipid profile in these patients (27–29). We have also observed that some specific SLE-related factors, such as complement system factors and antiphospholipid antibodies (aPL), are also associated with carotid IMT thickness and some lipoproteins measured by NMR, such as intermediate-density lipoprotein (IDL) particles and small dense high-density lipoprotein (HDL) particles (30,31).

The aim of the current study was to investigate whether an earlier vascular test of atherosclerosis in SLE patients, such as arterial stiffness measured by the AIx, is associated with other subclinical markers of atherosclerosis, such as SLE-associated factors and the lipoprotein populations analyzed by NMR.

PATIENTS AND METHODS

Subjects. In this cross-sectional study, 69 female patients with SLE attending the autoimmune diseases outpatient clinic at Sant Joan University Hospital (Reus, Spain) were recruited. The patients fulfilled at least 4 criteria for SLE as defined by the revised American College of Rheumatology classification system (32). None of the patients presented with active disease as defined by the SLE Disease Activity Index score >4. Thirty-four healthy women without differences regarding age were recruited from the same region to serve as controls. Neither diabetes mellitus nor impaired renal function had been evident in the patients, and none of them presented with ischemic or adverse cardiovascular events. All subjects provided fully informed consent to participate, and the Ethics Committee of Sant Joan University Hospital approved the study.

Biochemical analyses. Fasting venous blood samples were collected in EDTA or serum tubes and immediately centrifuged at 1,500*g* for 15 minutes at 4°C. The samples were then divided into aliquots and stored at –80°C until analyzed.

Standard laboratory methods were used to quantify glucose, hemoglobin A1c, total cholesterol, triglycerides, and HDL cholesterol. The LDL cholesterol concentration was calculated using the Friedewald formula (33).

Apolipoprotein (Apo) measurements were performed with immunoturbidimetric assays using antisera specific for Apo A-1 and Apo B (Hoffmann-La Roche). High-sensitivity C-reactive protein (CRP) was measured using highly sensitive rate near-infrared particle immunoassay (NIPIA) methodology (Beckman Coulter) on a Synchron LXi PRO automated autoanalyzer (Beckman Coulter). Insulin was measured in fasting sera using commercial enzyme-linked immunoassay (ELISA) kits (Mercodia AB and BioVendor Laboratory Medicine Inc., respectively). Insulin resistance was estimated using a homeostasic model of insulin resistance, calculated as fasting glucose (in mmoles/liter) multiplied by fasting insulin (in mIU/liter) divided by 22.5.

Two-dimensional NMR LipoProfile analysis and separation and quantification of remnant lipoprotein cholesterol. Total plasma lipids and the distribution of subclasses of lipoproteins were analyzed using an NMR LipoProfile test. Subclasses were of a given average size. This technique allows for the determination of 3 discrete subclasses of very low-density lipoprotein (VLDL), IDL, 4 low-density lipoprotein (LDL) subclasses, and 3 HDL subclasses. NMR was carried out on EDTA plasma, stored at –80°C, and thawed just prior to the analysis (27). Additionally, remnant lipoprotein cholesterol was measured in plasma using the method described by Nakajima et al, using an RLP C ELISA kit (Jimro-II; Japanese Immunoresearch Laboratories (34).

Cardiovascular (CVD) risk assessment and carotid IMT assessment. The 10-year CVD risk was assessed in all SLE patients by applying the Systematic Coronary Risk

Table 1. General characteristics of the SLE patients and control subjects and differences between these groups*

Variable	SLE patients (n = 69)		Control subjects (n = 34)		
	Mean ± SD	r	Mean ± SD	r	*P*
Anthropometric					
Age, years	49 ± 16.8	0.365†	48.7 ± 13.2	0.479†	NS
Body mass index, kg/m^2	26.3 ± 5.8	NS	24.5 ± 3.2	NS	NS
Systolic BP, mm Hg	118.5 ± 19.3	0.270‡	111.26 ± 14.8	0.406‡	NS
Diastolic BP, mm Hg	75.7 ± 11	NS	72.2 ± 7.7	NS	NS
Mean BP, mm Hg	89.26 ± 12.62	0.248‡	85.59 ± 9.2	0.255‡	NS
Waist circumference, cm	86.7 ± 1.7	NS	81.2 (8.9)	NS	NS
Surrogate markers of subclinical atherosclerosis and cardiovascular risk estimation					
Mean carotid IMT, mm	0.702 ± 0.14	0.503†	0.633 ± 0.891	0.376‡	<0.001
RHI	1.75 ± 0.47	NS	1.92 ± 0.63	NS	NS
REGICOR	2.19 ± 1.86	0.480†	1.66 ± 1.16	0.357†	NS
FRS	4.03 ± 3.95	0.418†	3.56 ± 1.95	0.454†	NS
SCORE	0.67± 1.15	0.349†	1.66 ± 1.16	0.426†	NS
Metabolism					
Glucose, mmoles/liter	5.1 ± 0.6	NS	5.0 ± 0.6	0.499	NS
Insulin, mIU/liter	8.0 ± 5.3	NS	6.6 ± 3.1	0.203	NS
HOMA-IR	1.7 ± 1.2	NS	1.5 ± 0.9	0.346	NS
Hemoglobin A1$_c$, %	4.7 ± 0.6	NS	–	–	–
Apo A-1, gm/liter	1.45 ± 0.1	NS	1.51 ± 0.4	0.482†	NS
Apo B-100, gm/liter	0.86 ± 0.2	0.290‡	0.94 ± 0.2	0.379*	NS
Total cholesterol, mmoles/liter	4.9 ± 1.1	NS	5.01 ± 0.8	0.460†	NS
Triglycerides, mmoles/liter	0.97 ± 0.5	0.480†	0.77 ± 0.3	NS	0.048
LDL cholesterol, mmoles/liter	2.82 ± 0.8	NS	3.1 ± 0.7	0.428‡	NS
HDL cholesterol, mmoles/liter	1.7 ± 0.4	NS	1.54 ± 0.4	NS	NS
Creatinine, µmoles/liter	67.5 ± 15.4	NS	64.7 ± 10.6	NS	NS
Factors associated with disease activity and inflammation					
Anti-DNA antibodies, IFI	23.9 ± 5.7	NS	–	–	–
C3, gm/liter	1.049 ± 0.3	NS	–	–	–
C4, gm/liter	0.174 ± 0.1	0.259‡	–	–	–
CH50, arbitrary units	49.55 ± 16.1	NS	–	–	–
IgM anticardiolipin, MPL units/ml	8.87 ± 12.84	NS	–	–	–
IgG anticardiolipin, GPL units/ml	17.69 ± 32.0	NS	–	–	–
IgG anti–β_2GPI units/ml	7.21 ± 12.7	NS	–	–	–
IgM anti–β_2GPI, units/liter	6.42 ± 14.8	0.289‡	–	–	–
ESR, mm/hour	17.98 ± 2.5	NS			
hsCRP, mg/liter	2.47 ± 2.6	NS	1.93 ± 1.71	NS	NS

* r = bivariate relationship between the augmentation index and the variable with a statistical significance of $P < 0.05$ or $P < 0.001$. SLE = systemic lupus erythematosus; NS = not significant; BP = blood pressure; IMT = intima-media thickness; RHI = reactive hyperemia index; FRS = Framingham risk score; SCORE = Systematic Coronary Risk Evaluation; HOMA-IR = homeostatic assessment of insulin resistance; Apo A-1 = apolipoprotein A-1; LDL = low-density lipoprotein; HDL = high-density lipoprotein; IFI = indirect immunofluorescence reaction; MPL = IgM phospholipid; GPL = IgG phospholipid; anti-β_2GPI = anti–β_2-glycoprotein I; ESR = erythrocyte sedimentation rate; hsCRP = high-sensitivity C-reactive protein.
† $P < 0.001$, patients vs. controls.
‡ $P < 0.05$, patients vs. controls.

Evaluation (SCORE), the Framingham risk score (FRS), and REGICOR scales. For assessment of carotid IMT, we used a MyLab 50 XVision ultrasound system (Esaote SpA) with a linear array ultrasound probe of 8–12 MHz transducer to identify the intima-media complex in the far wall of the common carotid artery, the artery bulb, and the internal branch of the left and right carotid arteries. The images were digitalized and stored. Assessment of the carotid IMT was performed by radiofrequency in in vivo images. The images were obtained and measured by a single operator to reduce observer variability. We averaged the measurements of 3 images of the left and the right carotid arteries to obtain the mean IMT (carotid IMT) (35).

Arterial function measurements. Arterial stiffness was measured by the AIx using peripheral artery tonometry technology (EndoPAT 2000; Itamar Medical) (36). Patients were in a fasting state and had refrained from smoking or strenuous exercise in the previous 12 hours. The test was performed in a quiet room at 22–24°C. To obtain the measurements, 2 probes that detect pulse wave amplitude were placed on a finger in both hands. After a stabilization period, a 5-minute period of ischemia was induced by inflating a blood pressure cuff on one arm, and then the differences in pulse wave amplitude were analyzed before and after ischemia in comparison with the control arm. The software was used to calculate the reactive hyperemia index, as an indicator of microvascular reactivity and endothelial function, and the AIx, an indicator of systemic arterial stiffness. The AIx was obtained from the comparison of the systolic and diastolic waveforms. Increased stiffness is expressed in higher values of the AIx, in percentages. We used the AIx adjusted to 75 beats per minute for the analyses.

Statistical analysis. Analyses were performed using SPSS (version 24.0). All data are presented as the mean ± SD except where indicated otherwise. Normality distribution was assessed with the Kolmogorov-Smirnov test. Differences between means were assessed by analysis of variance. Pearson's correlation tests were used to compare the AIx and other continuous variables. Multiple linear stepwise regression analyses were performed to identify the variables that predicted AIx levels. We included the variables associated with the AIx in the univariate analyses and the bivariate correlations. We excluded lipoprotein subclasses with a bivariate correlation >0.7 to avoid confounding factors. Two-tailed *P* values less than 0.05 were considered significant.

RESULTS

Differences in central arterial stiffness between SLE patients and the control group. The general characteristics of and differences between SLE patients and control subjects are shown in Table 1. Patients with SLE had significantly increased arterial stiffness (as determined using the AIx) compared with the control group (mean ± SD 20.30 ± 21.54% versus 10.84 ± 11.51%; $P = 0.0021$) (Figure 1A).

SLE patients also had higher carotid IMT than the control group (0.702 ± 0.147 mm versus 0.633 ± 0.891 mm; $P = 0.012$), although we did not observe differences in the cardiovascular risk as assessed by SCORE, FRS, or REGICOR scales. With respect to the classic cardiovascular risk factors, SLE patients had higher triglyceride levels compared with controls (0.97 ± 0.5 mmoles/dl versus 0.77 ± 0.3 mmoles/dl; $P = 0.048$).

Variables associated with the AIx. Bivariate correlations between continuous variables and the AIx are shown in Table 1. In both the patient and control groups, the AIx values were correlated with age, systolic blood pressure, and FRS, REGICOR, and SCORE. We could confirm that the AIx was also well correlated with carotid IMT, another surrogate marker of subclinical atherosclerosis, in SLE patients ($r = 0.503$, $P < 0.001$) and the control group ($r = 0.376$, $P = 0.034$). We observed that higher tertiles of arterial stiffness were associated with higher values for carotid IMT (Figure 2).

With respect to lipids measured by standard laboratory methods, we observed that in SLE patients the AIx was correlated with triglycerides ($r = 0.480$, $P < 0.001$) and Apo B-100 ($r = 0.290$, $P < 0.001$). However, in the control group, the AIx was correlated with LDL cholesterol levels ($r = 0.428$, $P = 0.013$), Apo B-100 levels ($r = 0.379$, $P < 0.001$), and Apo A-1 levels ($r = 0.482$, $P < 0.001$). The only immunologic variables that correlated with the AIx were C4 levels ($r = 0.259$, $P = 0.046$) and IgM β_2-glycoprotein I (β_2GPI) antibodies ($r = 0.289$, $P = 0.284$) (Table 1).

Differences in the AIx and different treatments in patients with SLE. We analyzed differences between the AIx and the different treatments, such as antimalarial drugs, glucocorticoids, immunosuppressive drugs, antihypertensive drugs, and statins. With respect to the SLE therapies, the only differences observed were for antimalarial treatment. No other differences regarding the presence of glucocorticoids or immunosuppressive therapies were observed. Patients treated with antimalarial drugs showed significantly lower central arterial stiffness (11.44 ± 11.28% versus 24.97 ± 20.63%; $P = 0.024$) (Figure 1B).

Table 2 shows the characteristics of and differences between SLE patients according to antimalarial treatment. We observed no differences between patients treated with antimalarials and those not treated with antimalarials in terms of age, classic cardiovascular risk factors, or carotid IMT levels. It is also interesting that the HDL cholesterol levels measured by standard laboratory methods were higher in the group of antimalarial-treated patients (1.85 ± 0.49 mmoles/dl versus 1.57 ± 0.3 mmoles/dl; $P = 0.006$). With respect to the lipid profile analyzed with

NMR, we observed differences only between the numbers of large HDL particles, which were higher in the antimalarial-treated patients (11.32 ± 3.8 nmoles/dl versus 9.08 ± 3.09 nmoles/dl; $P < 0.001$). No other differences regarding the other lipoprotein subpopulations were observed.

Differences between patients treated with antimalarial agents and those who were not treated were mainly regarding the immunologic variables associated with SLE activity, with higher titers of anti-DNA antibodies (as determined by indirect immunofluorescence reaction) in treated patients (46.3 ± 90.1 versus 12.5 ± 21.7; $P = 0.025$). Anti-DNA antibody positivity by chytridia was observed in a higher proportion of treated patients compared with untreated patients, with the difference nearly statistically significant (42.1% versus 18.6%; $P = 0.053$) and lower levels of C3 (0.91 ± 0.29 gm/liter versus 1.1 ± 0.3 gm/liter; $P = 0.011$).

Regarding the pharmacologic treatments for the cardiovascular risk factors, we observed that patients treated with statins had significantly increased AIx levels (32.24 ± 27.69% versus 12.05 ± 18.9%; $P = 0.033$) and carotid IMT (0.79 ± 0.18 mm versus 0.67 ± 0.11 mm; $P = 0.012$). Antihypertensive treatment was associated with higher carotid IMT but did not influence the AIx in SLE patients.

Correlation between the AIx and the lipoprotein subclasses analyzed using NMR. When we analyzed the lipid profile in SLE patients by NMR, we observed that the AIx was positively associated in the bivariate correlations with the main Apo B–containing lipoproteins such as remnant lipoprotein cholesterol (r = 0.441, $P < 0.001$), total chylomicron and VLDL particles (r = 0.407, $P < 0.001$), large VLDL particles ($r = 0.269$, $P < 0.05$), medium VLDL particles (r = 0.446, $P < 0.001$), small VLDL particles (r = 0.307, $P < 0.05$), IDL particles (r = 0.374, $P < 0.005$), and medium-small LDL particles (r = 0.261, $P < 0.05$). Conversely, we also observed that the small HDL particles were associated with the AIx (r = 0.449, $P < 0.001$). These data are shown in Table 3.

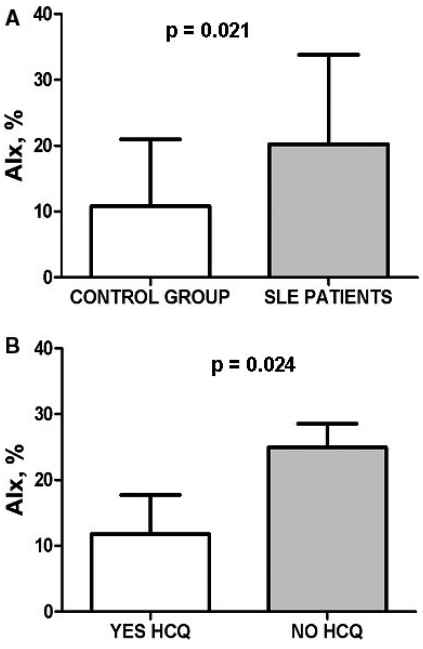

Figure 1. Arterial stiffness, as measured using the augmentation index (AIx) in patients with systemic lupus erythematosus (SLE) (n = 69) and healthy control subjects (n = 34) (**A**) and in SLE patients who were treated with hydroxychloroquine (HCQ) and those who were not treated (**B**). Bars show the mean ± SD.

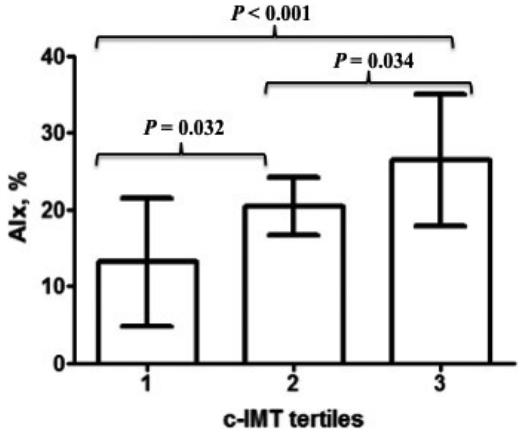

Figure 2. Differences in the augmentation index (AIx) according to carotid intima-medial thickness (cIMT) tertiles in patients with systemic lupus erythematosus (SLE). Bars show the mean ± SD.

Variables that predict arterial stiffness in SLE patients. Multivariate stepwise linear regression analysis was performed to assess the main predictors of arterial stiffness, using the AIx as a dependent variable. Variables included in the model were as follows: age, systolic blood pressure, IgM anti–β_2GPI, C4, treatment with hydroxychloroquine (HCQ) and statins, Apo B-100, remnant lipoprotein cholesterol, IDL particles, total number of VLDLs, chylomicrons, and small HDL particles. Using this multivariate model (Durbin-Watson statistic = 1.915, $R^2 = 0.541$), we observed that age ($\beta = 0.347$, 95% CI 0.020–0.669, $P = 0.035$), IgM β_2GPI ($\beta = 0.321$, 95% CI 0.024–0.618, $P = 0.035$), and small dense HDL particles ($\beta = 1.288$, 95% CI 0.246–2.32, $P = 0.017$) predicted AIx levels (Figure 3).

DISCUSSION

The current study showed that SLE patients had increased arterial stiffness compared with control subjects. No differences between the groups were observed regarding the presence of classic cardiovascular risk factors that could explain the increased arterial stiffness in SLE patients and increased carotid IMT. We observed a good correlation between the AIx and carotid IMT, age, systolic blood pressure, and certain lipid parameters in both the SLE group and the control group. These results show that arterial stiffness as measured by the AIx could be a good surrogate marker of atherosclero-

Table 2. Characteristics of and differences between SLE patients according to antimalarial treatment*

	HCQ treatment (n = 22)	No HCQ treatment (n = 47)	*P*
Age, years	47.8 ± 16.1	49.2 ± 17.1	NS
Body mass index, kg/m^2	25.4 ± 4.1	26.5 ± 6.5	NS
Systolic BP, mm Hg	114.6 ± 19.3	111.26 ± 14.8	NS
Diastolic BP, mm Hg	75.7 ± 11	74.3 ± 7.7	NS
Waist circumference, cm	86.7 ± 18.9	89.6 ± 11.3	NS
Mean carotid IMT, mm	707 ± 150	692 ± 142	NS
RHI	1.85 ± 0.68	1.97 ± 0.62	NS
REGICOR	1.79 ± 1.49	2.4 ± 2.0	NS
FRS	3.41 ± 2.26	4.38 ± 4.4	NS
SCORE	0.41 ± 0.61	0.78 ± 1.28	NS
Glucose, mmoles/liter	4.8 ± 0.6	5.2 ± 0.6	NS
Insulin, mIU/liter	9.2 ± 6.4	7.5 ± 4.7	NS
HOMA-IR	1.9 ± 1.2	1.6 ± 1.1	NS
Hemoglobin A1$_c$, %	4.8 ± 0.8	4.7 ± 0.5	NS
Apo A-1, gm/liter	1.48 ± 0.1	1.41 ± 0.2	0.066
Apo B-100, gm/liter	0.86 ± 0.2	0.82 ± 0.3	NS
Total cholesterol, mmoles/liter	5.1 ± 1.3	4.8 ± 0.9	NS
Triglycerides, mmoles/liter	0.89 ± 0.51	0.98 ± 0.45	NS
LDL cholesterol, mmoles/liter	2.37 ± 1.4	2.5 ± 1.07	NS
HDL cholesterol, mmoles/liter	1.85 ± 0.49	1.57 ± 0.3	0.006
Creatinine, μmoles/liter	67.5 ± 15.4	64.7 ± 10.6	NS
Anti-DNA antibodies, IFI	46.3 ± 90.1	12.5 ± 21.73	0.025
Anti-DNA antibody positive, %	42.1	18.6	0.053
C3, gm/liter	0.91 ± 0.29	1.1 ± 0.3	0.011
C4, gm/liter	0.15 ± 0.07	1.1 ± 0.24	NS
CH50, arbitrary units	46.7 ± 17.9	50.1 ± 14.9	NS
IgM anticardiolipin, MPL units/ml	9.68 ± 8.5	8.96 ± 10.8	NS
IgG anticardiolipin, GPL units/ml	17.3 ± 30.8	17.3 ± 32.1	NS
IgG anti-β_2GPI, units/ml	9.01 ± 15.7	6.1 ± 11.1	NS
IgM anti-β_2GPI units/ml	5.1 ± 7.4	7.25 ± 16.9	NS
Anti-LAC antibody positive, %	10.5	17.2	NS
ESR, mm/hour	16.21 ± 10.03	19.03 ± 14.01	NS
hsCRP, mg/liter	3. 1 ± 4.5	3.7 ± 3.2	NS

* Except where indicated otherwise, values are the mean ± SD. SLE = systemic lupus erythematosus; HCQ = hydroxychloroquine; BP = blood pressure; IMT = intima-media thickness; RHI = reactive hyperemia index; FRS = Framingham risk score; SCORE = Systematic Coronary Risk Evaluation; HOMA-IR = homeostatic assessment of insulin resistance; Apo A-1 = apolipoprotein A-1; LDL = low-density lipoprotein; HDL = high-density lipoprotein; IFI = indirect immunofluorescence reaction; MPL = IgM phospholipid; GPL = IgG phospholipid; anti-β_2GPI = anti–β_2-glycoprotein I; LAC = lupus anticoagulant; ESR = erythrocyte sedimentation rate; hsCRP = high-sensitivity C-reactive protein.

sis in SLE patients, considering that this is a premature atherosclerotic process and that the cardiovascular risk estimation in SLE patients does not appear to reflect the real vascular damage identified using cardiovascular risk scores from the general population.

Recent efforts have standardized methods to evaluate arterial elasticity. From the noninvasive methods, the use of PWV has been generalized (37,38). One of the limitations of this study is use of the AIx to evaluate arterial stiffness. The AIx is obtained from a comparison of the systolic and diastolic waveforms, and this is the result of several factors. Compared with PWV, the AIx reflects systemic vascular stiffness not only in a regional territory. To avoid some confounding factors, we corrected the AIx by the cardiac frequency and examined whether it was correlated with other surrogate markers of atherosclerosis such as carotid IMT.

Table 3. Correlations between the AIx and lipoprotein particles in 69 patients with SLE, as analyzed by NMR*

Variable	r
Remnant lipoprotein cholesterol, mg/dl	0.441†
VLDL and chylomicron concentrations, nmoles/liter	
Total VLDL and chylomicrons	0.407†
Large VLDL and chylomicrons	0.269‡
Medium VLDL	0.440†
Small VLDL	0.307†
LDL concentrations, nmoles/liter	
Total LDL	0.290‡
IDL	0.374‡
Large LDL	NS
Small LDL	NS
Medium-small LDL	0.261‡
Very small LDL	NS
HDL concentrations, nmoles/liter	
Total HDL	0.307†
Large HDL	NS
Medium HDL	NS
Small HDL	0.449†
Mean particle size, nm	
VLDL	NS
LDL	NS
HDL	NS

* NMR = nuclear magnetic resonance; SLE = systemic lupus erythematosus; VLDL = very low-density lipoprotein; LDL = low-density lipoprotein; HLD = high-density lipoprotein.
† $P < 0.001$.
‡ $P < 0.05$.

We found that the AIx was associated with some specific immunologic variables related to SLE, such as IgM aPL, IgM anti-β_2GPI, and the complement system. Activation of the immune system in SLE patients could affect vascular elasticity as a trigger of the atherosclerotic process (39,40). The AIx could reflect changes that are not shown in studies in which other methods (e.g., PWV) were used, because the AIx reflects alterations in the wave reflection analysis from vascular territories from the small to the bigger vessels (41).

We did not identify an association between systemic inflammatory markers such as the erythrocyte sedimentation rate and the CRP level, as has been published previously (20,24,42,43). This finding could be related to the selection of the SLE patients for this study. Patients were experiencing clinical remission 6 months before the study, and we excluded patients with impaired renal function and diabetes mellitus, because these conditions are already associated with a high risk of cardiovascular complications. Activation of the immune system and inflammation throughout the evolution of SLE could affect vascular elasticity as a trigger of the atherosclerosis process.

We observed a positive correlation between complement component C4 and the AIx in the bivariate correlation, although we could not confirm this result in the multivariate analysis. Interestingly, activation of the complement system is related to pathogenic processes such as SLE disease and atherosclerosis (5–8,31,40,43). SLE patients with more active disease show lower plasma levels of complement, but high levels of C3 and C4 have also been linked to atherosclerosis and metabolic syndrome. On the basis of these data, we could consider that in SLE patients with normal levels of complement, inflammation, and activation of the complement system in the subendothelial space that lead to an increase in cardiovascular complications still persists.

SLE patients being treated with HCQ had significantly lower AIx levels. The cardiovascular and metabolic protective effects of HCQ in SLE have been associated with diverse mechanisms, such as an improvement in endothelial function, antiinflammatory properties, and reducing the presence of atherogenic dyslipidemia and insulin resistance (44,45). We did not observe a clear relationship between HCQ and a better cardiovascular risk profile in our patients. Although patients had higher levels

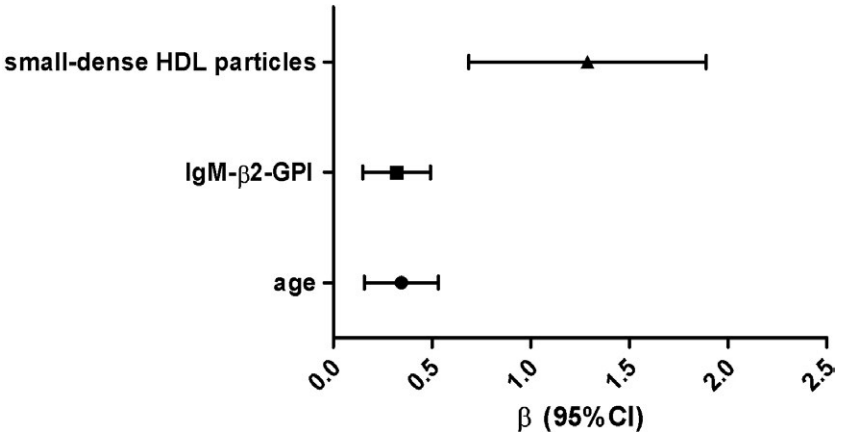

Figure 3. Multivariate analyses and predictors of the augmentation index in SLE patients. HDL = high-density lipoprotein; β_2GPI = β_2-glycoprotein I; 95% CI = 95% confidence interval. Bars show the mean ± SD.

of HDL cholesterol, we could not confirm that this association was related to the decrease in the AIx, because we observed an association only between the AIx and the small dense HDL particles. Differences between patients who were treated with antimalarials and those who were not treated were mainly regarding the immunologic variables associated with SLE activity. Treated patients had higher levels of anti-DNA antibodies and lower levels of complement component C3.

These data indicate that antimalarial treatment was indicated in patients who had laboratory parameters indicating active disease, although they were experiencing clinical disease remission. Antimalarial treatment has been demonstrated to improve the risk of flares and long-term survival in SLE patients (46). Because a previous study showed an association between disease activity and arterial stiffness and HCQ (47), perhaps the effect of HCQ treatment on disease activity could be monitored through the arterial stiffness measurement.

We did not observe that HCQ treatment predicted the AIx in multivariate analyses, which may be attributable to the fact that we could not include other variables that affect arterial stiffness, such as the length of time during which patients were receiving treatment and the total dose administered, in the analyses. The cross-sectional observational study design, small sample size, and selection criterion that patients had to have inactive disease 6 months before the study are limitations that confirm this hypothesis. We found that patients being treated with statins had increased AIx levels but also had increased carotid IMT. This finding seems to indicate that patients treated with statins have a higher cardiovascular risk or worse lipid profiles.

Another result of this study is that we were able to confirm an association between the atherogenic lipoprotein subclasses and arterial stiffness in SLE patients (which has not been previously confirmed), using a more detailed analysis of the lipoprotein subclasses, by NMR. This result is important, because the cardiovascular risk profile determined by the lipids in this population again appeared to underestimate the real atherogenic profile in SLE patients. We observed that the atherogenic Apo B–containing lipoproteins and the small dense HDL particles that have been previously described as being proinflammatory and proatherogenic in SLE patients were associated with a worse AIx (48,49).

Finally, the multivariate model showed that only age and variables associated with SLE such as IgM anti-β_2GPI and atherogenic small HDL particles predicted AIx levels. We did not find that the AIx was associated with the classic cardiovascular risk factors, such as blood pressure levels, glucose, or Apo B–containing lipoproteins.

The association that we have described between small dense HDL particles and arterial stiffness is in accordance with the results of a previous study that indicated a proatherosclerotic and proinflammatory function of HDL in SLE patients (50). HDLs contain proteins involved in the innate immune system as part of the complement system (32). The analysis of HDL subpopulations by NMR in SLE patients can detect the lipoprotein subclasses with functions other than reverse cholesterol transport. These HDL particles in patients with SLE have a proatherogenic action from the initial states with an increase in arterial stiffness that possibly may reflect activation of the immune system and inflammation in the vascular territory.

We found the association in the multivariate analysis between aPL compared with IgM anti-β_2GPI and the AIx to be of particular interest. Although the association between aPL and the risk of thrombosis was evident, the association between increased carotid IMT and arterial stiffness has not been well established (39,50). It is necessary to validate these findings in a larger cohort of patients in order to confirm these results. An investigation of the impact of non-classic cardiovascular factors such as SLE-related antibodies on progression of the atherosclerosis process from the beginning of the atherosclerotic process could demonstrate that immunologic activation triggers the atherosclerosis process.

In conclusion, SLE patients had increased arterial stiffness compared with healthy control subjects, as measured by the AIx. Patients treated with antimalarial drugs had less arterial stiffness that is predicted by age, IgM anti-β_2GPI, and the number of small dense HDL particles.

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. Parra 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. Parra.

Acquisition of data. Parra, Ibarretxe, de las Heras, Català, Benavent, Garcés, Navarro, Castro.

Analysis and interpretation of data. Parra, Lopez-Dupla, Amigó, Castro.

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Obesity is Independently Associated With Worse Patient-Reported Outcomes in Women with Systemic Lupus Erythematosus

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Objective. To determine whether obesity in women with systemic lupus erythematosus (SLE) is independently associated with worse patient-reported outcomes (PROs).

Methods. Data were derived from a prospective study of adult women with a diagnosis of SLE that was verified by medical record review. Two established definitions for obesity were used: fat mass index (FMI) ≥13 kg/m^2 and body mass index (BMI) ≥30 kg/m^2. Dependent variables included 4 validated PROs: disease activity as assessed by the Systemic Lupus Activity Questionnaire (SLAQ), depressive symptoms as assessed by the Center for Epidemiologic Studies Depression Scale (CES-D), pain as assessed by the Short Form 36 (SF-36) pain subscale, and fatigue as assessed by the SF-36 vitality subscale. We used multivariable linear regression to evaluate the associations of obesity with PROs, while controlling for potential confounders (age, race, education, income, smoking, disease duration, disease damage, and prednisone use).

Results. The analysis included 148 participants, 32% of whom were obese. In the multivariate regression model, obesity was associated with worse scores for each PRO. Mean adjusted scores for the SLAQ and CES-D comparing obese versus non-obese participants were 14.8 versus 11.5 ($P = 0.01$) and 19.8 versus 13.1 ($P < 0.01$), respectively. The obese group also reported worse mean adjusted scores for pain (38.7 versus 44.2; $P < 0.01$) and fatigue (39.6 versus 45.2; $P = 0.01$).

Conclusion. In a representative sample of women with SLE, obesity (as defined by both FMI and BMI) was independently associated with worse PROs, including disease activity, depressive symptoms, and symptoms of pain and fatigue. Obesity may represent a modifiable target for improving outcomes among obese women with SLE.

INTRODUCTION

Patients with systemic lupus erythematosus (SLE) experience a detriment in health-related quality of life and other patient-reported outcomes (PROs) relative to both healthy individuals (1–9) and those with other chronic conditions such as rheumatoid arthritis (RA) and noninflammatory rheumatic disease (10). The prevalence of poor PROs in lupus relative to other disease states has been established, but the cause of unfavorable results for the most impactful PROs in this patient population—namely pain, fatigue, and depressive symptoms—is not completely understood (1,11–13). For example, clinical measures of disease activity and damage do not fully explain the observed severity of these symptoms (1). Multiple studies have shown the impact of sociodemographic factors such as poverty on PROs, but again, much of the variation in PROs remains unexplained (14). Previous studies of other inflammatory conditions have shown an association between excess adiposity and worse PROs (15–17), but prior research designed to understand the contribution of obesity to PROs in SLE is scant and conflicting (18,19).

In this study, we aimed to investigate the relationship between excess fat mass and PROs in women with SLE. We conducted a cross-sectional observational study in women with SLE to measure the association of obesity with 4 PROs: self-reported disease activity, fatigue, pain, and depressive symptoms.

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SIGNIFICANCE & INNOVATIONS

- This is one of the first studies of systemic lupus erythematosus (SLE) in which the impact of excess adiposity on patient-reported outcomes (PROs) is evaluated, and is the first to use dual-energy x-ray absorptiometry to quantify fat mass in the investigation of this relationship.
- Among adult women with SLE, obesity was common (32% of the cohort) and was independently associated with worse PROs, including self-reported disease activity, depressive symptoms, and symptoms of pain and fatigue.
- The association between excess adiposity and worse PROs remained stable, using multiple measurements of adiposity and definitions of obesity.
- These findings highlight the need for lifestyle interventions targeting lupus patients who are overweight, given the potential to reduce both cardiovascular risk and debilitating symptoms that are common in this disease.

PATIENTS AND METHODS

Study design and participants. The sample for the current study was drawn from participants in the University of California, San Francisco (UCSF) Lupus Outcomes Study (LOS). Participants in the LOS had formerly participated in a study of genetic risk factors for SLE outcomes (20,21) and were recruited from both clinically based and community-based sources, including UCSF-affiliated clinics (22%), non-UCSF rheumatology offices (11%), lupus support groups and conferences (26%), and newsletters, web sites, and other forms of publicity (41%). A diagnosis of SLE was based on the American College of Rheumatology (ACR) criteria (22) and was verified by medical record review. LOS participants who lived in the greater San Francisco Bay area were recruited for an in-person assessment, which included measurement of body composition, at the UCSF Clinical and Translational Science Institute Clinical Research Center. Exclusion criteria were non–English-speaking, age <18 years, current oral prednisone dose ≥50 mg, current pregnancy, uncorrected vision problems that would interfere with reading ability, and joint replacement within 1 year.

A total of 325 individuals were asked to participate, of whom 74 (22.8%) were ineligible (35 lived too far away, 25 were too ill, 9 had recent surgery, 2 were pregnant, 2 had poor English skills, and 1 had cognitive problems). Of the 251 eligible individuals, 84 (33.5%) declined participation. Reasons for declining were primarily related to transportation (n = 12) and scheduling difficulties (n = 39). A total of 163 individuals completed the study visits, and body composition data were obtained from 145 participants. Because of the substantial differences in body composition between men and women and the small number of men in the sample, only women were included in these analyses (n = 145). Additionally, 3 participants met the criterion for being underweight (body mass index [BMI] <18.5 kg/m^2). Because being underweight may also be associated with poor outcomes, but for reasons that differ from those associated with obesity (e.g., cachexia from very active disease), the 3 underweight women were excluded, resulting in a sample size of 142 for the current analysis. The study was approved by the UCSF Committee on Human Research and was completed in accordance with the ethics guidelines described in the Declaration of Helsinki. All subjects provided written informed consent.

Measures. *Body composition measures.* Height was measured using a wall-mounted stadiometer. Weight was measured with subjects wearing light indoor clothing and no shoes. BMI was calculated as weight (kg) divided by height (m^2). Body composition was further assessed using a Lunar Prodigy dual-energy x-ray absorptiometry (DXA) system (GE Healthcare). DXA has been validated as a method of assessing body composition in both younger and older persons, has good reported reproducibility, is sensitive to small changes in body composition, and can be used to measure fat mass with a precision error (1 SD) of 1 kg (23–26). The fat mass index (FMI), a measure of total fat mass adjusted for height, is calculated as fat mass (kg) divided by height (m^2). Two established definitions of obesity were used: FMI ≥13 kg/m^2 (27) and BMI ≥30 kg/m^2 (28).

Patient-reported outcomes. PROs were assessed at the study visit, using validated questionnaires. We assessed 4 different PROs: patient-reported disease activity, depressive symptoms, pain, and fatigue. Patient-reported disease activity was measured using the Systemic Lupus Activity Questionnaire (SLAQ), which has been shown to have good reliability (Cronbach's α = 0.87) and validity in observational studies (29–31). The SLAQ assesses SLE disease activity by way of 24 items in 9 organ systems, with total scores ranging from 0 to 44, and with higher scores indicating greater disease activity. Depressive symptoms were measured with the Center for Epidemiologic Studies Depression Scale (CES-D), a validated 20-item scale used to evaluate depressive symptom severity; scores range from 0 to 60 (32). Symptoms of pain and fatigue were measured using the Short Form 36 (SF-36) body pain and vitality subscales, respectively. Although the SF-36 includes a total of 8 subscales, we focused on the 2 subscales measuring pain and fatigue, because prior research has identified these symptoms as being the most commonly reported and representing the greatest area of unmet need in SLE (1,11–13). The SF-36 subscales have demonstrated excellent reliability and validity in previous studies and are the PROs most commonly used in studies of SLE (33). The SF-36 subscales are scored on a scale of 0–100, with higher scores reflecting better status (e.g., less pain and fatigue).

SLE-specific disease factors. Disease duration was obtained by self-report. The Brief Index of Lupus Damage (BILD) was used to measure lupus-related cumulative organ damage (34,35). The BILD was developed from the Systemic Lupus International Collaborating Clinics/ACR Damage Index (36) and includes items for important comorbid conditions such as cardiovascular events and diabetes mellitus. Participants were also queried regarding current immunomodulatory medications and glucocorticoids, including dosage and frequency.

Other variables. Sociodemographic characteristics included age, race, educational attainment (education beyond high school or not), and poverty status (household income ≤125% or >125% of the federal poverty level [37]). Participants were also asked about smoking status, with potential answers that included current, former, or never.

Differences in characteristics of obese and non-obese participants were tested with *t*-tests and chi-square analyses. Bivariate linear regression was used to quantify the cross-sectional association between obesity and each PRO. Multiple linear regression was then used to model each of the PROs as a function of obesity, adjusting for age, race, educational attainment, poverty status, smoking, disease duration, disease damage, and

Table 1. Characteristics of the patients with SLE according to obesity category*

	Overall (n = 143)	Non-obese (n = 96)	Obese (n = 47)†	*P*
Demographic characteristics				
Age, mean ± SD	47.9 ± 12.3	47.3 ± 12.7	48.9 ± 11.7	0.47
Race				0.03
White	92 (64.8)	68 (71.6)	24 (51.1)	
African American	20 (14.1)	9 (9.5)	11 (23.4)	
Asian	18 (12.7)	14 (14.7)	4 (8.5)	
Latino	25 (17.6)	15 (15.8)	10 (21.3)	
Not specified or other	4 (2.8)	1 (1.1)	3 (6.4)	
Education beyond high school	123 (86.6)	86 (90.5)	37 (78.7)	0.05
Poverty level income‡	21 (15.3)	8 (8.7)	13 (28.9)	0.002
Health-related characteristics				
Cardiovascular disease§	5 (3.5)	3 (3.2)	2 (4.3)	0.74
Diabetes mellitus, treated	8 (5.6)	2 (2.1)	6 (12.8)	0.01
SLE disease duration, years	15.5 ± 8.9	14.9 ± 8.4	16.9 ± 9.9	0.21
CRP level, mean ± SD mg/liter	4.2 ± 7.6	3.2 ± 7.0	6.2 ± 8.4	<0.01
Smoking, current	8 (5.6)	6 (6.3)	2 (4.3)	0.62
Smoking, ever	53 (37.6)	37 (39.0)	16 (34.8)	0.63
Medication use¶				
Glucocorticoid	63 (45.3)	42 (45.2)	21 (45.7)	0.96
Prednisone dosage ≥7.5 mg/day	29 (20.1)	18 (19.4)	11 (23.9)	0.53
Hydroxychloroquine	63 (44.4)	44 (46.3)	19 (40.4)	0.51
Oral DMARD#	50 (35.2)	35 (36.8)	15 (31.9)	0.56
Cyclophosphamide	7 (4.9)	7 (7.4)	0 (0.0)	0.06
Rituximab	5 (3.5)	5 (5.3)	0 (0.0)	0.12

* *P* values were calculated using the chi-square test for categorical measures, *t*-test for normally distributed continuous measures, and Wilcoxon's rank sum test for skewed continuous measures. Except where indicated otherwise, values are the number (%). SLE = systemic lupus erythematosus; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug.

† Defined as a fat mass index ≥13 kg/m^2.

‡ Household income ≤125% of the federal poverty level.

§ History of transient ischemic attack, stroke, or myocardial infarction.

¶ Reported use within the previous 12 months.

Including azathioprine, mycophenolate mofetil, methotrexate, and tacrolimus.

Table 2. Raw medians (interquartile ranges) for patient-reported outcomes according to obesity status*

	Total	Obese†	Non-obese	*P*
Disease activity (SLAQ) (range 0–44)	12.0 (8.0–18.0)	15.0 (11.0–19.0)	10.0 (5.0–15.0)	<0.001
Depression (CES-D) (range 0–60)	13.5 (5.0–23.0)	20.0 (11.0–31.0)	10.0 (4.0–21.0)	<0.001
Pain (SF-36 pain) (range 0–100)‡	41.4 (33.4–50.3)	37.2 (33.0–41.4)	46.1 (33.4–55.4)	<0.001
Fatigue (SF-36 vitality) (range 0–100)‡	42.7 (33.4–52.1)	36.5 (30.2–45.8)	45.8 (36.5–55.2)	<0.001

* *P* values were calculated using Wilcoxon's rank sum test. SLAQ = Systemic Lupus Activity Questionnaire; CES-D = Center for Epidemiologic Studies Depression Scale; SF-36 pain = Short Form 36 pain subscale; SF-36 vitality = SF-36 vitality subscale.
† Defined as fat mass index ≥13 kg/m^2.
‡ Higher scores indicate better status (less pain/fatigue).

use of a moderate dosage of prednisone (defined as ≥7.5 mg/day). Several procedures were used to ensure the integrity of the model: the normality assumption was evaluated visually with box plots and normal probability plots; collinearity was assessed by calculating a variance inflation factor (VIF) for each covariate and removing colinear variables based on a VIF ≥10 from the final model; and homoscedasticity was confirmed by plots of fitted values versus residuals. We also conducted sensitivity analyses in which additional measurements of adiposity were used as the dependent variable (including BMI ≥30 kg/m^2, BMI as a continuous measure, FMI as a continuous measure, and percent body fat) in order to determine whether the relationship between adiposity and each PRO varied depending on the measure of adiposity used. We then calculated adjusted means for each outcome based on the multivariable regression. All analyses were performed using Stata version 14.

RESULTS

Characteristics of the participants. The demographic and disease-specific characteristics of the study participants are shown in Table 1. Thirty-two percent and 30% of participants met the criteria for obesity according to the FMI and BMI definitions, respectively. Five participants (4%) were obese according to the FMI definition but not the BMI definition, 2 participants (1%) were obese according to the BMI definition but not the FMI definition, and the remaining 95% of patients demonstrated concordance across the 2 definitions. Study participants who were obese were more likely to be African American, living at or below poverty level income, and have a low education level. Additionally, more participants in the obese group were receiving treatment for diabetes mellitus and had elevated serum levels of C-reactive protein.

Bivariate associations of obesity with PROs. In bivariate regression analyses, obesity as defined by the FMI was significantly associated with higher disease activity as measured by the SLAQ ($\beta = 4.55$, $P < 0.001$), more symptoms of depression ($\beta = 7.74$, $P < 0.001$), and higher levels of pain ($\beta = -7.16$, $P < 0.001$) and fatigue ($\beta = -6.98$, $P = 0.001$) (Table 2). These relationships remained stable when we repeated the analysis using alternative definitions for obesity and adiposity, including the traditional obesity definition of BMI ≥30 kg/m^2.

Multivariate analysis. In the multivariate regression model, obesity defined by the FMI was associated with significantly worse scores for each PRO after adjustment for age,

Table 3. Adjusted means (95% CIs) for patient-reported outcomes according to obesity status*

	Obesity defined as FMI ≥13 kg/m^2			Obesity defined as BMI ≥30 kg/m^2		
	Yes	No	*P*	Yes	No	*P*
Disease activity (SLAQ)	14.8 (12.7–16.9)	11.5 (10.1–12.9)	0.01	14.7 (12.6–16.9)	11.6 (10.2–13.1)	0.02
Depression (CES-D)	19.8 (16.1–23.4)	13.1 (10.6–15.6)	0.004	20.3 (16.5–24.0)	13.1 (10.7–15.5)	0.003
Pain (SF-36 pain)†	38.7 (35.7–41.7)	44.2 (42.2–46.3)	0.004	38.2 (35.1–41.3)	44.2 (42.1–46.1)	0.003
Fatigue (SF-36 vitality)†	39.6 (36.2–43.0)	45.2 (42.9–47.6)	0.01	38.0 (34.5–41.4)	45.7 (43.4–47.9)	<0.001

* Adjusted means were calculated based on multivariate linear regression adjusted for age, race, education, income, smoking, disease duration, disease damage (Brief Index of Lupus Damage score), and prednisone use. *P* values were determined using Wilcoxon's rank sum test. 95% CIs = 95% confidence intervals; FMI = fat mass index; BMI = body mass index; SLAQ = Systemic Lupus Activity Questionnaire; CES-D = Center for Epidemiologic Studies Depression Scale; SF-36 pain = Short Form 36 pain subscale; SF-36 vitality = SF-36 vitality subscale.
† Higher scores indicate better status (less pain/fatigue).

Table 4. Bivariate relationships of obesity and covariates with patient-reported outcomes*.

	SLAQ	CES-D	SF-36 pain	SF-36 vitality
Body composition				
Obesity defined as FMI ≥13 kg/m^2	4.55 (<0.001)	7.74 (<0.001)	−7.16 (<0.001)	−6.98 (0.001)
Obesity defined as BMI ≥30 kg/m^2	4.54 (0.001)	8.17 (<0.001)	−7.30 (<0.001)	−8.66 (<0.001)
Covariates				
Age	0.02 (0.68)	−0.01 (0.90)	−0.07 (0.31)	−0.11 (0.17)
Race	−0.78 (0.55)	2.76 (0.20)	0.77 (0.68)	−2.91 (0.15)
Low education†	1.27 (0.48)	2.67 (0.38)	−2.95 (0.26)	−2.90 (0.31)
Poverty level income‡	4.26 (0.01)	8.87 (0.001)	−5.49 (0.02)	−5.35 (0.04)
Smoking, current	5.13 (0.04)	2.18 (0.62)	−5.29 (0.16)	−2.15 (0.60)
Smoking, ever	0.79 (0.53)	−1.01 (0.64)	−3.90 (0.04)	0.23 (0.91)
Disease duration	−0.09 (0.16)	−0.01 (0.90)	−0.05 (0.61)	0.02 (0.81)
BILD score	0.57 (0.055)	0.46 (0.36)	−1.22 (0.01)	−0.83 (0.08)
Prednisone use (yes/no)	2.20 (0.08)	1.47 (0.49)	−3.31 (0.07)	−2.41 (0.23)
Prednisone dose	0.18 (0.08)	0.09 (0.60)	−0.25 (0.10)	−0.04 (0.81)
Prednisone ≥7.5 mg/day	4.64 (0.002)	4.20 (0.11)	−5.70 (0.01)	−2.92 (0.23)
Oral DMARD§	−0.52 (0.69)	2.16 (0.32)	−2.53 (0.18)	−4.80 (0.02)
Immunosuppressive agent¶	−0.48 (0.70)	3.23 (0.13)	−2.74 (0.14)	−5.13 (0.01)

* Values are β coefficients (*P* values). SLAQ = Systemic Lupus Activity Questionnaire; CES-D = Center for Epidemiologic Studies Depression Scale; SF-36 pain = Short Form 36 pain subscale (higher scores indicate less pain); SF-36 vitality = SF-36 vitality subscale (higher scores indicate less fatigue); FMI = fat mass index; BMI = body mass index; BILD = Brief Index of Lupus Damage; DMARD = disease-modifying antirheumatic drug.
† No education beyond high school.
‡ Household income ≤125% of the federal poverty level.
§ Includes azathioprine, mycophenolate mofetil, methotrexate, and tacrolimus.
¶ Includes azathioprine, mycophenolate mofetil, methotrexate, and tacrolimus, cyclophosphamide, and rituximab.

race, education, poverty status, smoking, disease duration, disease damage (using the BILD), and glucocorticoid use (Table 3). Patient-reported disease activity was higher in the obese group: the mean adjusted SLAQ score was 14.8 (95% confidence interval [95% CI] 12.7–16.9) versus 11.5 (95% CI 10.1–12.9) in non-obese participants. When the CES-D was used to compare the severity of depressive symptoms, the mean adjusted score was 19.8 (95% CI 16.1–23.4) in the obese group versus 13.1 (95% CI 10.6–15.6) for the rest of the cohort. Similarly, the obese group reported a significantly higher burden of pain (P = 0.005 versus non-obese group) and fatigue (P = 0.01 versus non-obese group), as assessed using the SF-36 subscales. The same independent relationship between obesity and each PRO was observed after repeating the analyses using the BMI ≥30 kg/m^2 cutoff. The associations for obesity and each covariate with each PRO from the bivariate and multivariate regression analyses are shown in Tables 4 and 5.

DISCUSSION

Among a representative sample of women with SLE, one-third were obese. The obesity prevalence reported here is consistent with that in other reports in the limited literature on this topic. One study showed a 39% prevalence of obesity among a group of women with lupus (38), while a more recent study showed a prevalence of 29–50% depending on the method of ascertainment (39). The proportion of obese participants in the lupus cohort in the current study was slightly lower than that in the general population in the US during the same time frame. According to the Centers for Disease Control and Prevention National Health and Nutrition Examination Survey, the prevalence of obesity among women was 35.8% across all age groups, 31.9% among women ages 20–39 years, and 42.3% among women ages ≥60 years older (40).

We investigated the impacts of obesity in SLE and observed a significant independent association with worse PROs, including self-reported disease activity, depressive symptoms, and symptoms of pain and fatigue. The raw differences in scores for the PROs between the obese and overweight/normal BMI groups were more than one-half the SD of the mean for each measure, suggesting a difference that is clinically meaningful (41). After we adjusted for relevant variables, the association between obesity and all 4 PROs remained statistically significant.

Table 5. Multivariate relationships of obesity and covariates with patient-reported outcomes*

	SLAQ	CES-D	SF-36 pain	SF-36 vitality
Obese†	3.33 (0.01)	6.67 (0.004)	−5.55 (0.004)	−5.66 (0.01)
Age	0.11 (0.06)	0.02 (0.82)	−0.16 (0.05)	−0.20 (0.03)
Race	0.82 (0.52)	5.96 (0.01)	−1.62 (0.38)	−4.77 (0.02)
Low education‡	−0.64 (0.72)	−2.57 (0.41)	−0.45 (0.86)	−1.00 (0.73)
Poverty level income§	3.01 (0.10)	8.67 (0.01)	−3.06 (0.24)	−6.39 (0.03)
Smoking, current	3.91 (0.14)	0.80 (0.86)	−2.95 (0.44)	−0.24 (0.96)
Disease duration	−0.19 (0.01)	−0.01 (0.92)	0.08 (0.45)	0.18 (0.15)
BILD score	0.69 (0.02)	0.51 (0.31)	−1.23 (0.004)	−0.90 (0.06)
Prednisone ≥7.5 mg/day	3.33 (0.03)	2.65 (0.31)	−5.73 (0.01)	−2.38 (0.33)
Model F value (df)	3.72	2.98	3.98	3.28
Model R^2	0.21	0.18	0.23	0.19
Model-adjusted R^2	0.16	0.12	0.17	0.13

* Except where indicated otherwise, values are β coefficients (*P* values). SLAQ = Systemic Lupus Activity Questionnaire; CES-D = Center for Epidemiologic Studies Depression Scale; SF-36 pain = Short Form 36 pain subscale (higher scores indicate less pain); SF-36 vitality = SF-36 vitality subscale (higher scores indicate less fatigue); BILD = Brief Index of Lupus Damage.
† Defined as a fat mass index (FMI) ≥13 kg/m^2.
‡ No education beyond high school.
§ Household income ≤125% of the federal poverty level.

Body composition, and specifically excess adiposity, has been recognized as an important predictor of worse PROs in the general population and in several rheumatic diseases. We now understand that adipose tissue is an active endocrine tissue that secretes proinflammatory cytokines and adipokines (including leptin, adiponectin, and resistan) into the systemic circulation, with the potential to impact joint disease (42–45). A study in patients with osteoarthritis of the shoulder showed that higher levels of adiponectin and leptin in synovial fluid were independently associated with greater patient-reported shoulder-specific pain (46), which supports the hypothesis that adiposity contributes to pain in OA via both local mechanical and systemic biomechanical mechanisms. A meta-analysis designed to assess the impact of obesity on outcomes in RA demonstrated that obese patients had significantly worse Health Assessment Questionnaire scores and higher pain scores at follow-up relative to non-obese patients, even after controlling for relevant covariates (15). Similarly, studies evaluating the relationship between obesity and PROs in patients with sarcoidosis or axial spondyloarthritis have demonstrated an independent association between the presence of obesity and worse PROs, including pain, fatigue, and indices of global health status (16,17).

Our study builds on the limited literature, in which findings regarding the relationship between obesity and PROs in SLE are inconsistent, and is the first to demonstrate a significant independent association between obesity and greater levels of pain and fatigue in this patient population. Oeser et al examined these relationships using a sample of 100 patients with SLE, and although they observed an association between obesity and pain in the bivariate analysis, the relationship was not statistically significant in the adjusted multivariable model (19). In our study, we observed a significant association between obesity and pain, even after adjusting for covariates. Similarly, 2 previous studies of obesity in SLE (18,19) showed significant associations with fatigue in the bivariate, but not the multivariate, regression models. Our finding of a more robust association between obesity and both pain and fatigue may be attributable to differences in power (larger sample size), measurement tools (e.g., Fatigue Severity Scale versus SF-36 vitality subscale), or the composition of the multivariable models. Our multivariable regression model was constructed to include all major covariates with potential for confounding while eliminating those that demonstrated colinearity. The results remained consistent after testing multiple iterations of the model.

The primary limitation of this study is the cross-sectional design, which precludes the ability to infer causation or directionality between variables. We hypothesize that obesity adversely impacts PROs via both physiologic and psychosocial mechanisms. However, it is also possible that individuals who report greater disease activity and symptom burden are more sedentary, and therefore are more likely to become obese. In the future, longitudinal data evaluating the relationship between obesity and changes in PROs over time will be helpful for elucidating the most proximal variable in these relationships. Additionally, future work should address whether the association between obesity and worse outcomes in obese patients with SLE includes less favorable scores on physician-reported instruments or whether the association is limited to PROs.

As with most human studies, there is a risk of selection bias in the current study. Less than one-half of the initially screened

individuals were eligible and agreed to participate. The requirement that participants be well enough to attend study visits, as well as self-selection, may have resulted in a sample skewed toward women in whom disease is less severe. Also, because this analysis included only female participants, the results are not generalizable to men with SLE. It is also possible that analysis of other PROs may yield different results.

The limitations of this study are outweighed by several strengths. The independent variable was measured using multiple definitions of obesity, including both BMI and FMI. Although BMI has been the traditional measure of obesity and is easy to determine in clinical practice, it comes with limitations, including the inability to distinguish between fat mass and lean mass (47). We overcame this limitation by using FMI as measured by DXA, which allows for distinction between fat mass and lean mass, as our primary measure of obesity. Additionally, the sample included individuals with physician-confirmed lupus who were recruited from a variety of practice settings and represented a diverse range of racial and socioeconomic groups.

In conclusion, we observed that excess adiposity is common in SLE and is independently associated with a greater symptom burden and self-reported disease activity. This finding has important clinical implications, because the symptoms assessed in our study are known to have profound effects on quality of life and remain an area of unmet need for the majority of patients with SLE. The relationship observed in the current study between body composition and PROs further underscores the need to examine the impact of lifestyle interventions for lupus patients who are overweight. In addition to reducing the risk of important comorbidities such as cardiovascular disease, such interventions may reduce the severity of debilitating symptoms experienced by patients with SLE.

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. Katz 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. Katz.

Acquisition of data. Katz.

Analysis and interpretation of data. Patterson, Schmajuk, Jafri, Yazdany, Katz.

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The Impact of Systemic Lupus Erythematosus on the Clinical Phenotype of Antiphospholipid Antibody–Positive Patients: Results From the AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Clinical Database and Repository

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Objective. Although systemic lupus erythematosus (SLE) is the most common autoimmune disease associated with antiphospholipid antibodies (aPL), limited data exist regarding the impact of SLE on the clinical phenotype of aPL-positive patients. The primary objective of this study was to compare the clinical, laboratory, and treatment characteristics of aPL-positive patients with SLE with those of aPL-positive patients without SLE.

Methods. A secure web-based data capture system was used to store patient demographic characteristics and aPL-related clinical and laboratory characteristics. Inclusion criteria included positive aPL according to the updated Sapporo classification criteria. Antiphospholipid antibody–positive patients fulfilling the American College of Rheumatology criteria for the classification of SLE ("aPL with SLE") and those with no other autoimmune diseases ("aPL only") were included in the analysis.

Results. Six hundred seventy-two aPL-positive patients were recruited from 24 international centers; 426 of these patients did not have other autoimmune disease, and 197 had SLE. The frequency of thrombocytopenia, hemolytic anemia, low complement levels, and IgA anti–β_2-glycoprotein I (anti-β_2GPI) antibodies was higher in the aPL-positive patients with SLE, whereas the frequency of cognitive dysfunction and IgG anti-β_2GPI antibodies was higher in the aPL-only group. The frequency of arterial and venous thromboses (including recurrent) as well as pregnancy morbidity was similar in the 2 groups. The prevalence of cardiovascular disease risk factors at the time of entry into the registry entry did not differ between the 2 groups, with the exception of current smoking, which was more frequent in aPL-positive patients with SLE.

Conclusion. Although the frequencies of thrombosis and pregnancy morbidity are similar in aPL-positive patients with and those without SLE, the diagnosis of SLE in patients with persistently positive aPL is associated with an increased frequency of thrombocytopenia, hemolytic anemia, low complement levels, and positive IgA anti-β_2GPI antibodies.

INTRODUCTION

Antiphospholipid syndrome (APS) is characterized by thromboses and/or pregnancy morbidity associated with persistently positive antiphospholipid antibodies (aPL), lupus anticoagulant (LAC), anticardiolipin antibodies (aCL), and/or anti–β_2-glycoprotein I (anti-β_2GPI) antibodies (1). Thrombocytopenia, autoimmune hemolytic anemia, livedo reticularis/racemosa, aPL-associated nephropathy, cardiac valve disease, cognitive dysfunction, and skin ulcers can also occur in aPL-positive patients (1,2), characterized as "non-criteria" APS manifestations.

APS can occur in individuals without an underlying systemic autoimmune disease (primary APS) or in the context of other systemic autoimmune diseases, with systemic lupus erythe-

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SIGNIFICANCE & INNOVATIONS

- Although systemic lupus erythematosus (SLE) is the most common autoimmune disease associated with antiphospholipid antibodies (aPL), limited data exist regarding the impact of SLE on the clinical phenotype of aPL-positive patients.
- Based on the analysis of a large-scale international registry, our study demonstrates that a concomitant SLE diagnosis in patients with persistently positive aPL does not increase the frequency of thrombosis (including recurrent) and pregnancy morbidity. However, aPL-positive patients with SLE have an increased frequency of thrombocytopenia, hemolytic anemia, low complement levels, and IgA anti–β_2-glycoprotein I antibody positivity compared with aPL-positive patients without other autoimmune diseases.
- Additionally, aPL-positive patients with SLE had a significantly higher frequency of current smoking, while aPL-positive patients without other autoimmune diseases had an increased frequency of cognitive dysfunction.
- Although hydroxychloroquine (HCQ) use was more common in aPL-positive patients with SLE, 40% of aPL-positive patients with no other autoimmune diseases, especially those with lupus-related clinical and serologic manifestations, also received HCQ.

matosus (SLE) being the most common (30–50%) (3). Variable clinical features ranging from mild joint and skin involvement to life-threatening renal, hematologic, and/or central nervous system manifestations can occur in patients with SLE. (4). Thirty percent to forty percent of SLE patients are positive for aPL (5); the prevalence of a "clinically significant" aPL profile (positive LAC test result based on the International Society of Thrombosis and Hemostasis [ISTH] guidelines [6]), IgG/IgM aCL levels ≥40 IgG phospholipid (GPL)/IgM phospholipid (MPL) units and/or IgG/IgM anti-β_2GPI levels ≥40 GPL/MPL units, tested twice at least 12 weeks apart is ~30% (7). Although persistently positive aPL has an impact on the clinical presentation and prognosis of patients with SLE (5), a limited number of studies have analyzed the impact of SLE on the clinical phenotype and prognosis of aPL-positive patients (8).

The AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) is an international network created to design and conduct large-scale, multicenter studies and clinical trials in patients with persistent aPL positivity (9). The APS ACTION clinical database and repository ("registry") was created to study the natural disease course in patients with persistently positive aPL with or without autoimmune disorders over at least 10 years; the registry allows us to perform cross-sectional and prospective analyses.

In this international multicenter study, our primary objective was to compare the clinical, laboratory, and treatment characteristics of aPL-positive patients with SLE and those without SLE. Second, we analyzed the frequencies of traditional cardiovascular disease (CVD) risk factors in aPL-positive patients with and those without SLE, and the pattern of use of hydroxychloroquine (HCQ), an immunoregulatory agent with antithrombotic effects, among aPL-positive patients with no other autoimmune diseases. We hypothesized that aPL-positive patients with SLE have increased rates of aPL-related clinical manifestations, traditional CVD risk factors, lupus-related antibodies, and immunosuppressive use (including HCQ), compared with those without SLE.

PATIENTS AND METHODS

APS ACTION registry and data collection. An international web-based application, Research electronic data capture (REDCap) (10), captures data on patient demographics, aPL-related clinical and laboratory characteristics, and medications. Data are collected once each year and at the time of a new aPL-related thrombosis or pregnancy morbidity. The inclusion criteria are age 18–60 years and persistent (at least 12 weeks apart) aPL positivity within 12 months prior to screening. Positivity is defined as the presence of IgG/IgM/IgA aCL at medium-to-high levels (≥40 GPL/MPL/IgG antiphospholipid [APL] units and/or greater than the 99th percentile) and/or the presence of IgG/IgM/IgA anti-β_2GPI antibodies at medium-to-high levels (≥40 GPL/MPL/APL units and/or greater than the 99th percentile), and/or positive LAC tests based on the ISTH guidelines (6). Patients are followed up every 12 ± 3 (mean ± SD) months with clinical data and blood collection; they also receive advice on CVD and thrombosis prevention at each visit.

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Table 1. Clinical and laboratory characteristics (historic and/or at registry entry) of patients with persistent aPL positivity, overall and stratified by SLE*

Variables	All aPL-positive patients (n = 623)	aPL-positive patients without SLE (n = 426)	aPL-positive patients with SLE (n = 197)	*P*
Demographics				
Age at entry into registry, mean ± SD years	44.2 ± 12.8	44.58 ± 12.9	43.24 ± 12.5	0.22
Female sex	459 (74)	307 (72)	152 (77)	0.18
Race†				
White	397 (71)	274 (71)	123 (71)	
Latin American Mestizos	81 (15)	66 (17)	15 (9)	
Asian	48 (9)	28 (7)	20 (12)	
Black	21(4)	10 (3)	11 (6)	
American Indian or Alaskan Native	1 (0.2)	0	1 (0.6)	
Reported as "other"	12 (2)	9 (2)	3 (2)	
Ethnicity‡				
US, Canada, Europe	261 (51)	183 (50)	78 (55)	
Non–Latin American	242 (48)	168 (46)	74 (48)	
Latin American	19 (4)	15 (4)	4 (3)	
South America	124 (24)	96 (26)	28 (20)	
Afro-descendant	16 (3)	8 (2)	8 (6)	
Mestizo	67 (13)	54 (15)	13 (9)	
Caucasian	41 (8)	34 (9)	7 (5)	
Australia	3 (0.6)	2 (0.5)	1 (0.7)	
Aboriginal	0	0	0	
Not Aboriginal	3 (0.6)	2 (0.5)	1 (0.7)	
Other	121 (24)	85 (23)	36 (24)	
Clinical manifestations				
Arterial thrombosis (AT)	193 (31)	139 (33)	54 (27)	0.26
Venous thrombosis (VT)	272 (44)	185 (43)	87 (44)	0.13
Microthrombosis (MT)	37 (6)	27 (6)	10 (5)	0.23
Any vascular event (AT/VT/MT)	422 (68)	297 (70)	125 (64)	0.12
Recurrent vascular event	198/422 (47)	163/297 (55)	61/125 (49)	0.25
Pregnancy (ever)	318 (51)	221(52)	97 (49)	0.06
Pregnancy morbidity	210 (34)	154 (36)	56 (28)	0.1
≥1 fetal death after 10th week of gestation	110 (18)	76 (18)	34 (17)	0.15
≥1 premature birth before 34th week of gestation	54 (9)	43 (10)	11 (6)	0.09
≥3 consecutive unexplained spontaneous abortions before 10th week of gestation	23 (4)	19 (5)	4 (2)	0.1
Catastrophic APS	6 (1)	4 (1)	2 (1)	0.24
Livedo reticularis/racemosa	80 (13)	52 (12)	28 (14)	0.48
Persistent thrombocytopenia	124 (20)	69 (16)	55 (28)	0.001
Autoimmune hemolytic anemia	32 (5)	9 (2)	23 (12)	<0.001
ECG-proven cardiac valve disease	50/518 (10)	30/349 (9)	20/169 (12)	0.31
Biopsy-proven aPL-associated nephropathy	19/577 (3)	11/397 (3)	8/180 (4)	0.30
Skin ulcers	32 (5)	21 (5)	11 (6)	0.12
Cognitive dysfunction	19/148 (13)	14/90 (16)	5/58 (9)	<0.001

(continued)

Table 1. (*Cont'd*)

Variables	All aPL-positive patients (n = 623)	aPL-positive patients without SLE (n = 426)	aPL-positive patients with SLE (n = 197)	*P*
Complement level				
Low complement 3 (C3) level	93/240 (39)	29/126 (23)	64/114 (56)	<0.001
Low complement 4 (C4) level	92/240 (38)	30/126 (24)	62/114 (54)	<0.001
Antiphospholipid antibodies				
Lupus anticoagulant (LAC)	417 (67)	288 (68)	129 (66)	0.6
Anticardiolipin antibody (aCL)				
IgG (positive defined as ≥20 GPL)	357 (57)	245 (58)	15/89 (17)	0.87
IgG (positive defined as ≥40 GPL)	280 (45)	202 (47)	112 (57)	0.07
IgM (positive defined as ≥20 MPL)	223 (36)	154 (36)	78 (40)	0.79
IgM (positive defined as ≥40 MPL)	139 (22)	96 (23)	43 (22)	0.84
IgA (positive defined as ≥20 APL)	41/149 (28)	24/89 (27)	17/60 (28)	0.85
IgA (positive defined as ≥40 APL)	26/149 (17)	15/89 (17)	11/60 (18)	0.81
Anti-β_2GPI§				
IgG (positive defined as ≥20 GPL)	265 (43)	194 (46)	71 (36)	0.03
IgG (positive defined as ≥40 GPL)	208 (33)	157 (37)	51 (26)	0.01
IgM (positive defined as ≥20 MPL)	173 (28)	124 (29)	49 (25)	0.27
IgM (positive defined as ≥40 MPL)	114 (18)	81 (19)	33 (17)	0.5
IgA (positive defined as ≥20 APL)	58/160 (36)	30/104 (29)	28/56 (50)	0.02
IgA (positive defined as ≥40 APL)	37/160 (23)	19/104 (18)	18/56 (32)	0.04
Double aPL positive (LAC + aCL, LAC + anti-β_2GPI, or aCL + anti-β_2GPI)	187 (30)	121 (28)	66 (34)	0.1
Triple aPL positive (LAC + aCL + anti-β_2GPI)	209 (34)	158 (37)	51 (26)	0.1
Medications at registry entry				
Low-dose aspirin	273 (44)	183 (43)	90 (44)	0.52
Warfarin	344 (55)	245 (58)	99 (50)	0.09
Direct oral anticoagulants	15 (2)	10 (2)	5 (3)	0.89
Glucocorticoids	111 (18)	39 (9)	72 (37)	<0.001
Hydroxychloroquine	276 (44)	133 (31)	143 (72)	<0.001
Immunosuppressive agents				
IV immunoglobulin	2 (0.3)	1 (0.2)	1 (1)	0.58
Rituximab	7 (1)	3 (1)	4 (2)	0.14
Azathioprine	46 (7)	11 (3)	35 (18)	<0.001
Cyclophosphamide	8 (1)	2 (1)	6 (3)	0.008
Cyclosporine	4 (1)	2 (1)	2 (1)	0.43
Methotrexate	17 (3)	4 (1)	13 (7)	<0.001
Mycophenolate mofetil	45 (7)	11 (3)	34 (17)	<0.001

* Except where indicated otherwise, values are the number (%). aPL = antiphospholipid antibody; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome; ECG = electrocardiography; GPL = IgG phospholipid; MPL = IgM phospholipid; anti-β_2GPI = anti–β_2-glycoprotein I; LAC = lupus anticoagulant; IV = intravenous.
† Information was collected for 560 patients (387 in the aPL only group and 173 in the aPL with SLE group).
‡ Information was collected for 509 patients (366 in aPL only group and 143 in the aPL with SLE group).

Study cohort. Although the APS ACTION registry captures data for patients with a variety of autoimmune diseases, for the purpose of this analysis, patients with autoimmune diseases other than SLE were excluded. Thus, 2 mutually exclusive groups were included: aPL-positive patients with no other systemic autoimmune diseases ("aPL only") and aPL-positive patients who also met the American College of Rheumatology (ACR) SLE classification criteria ("aPL with SLE") (11).

Covariates. We evaluated demographic characteristics at the time of cohort entry, including mean age, race (white, Latin American Mestizos, Asian, black, American Indian or Alaskan, Native American, "other"), ethnicity (non–Latin American or Latin American [for US, Canada, Europe], Afro-descendent, Mestizo, or Caucasian [for South America], Aboriginal or non-Aboriginal [for Australia], or "other"). Clinical data retrieved were history of arterial and venous thrombosis, biopsy-proven microthrombosis (pulmonary, skin, kidney, and "other"), pregnancy morbidity based on the updated Sapporo classification criteria, catastrophic APS based on the preliminary classification criteria (12), livedo reticularis/racemosa, persistent thrombocytopenia (defined as a platelet count <100,000/μl [2 tests performed at least 12 weeks apart]), autoimmune hemolytic anemia, echocardiography-proven cardiac valve disease, biopsy-proven aPL nephropathy, skin ulcers, and neuropsychiatric test–proven cognitive dysfunction. Laboratory data retrieved at baseline were aPL-related (LAC, IgG/IgM/IgA aCL, and IgG/IgM/IgA anti-β_2GPI antibodies) and lupus-related antibodies (antinuclear antibody, anti–double-stranded DNA antibodies), anti-Sm, and complement components C3 and C4). Cardiovascular risk factors assessed at the time of entry into the registry were hypertension, diabetes mellitus, and hyperlipidemia requiring treatment; current and past smoking; estrogen use; obesity; family history of CVD; and sedentary lifestyle. Medications (low-dose aspirin, warfarin, direct oral anticoagulants, glucocorticoids, HCQ, intravenous immunoglobulin, rituximab, azathioprine, cyclophosphamide, cyclosporine, methotrexate, and mycophenolate mofetil) were included in the analysis as "ever used" or "never used."

Statistical analysis. Data from the APS ACTION registry were locked in on February 2017. We compared the prevalence of covariates (historical or baseline) in the aPL only and aPL with SLE groups using the chi-square test for categorical variables. One-way analysis of variance was used to test the differences in means between multiple independent groups, and Student's *t*-test was used for 2-group comparisons. We calculated 2-sided *P* values to determine the significance of all findings, with the significance level set at $P < 0.05$. Analyses were conducted using SPSS version 24.0.

RESULTS

As of February 2017, 672 aPL-positive patients were recruited from 24 centers; 43 patients (6%) were excluded due to underlying autoimmune diseases other than SLE, and 6 (1%) were excluded due to missing data. Of the remaining 623 patients, 426 did not have other autoimmune diseases (aPL only) and 197 had SLE (aPL with SLE). Fifty-nine patients in the aPL only group had SLE-like diseases (3 of 11 ACR SLE classification criteria were met) (11).

Table 1 shows the clinical, laboratory, and treatment characteristics collected at the time of entry into the registry. The mean ± SD age of the participants was 44.2 ± 12.8 years, and the majority of patients (74%) were categorized as white. Three hundred thirty-eight (79%) of 426 patients in the aPL only group and 137 (70%) of 426 patients in the aPL with SLE group were classified as having APS according to the updated Sapporo classification criteria (1). Overall, 422 (68%) of 623 patients had a history of thrombotic APS, and 57 (9%) had obstetric APS only. The mean ± SD disease duration (time from the first available positive aPL test result to the enrollment date) was similar in the 2 groups (5.6 ± 4.9 years in the aPL only group and 6.3 ± 5.1 years in the aPL with SLE group ($P = 0.1$).

Antiphospholipid antibody–positive patients with SLE had higher rates of persistent thrombocytopenia, autoimmune hemolytic anemia, low C3 and C4 levels, and IgA anti-β_2GPI antibody positivity, whereas the aPL only group had significantly higher rates of cognitive dysfunction and IgG anti-β_2GPI antibody positivity. Glucocorticoids, HCQ, azathioprine, cyclophosphamide, methotrexate, and mycophenolate mofetil were more frequently used in the aPL with SLE group.

The prevalence of traditional CVD risk factors at the time of entry into the registry did not differ between the 2 groups, with the exception of current smoking, which was more frequent in aPL-positive SLE patients (15% versus 9% in the aPL only group; $P = 0.03$) (Table 2). In the aPL only group, 262 patients (62%) were never treated with HCQ, 133 (31%) were current users (200–400 mg daily), and 31 (7%) were past users; 99 (74%) of the 133 current users and 26 (84%) of the 31 past users were classified as having APS. Patients with lupus-related clinical manifestations, low C4 levels, and lupus-related autoantibodies were more likely to be treated with HCQ (Table 3). After patients with SLE-like diseases (i.e., 3 of 11 ACR classification criteria for SLE were met) (n = 59) were excluded, when we analyzed 367 patients in the aPL only group, we observed a higher frequency of HCQ treatment in patients with low C4 levels and lupus-related autoantibodies.

DISCUSSION

Based on the analysis of a large-scale international registry of patients with persistently positive aPL, our study demonstrated that the frequencies of thrombosis (including recurrent) and pregnancy morbidity were similar between aPL-positive patients with SLE and aPL-positive patients without SLE. However, a concomitant SLE diagnosis in patients with persistent aPL positivity was associated with an increased frequency of

Table 2. Prevalence of CVD and thrombosis risk factors at the time of registry entry among patients with persistent aPL positivity, stratified by the presence of SLE*

Variable	aPL only (n = 426)	aPL with SLE (n = 197)	*P*
Hypertension	118 (28)	66 (34)	0.14
Diabetes	22 (5)	8 (4)	0.55
Hyperlipidemia	103 (24)	36 (18)	0.1
Smoking ever	116 (27)	49 (25)	0.65
Current smoking	40 (9)	30 (15)	0.03
Estrogen use	3 (1)	3 (2)	0.54
Obesity	107 (25)	59 (30)	0.37
Family history of CVD	67 (16)	21 (11)	0.18
Sedentary lifestyle	197 (46)	94 (48)	0.73

* Values are the number (%). CVD = cardiovascular disease; aPL = antiphospholipid antibody; SLE = systemic lupus erythematosus.

thrombocytopenia, hemolytic anemia, low C3 and C4 levels, and IgA anti-β_2GPI antibody positivity compared with the frequency in aPL-positive patients without other autoimmune diseases. Additionally, aPL-positive patients with SLE had a significantly higher frequency of current smoking, while aPL-positive patients without other autoimmune diseases had an increased prevalence of cognitive dysfunction. Although HCQ use was more common in the aPL with SLE group, 40% of the aPL only group also received HCQ, especially those with lupus-related clinical and serologic manifestations.

Although the impact of aPL on SLE is well studied (5,7), limited data exist regarding the impact of SLE on the clinical phenotype of patients with persistently positive aPL. In a European multicenter cohort of 1,000 mainly Caucasian patients with APS, patients with concomitant SLE had a higher prevalence of livedo reticularis, thrombocytopenia, arthritis, and leukopenia (13). Our multiethnic study also showed an increased frequency of thrombocytopenia and autoimmune hemolytic anemia in aPL-positive patients with SLE compared with the frequency in those without SLE; however, with the exception of cognitive dysfunction, similar frequencies of the classification criteria or other non-criteria aPL manifestations, namely livedo reticularis, cardiac valve disease, and aPL-associated nephropathy, were observed in the 2 groups. Given that our SLE patients were classified based on the ACR classification criteria (11), which incorporate thrombocytopenia and autoimmune hemolytic anemia, the increased frequency of these hematologic abnormalities in aPL-positive patients with SLE was not unexpected.

Cognitive dysfunction is common in APS and SLE and is frequently associated with livedo reticularis and white matter lesions on brain magnetic resonance imaging in patients with APS. Tektonidou et al previously showed no difference in cognitive performance as assessed by a 3-hour battery of neurocognitive tests among patients with primary APS and those with SLE and APS (14). Kozora et al demonstrated that 12 (60%) of

Table 3. Analysis of 426 aPL-positive patients without other systemic autoimmune diseases, stratified by HCQ use*

Variable	HCQ use (n = 164)	No HCQ use (n = 262)	*P*
Clinical profile			
Thrombotic APS	89 (54)	148 (57)	0.65
Arterial thrombosis	52 (32)	87 (33)	0.84
Venous thrombosis	75 (46)	110 (42)	0.3
Microthrombosis	11 (7)	16 (6)	0.74
Obstetric APS	16 (10)	28 (11)	0.76
Thrombotic and obstetric APS	21 (13)	37 (14)	0.70
3 of 11 ACR SLE criteria met	42 (26)	17 (7)	<0.001
Laboratory profile			
Persistent triple aPL positive	60 (37)	98 (37)	0.87
Persistent double aPL positive	50 (30)	97 (27)	0.1
Persistent single aPL positive	102 (62)	67 (26)	0.16
ANA positive	30 (18)	86 (33)	<0.001
Anti-dsDNA positive	5 (3)	10 (4)	<0.001
Anti-Sm positive	17/66 (26)	0 (0)	0.008
Low complement 3 (C3) level	54 (33)	12/60 (20)	0.44
Low complement 4 (C4) level	20/66 (30)	10/60 (17)	0.02

* Patients were considered to be positive for antinuclear antibodies (ANAs), anti–double-stranded DNA (anti-dsDNA), or anti-Sm if they ever had a positive test result for these antibodies. A low C3 or C4 level was based on a level below normal and the most recent C3/4 tests before registry entry. Values are the number/number assessed (%). aPL = antiphospholipid antibody; HCQ = hydroxychloroquine; APS = aPL syndrome; ACR = American College of Rheumatology; SLE = systemic lupus erythematosus.

20 aPL-positive SLE patients and 8 (40%) of 20 aPL-positive patients without SLE had global cognitive impairment on a ACR-SLE cognitive impairment index, which is a validated neuropsychologic instrument; there were no group differences on the cognitive impairment index or on individual measures (15). Our study included SLE patients with persistently positive aPL and aPL-positive patients who did not meet the APS classification criteria (1) and still showed that neuropsychiatric test–proven cognitive dysfunction was more common in aPL-positive patients without SLE. These findings further support the importance of research for cognitive dysfunction and clinical assessment in aPL-positive patients without other systemic autoimmune diseases.

The updated Sapporo criteria for the classification of APS do not include IgA aCL and IgA anti-β_2GPI antibodies. Although the IgA isotype is common in black patients with SLE (16) and now is included in the revised Systemic Lupus International Collaborating Clinics criteria for the classification of SLE (17), the prevalence and clinical significance of this isotype have been controversial (18). We observed that although aPL types and isotypes as well as double or triple aPL positivity were generally comparable between the 2 groups, aPL-positive patients with SLE more frequently had IgA anti-β_2GPI antibodies, while IgG anti-β_2GPI antibodies were more frequent in those without SLE. Although it remains unknown why patients develop different isotypes of aPL, our findings support those of previous studies (19), thus demonstrating the potential diagnostic and clinical significance of the IgA isotype in lupus patients compared with those without lupus.

Traditional CVD risk factors, including diabetes mellitus and smoking, increase the risk of thrombosis in aPL-positive patients (20). SLE itself is an independent risk factor for CVD, which remains the major cause of mortality in patients with SLE (21). It is not well-studied whether CVD risk factors differ between aPL-positive patients with SLE and those without SLE; our study demonstrated that the prevalence of CVD risk factors was similar between aPL-positive patients with and those without SLE, with the exception of current smoking. In addition, although the role of smoking in the development of aPL, APS, and/or SLE is not well-established (22), smoking is associated with worse outcomes and venous thrombosis in patients with SLE as well as the development of SLE subtypes, as defined by autoantibody status (23). All of these findings support the importance of similar diligence in CVD risk assessment and management measures in both aPL-positive patients with SLE and aPL-positive patients without SLE.

In our study, use of glucocorticoids, HCQ, azathioprine, cyclophosphamide, methotrexate, and mycophenolate mofetil was more frequent in aPL-positive patients with SLE compared with aPL-positive patients without SLE at the time of entry into the cohort. Use of HCQ in patients with SLE is well-established; however, no strong clinical data exist to recommend HCQ treatment for aPL-positive patients without other systemic autoimmune diseases. Given animal and in vitro studies showing that HCQ has a potential antithrombotic role in addition to its immunoregulatory and metabolic effects (24–29), HCQ has been used in some centers to prevent thrombosis in aPL-positive patients without other systemic autoimmune diseases (30–32). An international study aimed at determining the effectiveness of HCQ for thrombosis prevention in asymptomatic aPL-positive patients was terminated early for reasons related to logistics (33). In the current study, ~40% of aPL-positive patients without other systemic autoimmune diseases reported HCQ use, and the frequency of serologic features of SLE was higher in aPL-positive patients using HCQ. Our study was not designed to determine the prophylactic role of HCQ; however, we believe that prospective follow-up of patients in our registry will provide further valuable data on outcomes in HCQ-treated aPL-positive patients.

Although our study was limited due to its retrospective, cross-sectional study design, we used a large, multicenter, international patient cohort. Our data set is enriched by inclusion of granular sociodemographic, clinical, laboratory, and medication data. However, data for CVD risk factors were collected at the time of the patient's enrollment and not at the time of the thrombotic event, which may have resulted in inaccurate CVD prevalence estimates in different groups of aPL-positive patients.

In conclusion, our analysis of a large, multicenter, international cohort of patients who are persistently aPL-positive demonstrates an increased frequency of thrombocytopenia, hemolytic anemia, low complement levels, and IgA anti-β_2GPI antibody positivity but not the risk of thrombotic, obstetric, and non-criteria APS manifestations (except cognitive dysfunction) among aPL-positive patients with a concomitant SLE diagnosis compared with those without SLE. Our exploratory study provides pilot data for future risk-stratified prospective analyses using the APS ACTION registry, which will better determine the clinical impact of SLE on the presentation of aPL-positive patients.

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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. Dr. Unlu 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. Unlu, Erkan, Barbhaiya, Tektonidou.

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Analysis and interpretation of data. Unlu, Erkan, Barbhaiya, Tektonidou.

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Excess Productivity Costs of Systemic Lupus Erythematosus, Systemic Sclerosis, and Sjögren's Syndrome: A General Population–Based Study

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Objective. To determine excess productivity losses and costs of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and Sjögren's syndrome (SS) at the population level.

Methods. Administrative databases from the province of British Columbia, Canada, were used to establish population-based cohorts of SLE, SSc, and SS, and matched comparison cohorts were selected from the general population. Random samples from these cohorts were surveyed about time absent from paid and unpaid work and working at reduced levels/efficiency (presenteeism), using validated labor questionnaires. We estimated excess productivity losses and costs of each diagnosis (over and above nonsystemic autoimmune rheumatic diseases [non-SARDs]), using 2-part models and work disability rates (not employed due to health).

Results. Surveys were completed by 167 SLE, 42 SSc, and 90 SS patients, and by 375 non-SARDs (comparison group) participants. Altogether, predicted excess hours of paid and unpaid work loss were 3.5, 3.2, and 3.4 hours per week for SLE, SSc, and SS patients, respectively. Excess costs were $86, $69, and $84 (calculated as 2015 Canadian dollars) per week, or $4,494, $3,582, and $4,357 per person annually, respectively. Costs for productivity losses from paid work stemmed mainly from presenteeism (SLE = 69% of costs, SSc = 67%, SS = 64%, and non-SARDs = 53%), not from absenteeism. However, many working-age patients were not employed at all, due to health (SLE = 36%, SSc = 32%, SS = 30%, and non-SARDs = 18%), and the majority of total productivity costs were from unpaid work loss (SLE = 73% of costs, SSc = 74%, SS = 60%, and non-SARDs = 47%). Adjusted excess costs from these unpaid production losses were $127, $100, and $82 per week, respectively, among SLE, SSc, and SS patients.

Conclusion. In this population-based sample of prevalent SLE, SSc, and SS, lost productivity costs were substantial, mainly from presenteeism and unpaid work impairments.

INTRODUCTION

Systemic autoimmune rheumatic diseases (SARDs) include systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), systemic sclerosis/scleroderma (SSc), polymyositis/dermatomyositis, and forms of adult systemic vasculitis. These arthritides are frequently studied together due to shared pathogenesis, manifestations, and treatments. Immune dysregulation in SARDs leads to systemic inflammation, organ damage, and an array of physical and neurocognitive manifestations that can reduce functional status, health-related quality of life, and performance of paid and unpaid work. Approximately 2 to 5 per 1,000 Canadians have a SARD (1), and while many are not employed for pay (reviews suggest 54% of SLE patients [2] and 37% of SSc patients [3] are not employed), employed patients may still experience challenges and limitations (4,5) that reduce their workplace productivity.

In Canadian clinic-based cohorts, lost productivity costs averaged $55,827 over 4 years for SLE (6), and $18,639 and $12,804 per year for diffuse and limited SSc, respectively (7), while annual lost productivity costs for SS in the UK averaged $16,392 to $29,072 (8) (all converted to 2015 Canadian dollars). However, because tertiary clinic cohorts tend to have

All inferences, opinions, and conclusions in this article are those of the authors and do not reflect the opinions or policies of the data stewards.

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SIGNIFICANCE & INNOVATIONS

- These are the first population-level estimates of the adjusted excess productivity costs of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and Sjögren's syndrome (SS), from paid and unpaid work.
- Even in these unselected samples, patients with SLE, SSc, or SS were predicted to incur an additional $4,494, $3,582, and $4,357, respectively, in lost productivity costs each year, over and above a similar person without a systemic autoimmune rheumatic disease (SARD).
- Among employed individuals, absenteeism was not significantly elevated in patients with SARDs, but more patients with SARDs than individuals without SARDs (36% of working-age patients with SLE, 32% with SSc, 30% with SS, and 18% of the general population–based reference group) were not employed at all due to health.
- Unpaid work loss was a major cost contributor, even among employed individuals, with excess costs averaging $42–87 per employed person each week.

more severe disease (and likely higher costs) than those seen by community-based providers (9), these estimates have limited generalizability, and considerable gaps remain about the excess costs of SARDs, over and above the costs in the general population. Existing estimates mostly failed to incorporate presenteeism (working but at a reduced level/efficiency), a key driver in other arthritides (10), and time lost from unpaid work (i.e., cooking, cleaning, home maintenance); the latter is critical in SARDs (9), which predominantly affect females (1). From the societal perspective (which includes all costs, regardless of who bears them), excluding the unpaid production losses of work-disabled individuals (not employed for pay due to health), retirees, part-time workers, and homemakers, as well as those who remain employed but have difficulty performing their unpaid work (11), may lead to suboptimal and inequitable resource allocation decisions (9,12).

To address these gaps, we used administrative databases to establish a population-based SARD cohort and matched a non-SARD cohort selected from the general population of the Canadian province of British Columbia (BC). A random sample of each cohort was invited to complete a cross-sectional survey on their paid and unpaid work. Survey data were used to compare hours of lost productivity for those with and without a SARD and associated costs from the societal perspective. In the current study, we focused on the most frequent diagnoses in our sample: SLE, SSc, and SS.

MATERIALS AND METHODS

Data source. Publicly funded health care (including rheumatologist and other specialty care) is available to all residents of the province of BC, Canada (population of approximately 4.5 million). Population Data BC uses population-based linkable administrative data files to capture all provincially funded health care services, including all outpatient encounters (13) and hospitalizations (14) since 1990, and limited demographic (15) and vital statistics data (16).

Study population. From the administrative data, we assembled a population-based cohort of all adults who sought care for SARDs during 1996–2010. SARDs were identified from the International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10) diagnostic codes (see Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23573/abstract) recorded for outpatient encounters and hospitalizations: ≥2 ICD-9 codes for SARDs ≥2 months apart but within 2 years by a non-rheumatologist physician; 1 ICD-9 code from a rheumatologist; or 1 ICD-9 or ICD-10 code from hospitalization. In another Canadian province, the reported sensitivity of this definition for most SARDs was ≥88% and specificity was ≥95% (17). To establish the non-SARD comparison cohort, we obtained data for a random sample of BC residents registered with the provincial medical plan during the study period and selected up to 10 individuals (without a SARD diagnosis) matched for age, sex, and calendar year.

Survey. Recruitment and data collection procedures for the survey have been described previously (18). Briefly, administrative data files are released in de-identified form, but the BC Ministry of Health granted us contact information for a random sample of our population-based cohorts (n = 12,000 names from our initial survey sample of 9,335 individuals with a SARD and 55,431 individuals without SARDs). We randomly selected 2,400 names and mailed each person an invitation package. Ethics approval was granted by the University of British Columbia. Consenting participants completed a survey (paper or online) on their paid and unpaid work. Because we were blinded to diagnoses in the administrative data, the survey asked participants whether they had been diagnosed by a health professional with each SARD. Those reporting at least 1 diagnosis were classified as having SARDs, and the rest as non-SARDs. SLE, SSc, and SS groups consisted of individuals reporting these respective diagnoses. Participants could be included in >1 SARD group (i.e., SLE and SS), which was clinically plausible, with SLE and SSc occurring together as an overlap syndrome, and SS developing secondary to SLE or SSc.

Independent variables. Sociodemographic variables included sex, age, marital status (living with a partner yes/no), race/ethnicity (collapsed into white/nonwhite), children at home (yes/

no), educational attainment, and household income level. Disease duration was equal to the number of years between the self-reported year of diagnosis by a health professional and the year 2015. Health status and behavioral data included height, weight, smoking status (current or former versus never) and pack-years, the number of comorbidities (0, 1, 2, or ≥3), and levels of functional disability (using the Health Assessment Questionnaire disability index) (19), pain, fatigue, and health-related quality of life (using the EuroQol 5-domain 5-level version [20], scored according to US and Canadian [21] algorithms). Data on height and weight were used to calculate body mass index and determine overweight (≥25 kg/m^2) and obesity (≥30 kg/m^2) status.

Dependent variables. Our primary outcome was excess hours of paid and unpaid productivity loss for patients with SARDs and associated costs. Excess refers to adjusted differences in lost productive time (and its monetary value) between the disease group and the matched group from the general population. Such differences remove background productivity losses/costs in the general population and provide estimates that can be attributable to the disease of interest. However, since only employed individuals could have paid productivity losses, and employment and disability rates were expected to differ between patients with SARDs and participants without SARDs, we also computed the proportions of working-age individuals (ages <65 years) who were not employed due to health (work-disabled). We additionally assessed determinants of productivity costs among patients with SARDs.

Employment and productivity data were collected using 2 instruments, the Work Productivity and Activity Questionnaire (WPAI) (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23573/abstract) (22) and the Valuation of Lost Productivity (VOLP) (23). Responses to questions from the WPAI were used to determine absenteeism (number of hours missed from work over the past 7 days due to health) and presenteeism from paid work (number of hours worked × the percentage-impairment while working due to health), while time loss from unpaid work (production of goods/services not sold on the market) (12) was determined from the VOLP. Specifically, the VOLP asked about hours of paid and unpaid help received (for household chores, yard/maintenance work, shopping/errands, childcare, and volunteering) over the past 7 days due to health. This approach captures productivity losses only from essential, time-sensitive tasks, not all time available in the day for unpaid work (11). Both instruments asked about productivity losses over the past 7 days due to any health problem, not just SARDs (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23573/abstract). Per recommendations (24), lost leisure time was not included.

The WPAI permits the calculation of productivity losses as hours of lost labor input for the respondent, but the VOLP permits calculation of their workplace's lost output when the respondent is away from work or less productive. The costs to the workplace for this lost output have been shown to often exceed the value of that individual worker's lost hours (25,26). Responses to questions on job and workplace characteristics (specifically, how often one works in a team, size of the team, and substitutability) are used to derive a multiplier value (≥1), with lost output equal to the product of hours of lost input and this multiplier. Separate multipliers were calculated for absenteeism (mean ± SD 1.77 ± 1.44) and presenteeism (1.54 ± 1.10).

Cost calculation. Based on the stated job, participants were matched to the Canadian average hourly wage (27) for their occupational sector (28) (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23573/abstract). Wages were multiplied by hours of lost productivity to compute weekly productivity costs. If the participant was not employed for pay, or did not state their occupation, the overall average hourly wage for Canada in October 2015 ($25.38) was used (opportunity cost approach). All costs are expressed in 2015 Canadian dollars.

Statistical analysis. Group characteristics were compared (each SARD group versus the non-SARDs group) using *t*-tests and chi-square tests. Unadjusted estimates of productivity losses and costs were produced for each of the 4 groups (SLE, SSc, SS, and non-SARDs) and stratified by employment status. The differences between each SARD group and the non-SARDs group were taken as the unadjusted excess productivity losses and costs of SARDs. One unemployed person with SSc reported very high unpaid productivity losses (196 hours/week, confirmed as a special case, not an error); in the text we report hours and costs for SSc without this observation, while in the tables we report both estimates. Some individuals reported multiple diagnoses (i.e., SLE and SSc), and while such reporting might be considered overlap syndrome, we included them in each applicable SARD group because we were comparing costs of each SARD with non-SARDs, not costs between SARDs.

Productivity costs were initially expressed as raw estimates (hours × hourly wage). Then, in a secondary analysis, we applied the VOLP multipliers to the initial estimates of absenteeism and presenteeism from paid work, but not to unpaid productivity losses. We also performed a secondary analysis that included, for work-disabled individuals, the imputed costs of productivity loss from paid work: hours they would have spent in paid work (per Statistics Canada's General Social Survey [29], mean 3.18 hours per day × 7 = 22.28 hours per week) were multiplied by the Canadian overall hourly wage.

Raw estimates of productivity costs were subsequently adjusted for potential confounders, including sociodemographic factors and comorbidities, but not health status measures (i.e., fatigue, disability) or behaviors that were likely mediators rather

Table 1. Participant characteristics*

Characteristic	SLE	P†	SSc	P†	SS	P†	Non-SARDs
No.	167	NA	42	NA	90	NA	375
Female, no. (%)	157 (94)‡	0.01	37 (88)	0.73	87 (97)‡	0.01	323 (86)
Current age, years	54.6 ± 13.1‡	<0.01	59.5 ± 12.0	0.37	58.2 ± 12.0	0.82	57.8 ± 11.7
Age at diagnosis, years	36.5 ± 13.7	NA	46.3 ± 14.0	NA	46.4 ± 12.7	NA	NA
Disease duration, years	17.6 ± 9.9	NA	13.0 ± 11.9	NA	11.7 ± 8.3	NA	NA
Sociodemographics, no. (%)							
White/Caucasian	122 (73)‡	<0.01	38 (90)	0.32	68 (76)‡	0.04	318 (85)
Living with partner	116 (69)	0.89	31 (74)	0.61	58 (64)	0.30	262 (70)
Living with children	61 (37)	0.34	11 (26)	0.42	23 (26)	0.21	121 (32)
Education level, no. (%)							
High school or less	52 (32)	0.30	14 (33)	0.59	18 (20)‡	0.04	117 (31)
Some post-secondary	70 (43)	0.30	18 (43)	0.59	45 (50)	0.04	139 (37)
University degree	41 (25)	0.30	10 (24)	0.59	27 (30)	0.04	117 (31)
Household income, no. (%) $							
<40,000	42 (29)	0.74	12 (30)	0.80	26 (30)	0.35	88 (26)
40,000–80,000	43 (29)	0.74	13 (33)	0.80	31 (36)	0.35	110 (32)
>80,000	62 (42)	0.74	15 (38)	0.80	29 (34)	0.35	145 (42)
Health status							
Functional disability (HAQ DI score)	0.70 ± 0.64‡	<0.01	0.93 ± 0.70‡	<0.01	0.71 ± 0.64‡	<0.01	0.42 ± 0.56
Pain (range 0–100)	38 ± 25‡	<0.01	39 ± 28‡	0.03	39 ± 27‡	<0.01	29 ± 28
Fatigue (range 0–100)	52 ± 27‡	<0.01	47 ± 27‡	0.01	54 ± 28‡	<0.01	34 ± 29
EQ-5D-5L							
VAS score (range 0–100)	68 ± 20‡	<0.01	68 ± 17	0.10	66 ± 20‡	<0.01	73 ± 19
Health state utility, Canadian norms	0.72 ± 0.22‡	<0.01	0.70 ± 0.22‡	0.02	0.71 ± 0.23‡	<0.01	0.78 ± 0.21
Health state utility, US norms	0.73 ± 0.19‡	<0.01	0.68 ± 0.20‡	<0.01	0.71 ± 0.18‡	<0.01	0.78 ± 0.19
Comorbidity score (range 0–3)	2.1 ± 1.1‡	<0.01	2.0 ± 1.0	0.07	2.2 ± 1.1‡	<0.01	1.7 ± 1.2
Health behaviors							
Cigarette smoking							
Ever-smoker, no. (%)	75 (45)	0.49	19 (46)	0.80	35 (39)	0.10	181 (48)
Pack-years of smoking (among ever-smokers)	14.3 ± 14.7	0.31	15.7 ± 21.2	0.81	15.1 ± 17.0	0.63	17.0 ± 21.3
Years since cessation (among former smokers)	9.1 ± 12.6	0.05	15.7 ± 17.4	0.23	10.2 ± 14.9	0.35	12.2 ± 14.6
Body mass index (BMI), kg/m^2	25.8 ± 6.7	0.60	25.0 ± 6.0	0.27	26.6 ± 5.9	0.55	26.2 ± 6.2
Overweight (BMI ≥25), no. (%)	80 (48)	0.54	19 (46)	0.54	47 (52)	0.88	191 (51)
Obese (BMI ≥30), no. (%)	35 (21)	0.72	8 (20)	0.65	21 (23)	0.88	84 (23)

* Values are the mean ± SD unless indicated otherwise. SLE = systemic lupus erythematosus; SSc = systemic sclerosis; SS = Sjögren's syndrome; SARDs = systemic autoimmune rheumatic diseases; NA = not applicable; HAQ DI = Health Assessment Questionnaire disability index (range 0–3); EQ-5D-5L = EuroQol 5-domain 5-level version (measure of health status and health-related quality of life); VAS = visual analog scale (range 0–100).
† *P* value versus non-SARDs.
‡ Significant differences between each SARD and non-SARDs.

than confounders. However, because SARDs can increase the risk of certain comorbidities, analyses were also conducted without adjustment for comorbidity score. We constructed separate models for each SARD and aspect of productivity loss: absenteeism, presenteeism, any paid loss, any unpaid loss, and any paid or unpaid loss. Because many individuals reported no productivity loss, 2-part models were used. The first part, a multivariable logistic regression model, assessed (for each aspect of productivity loss) the probability of incurring any time loss/cost. The second, generalized linear model, with log-link and gamma

distribution, estimated time losses and costs expected for those with time loss/costs >0.

We subsequently used G-computation (30) to estimate absolute time loss/costs expected for each group and excess costs of SARDs. With this approach, odds and time loss/costs were predicted for each person twice, once coded as having the SARD and once as a non-SARDs participant, but with their other covariates the same. Difference between estimates (i.e., predicted odds × costs for the same person when coded as SLE, and when coded as non-SARDs) represented the excess costs of SARDs, with per person excess costs averaged across all eligible individuals. Parametric bootstrapping (100 replications each) was used to produce 95% credible intervals. Excess hours of productivity loss and excess productivity costs were determined using two-part models. For these outcomes, we report 95% credible intervals. For odds ratios and cost ratios, we report 95% confidence intervals. Due to small sample sizes, determinants of productivity costs within SARDs were assessed with correlational and univariable analysis rather than multivariable models. Analyses were conducted using SAS Enterprise Guide, version 4.3.

RESULTS

From 2,400 invitations distributed, 743 consents were received, and surveys were completed by 671 persons (69% online, 31% paper-based). Forty-four percent (n = 296) reported ≥1 SARD diagnosis. SLE was the most common (56%), followed by SS (30%) and SSc (14%); ≤5% reported other SARD diagnoses. Characteristics of the SLE, SSc, SS, and non-SARD groups are shown in Table 1. Sociodemographics and health behaviors were generally comparable, although the SLE patients were slightly younger than non-SARDs participants (mean ± SD age 54.6 ± 13.1 years versus 57.8 ± 11.7 years), and SLE and SS had larger proportions of women than non-SARDs.

Similar percentages of working-age SSc and SS patients and non-SARDs participants (54–58%) were employed for pay, though somewhat fewer SLE patients were employed (46%). The mean number of hours worked by employed individuals over the past week was also comparable across the 4 groups (Table 2). However, approximately twice as many working-age SARDs patients as non-SARDs participants were work disabled (not employed due to health); 24% of non-SARDs participants, versus 12–17% of SARDs patients, were unemployed for other reasons. Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23573/abstract, shows the occupational sectors for employed participants and corresponding wages. The majority of SLE patients (59%) were employed in business, health care, or management, while 52% of SS patients were employed in business or education/social services/law. Weekly hours of absenteeism did not differ between any SARD group and the non-SARDs group (means of 2.4, 2.5, 4.0, and 3.1 in SLE, SSc, SS, and non-SARDs, respectively), but SS had significantly greater hours of presenteeism than non-SARDs (7.6 versus 4.1; P = 0.01). Each SARD group averaged more unpaid time loss (hours of help received with unpaid work) than the non-SARDs group (Table 2), though only 44–50% of each SARD group and 25% of the non-SARDs group reported any loss. Most help was provided by family members (SS = 81%, SSc = 87%, non-SARDs = 87%, and SLE = 89%).

Unadjusted costs. Average weekly costs for time lost per person from paid work were $216, $158, $297, and $187 for SLE, SSc, SS, and non-SARDs, respectively, with presenteeism accounting for 64–69% of costs in SARDs and 53% in non-SARDs. When applying VOLP multipliers (representing the impact of the respondent's impairment on their workplace's productivity), mean costs were $347, $255, $482, and $307 per week for SLE, SSc, SS, and non-SARDs, respectively (Table 2).

Altogether, unadjusted per-person lost productivity costs from paid and unpaid work, averaged among all participants, were $301 in SLE, $240 in SSc, $271 in SS, and $149 in non-SARDs. Unpaid work loss accounted for 31–47% of costs for employed SARDs patients and just 21% for employed non-SARDs participants (Figure 1). When extrapolated (multiplied by 52), these weekly estimates translate to $15,636 per year for SLE, $12,501 for SSc, $14,092 for SS, and $7,743 for non-SARDs. When imputing time loss from paid work for work-disabled individuals (Table 2), annual costs were $23,774 for SLE, $18,236 for SSc, $19,599 for SS, and $11,144 for non-SARDs.

Adjusted analyses. After adjustment, patients with SLE had 2.4-times greater odds of work disability than participants without SARDs (95% CI 1.4, 4.1) and 2.0-times greater odds of experiencing any paid or unpaid productivity loss (Table 3), while odds were 1.8-times greater for SS (Table 4) and 2.6-times greater for SSc (Table 5). The 2-part regression model predicted time loss and costs for each group, while accounting for the probability of reporting any loss and adjusting for covariates. Altogether, excess productivity loss (the adjusted difference between SARDs and non-SARDs) averaged 3.5, 3.2, and 3.4 hours per week for SLE, SSc, and SS, respectively, with corresponding costs of $86, $69, and $84 per person. Estimates of excess costs were larger ($126, $84, and $107, respectively) when the comorbidity score was removed from the models. For unpaid work losses specifically, adjusted excess costs averaged $127 per week for SLE, $100 for SSc, and $82 for SS; these amounts were lower for employed individuals than for those not employed, but were still significant (Tables 3–5).

Determinants within SARDs. Completion of university was associated with 45% lower unpaid productivity costs among patients with SLE (cost ratio of 0.55 [95% CI 0.33, 0.93]) and 73% lower absenteeism costs among patients with SSc

Table 2. Employment and productivity outcomes*

Outcomes	SLE (n = 167)	*P*†	SSc (n = 42)	*P*†	SS (n = 90)	*P*†	Non-SARDs (n = 375)
Employment status							
Employed for pay, no. (%)‡	59 (46)§	0.03§	14 (56)	0.83	30 (54)	0.53	146 (58)
Hours worked, past 7 days¶	28.2 ± 16.2	0.64	29.2 ± 20.3	0.98	26.5 ± 16.6	0.38	29.3 ± 16.6
Work-disabled (not employed due to health), no. (%)‡	46 (36)§	<0.01§	8 (32)	0.10	17 (30)§	0.04§	46 (18)
Not employed, other reasons, no. (%)‡	22 (17)	0.17	<6	0.19	9 (16)	0.23	59 (24)
Paid work: absenteeism¶							
Any absenteeism, past 7 days, no. (%)	19 (30)§	0.02§	<6	0.13	12 (36)§	0.01§	26 (16)
Hours, past 7 days	2.4 ± 6.2	0.58	2.5 ± 6.1	0.80	4.0 ± 8.2	0.62	3.1 ± 9.6
Costs, $	66.01 ± 166.1	0.56	51.44 ± 107.3	0.60	107.80 ± 227.1	0.69	87.34 ± 273.1
Costs, with multiplier, $	116.80 ± 293.9	0.56	91.06 ± 189.9	0.60	190.70 ± 402.00	0.69	154.60 ± 483.3
Paid work: presenteeism#							
% impairment in paid work, past 7 days	0.21 ± 0.23§	0.02§	0.18 ± 0.20	0.56	0.33 ± 0.29§	<0.01§	0.14 ± 0.20
Any presenteeism, past 7 days, no. (%)	38 (67)	0.06	10 (83)§	0.04§	25 (83)§	<0.01§	77 (52)
Hours, past 7 days	5.8 ± 6.3	0.07	5.4 ± 4.2	0.46	7.6 ± 8.6§	0.01§	4.1 ± 6.2
Costs, $	165.30 ± 205.2§	0.04§	141.70 ± 94.6	0.49	208.00 ± 244.0§	0.01§	107.30 ± 169.6
Costs, with multiplier, $	254.50 ± 316.0§	0.04§	218.30 ± 145.7	0.49	320.20 ± 375.8§	0.01§	165.20 ± 261.2
Paid work: absenteeism and presenteeism							
Any absenteeism or presenteeism, past 7 days, no. (%)¶	41 (65)	0.09	11 (69)	0.21	27 (82)§	<0.01§	84 (53)
Hours, past 7 days¶	7.7 ± 9.4	0.63	6.6 ± 7.0	0.92	10.9 ± 11.6	0.08	6.9 ± 11.8
Costs, $¶	215.50 ± 293.1	0.55	157.70 ± 141.6	0.74	296.80 ± 336.6	0.09	186.60 ± 337.9
Costs, with multiplier, $¶	347.10 ± 480.6	0.63	254.80 ± 235.7	0.72	481.90 ± 556.2	0.11	307.40 ± 576.1
Costs, including work disability, $**	364.30 ± 282.9§	0.01§	293.60 ± 227.2	0.72	386.60 ± 301.7§	0.02	267.90 ± 338.9
Unpaid work††							
Any unpaid productivity loss, no. (%)	83 (50)§	<0.01§	21 (50)§	<0.01§	40 (44)§	<0.01§	93 (25)
Hours, past 7 days	8.5 ± 21.8§	<0.01§	11.4 ± 31.4§ 6.9 ± 11.7‡‡	<0.01§ <0.01‡‡	6.4 ± 13.1§	<0.01§	2.6 ± 7.5
Costs, $	219.40 ± 554.2§	<0.01§	293.00 ± 795.9§ 178.80 ± 296.6‡‡	<0.01§ <0.01‡‡	162.10 ± 331.0§	<0.01§	69.31 ± 199.9
Paid and unpaid work							
Any productivity loss, past 7 days, no. (%)††	104 (62)§	<0.01§	26 (62)§	0.01§	53 (59)§	<0.01§	148 (39)
Hours, past 7 days††	11.4 ± 22.8§	<0.01§	13.9 ± 31.4§ 9.5 ± 12.8§§	<0.01§ 0.05§§	10.4 ± 15.9§	<0.01§	5.5 ± 12.0
Costs, $††	300.70 ± 597.7§	<0.01§	353.10 ± 792.3§ 240.40 ± 310.7§§	<0.01§ 0.10§§	271.00 ± 412.8§	<0.01§	148.90 ± 341.9

(continued)

Table 2. *(Cont'd)*

Outcomes	SLE (n = 167)	*P*†	SSc (n = 42)	*P*†	SS (n = 90)	*P*†	Non-SARDs (n = 375)
Costs, including work disability, $¶¶¶	457.20 ± 682.1§	<0.01§	460.80 ± 817.5§ 350.70 ± 404.0‡‡	<0.01§ 0.04‡‡	376.90 ± 462.7§	<0.01§	214.30 ± 393.5

* Values are the mean ± SD unless indicated otherwise. Values are not reported for cell sizes <6. Cells with two sets of values report those determined both excluding and including an outlier response (one unemployed person with SSc who reported very high unpaid productivity losses). SLE = systemic lupus erythematosus; SSc = systemic sclerosis; SS = Sjögren's syndrome; SARDs = systemic autoimmune rheumatic diseases.
† Versus non-SARDs.
‡ Ages <65 years.
§ Significant differences between SARDs and non-SARDs.
¶ Employed.
# Employed who attended work in the past 7 days.
** Sum of actual costs of paid productivity loss incurred by employed participants, and imputed costs of paid productivity loss for work-disabled participants (ages <65 years and not employed due to health).
†† All participants.
‡‡ Estimates after the removal of the outlier, significant differences between SARDs and non-SARDs.
§§ Estimates after the removal of the outlier.
¶¶ Sum of actual costs of unpaid productivity loss for all participants, actual costs of paid productivity loss incurred by employed participants, and imputed costs of paid productivity loss for work-disabled participants (ages <65 years and not employed due to health).

(see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23573/abstract). Having ever-smoked was associated with greater unpaid productivity costs for SSc, while being overweight was associated with greater absenteeism costs in SSc and unpaid productivity costs in SLE and SS (cost ratios of 1.67 [95% CI 1.05–2.63] and 1.96 [95% CI 1.14–3.39], respectively). Functional disability, pain, and fatigue scores were significantly correlated with costs in SLE and SS.

DISCUSSION

These first population-based estimates of the excess lost productivity costs of SARDs suggest that those with SLE, SSc, or SS will incur an additional $4,494, $3,582, and $4,357, respectively, in lost productivity costs each year, over and above the costs for a similar person without a SARD diagnosis. Estimates were even larger ($6,530, $4,379, and $5,554, respectively) without adjustment for the elevated comorbidity burden present in SARDs. Though work disability was more common among the SARDs groups than the non-SARDs group, employed patients with SARDs still had more impairment at work than non-SARDs participants, and this fact accounted for 36–44% of their productivity costs.

Although presenteeism was elevated among SARDs patients, there were no substantive differences in mean hours worked, or hours/costs of absenteeism, among employed members of the 4 groups. This finding is congruent with a Canadian study of patients with rheumatoid arthritis, psoriatic arthritis, and osteoarthritis (mean age 51 years, 79% female) (10), where presenteeism accounted for 81% of costs and absenteeism just 19%. While we provide evidence to employers and other stakeholders that among employed individuals, SARDs do not adversely impact attendance at work, this finding must be interpreted carefully. Our participants had established disease (mean disease duration of 18 years in SLE, 13 in SSc, and 12 in SS), and more SARDs patients were unemployed for health reasons than were non-SARDs participants. Thus, a healthy-worker effect (31), wherein those with the greatest impairments left the paid workforce at an earlier time, likely contributed. Although we did not ask about employment at the time of diagnosis or subsequent job changes, this supposition is supported by data from other settings. For example, there was little change over time in the mean hours worked per day (32) or per year (33) among SLE patients employed continuously since diagnosis, and there was no significant difference between SS and non-SS participants in their time absent from paid work (8).

Another key finding was that unpaid work loss was a major cost contributor, even among employed individuals. After adjustment, employed SS and SLE patients had on average approximately 3 additional hours of unpaid productivity loss per week, with respective excess costs of $65 and $87 per person (over and above those of employed non-SARDs participants). Our estimates, which we believe are the first estimates of unpaid productivity costs specifically in employed SARDs patients, reinforce the fact that many individuals with health impairments remain employed and complete their paid work tasks, but with less time or capacity for housework and other unpaid work (11). While the majority of household help was provided by family members, at no direct cost, there is still a societal cost from this additional time expenditure.

Comparisons of our annualized estimates with those from prior studies are complicated by heterogeneity in source populations, productivity components, and approaches to measuring and valuing time loss (i.e., number of days, instead of hours, one was unable to work) (6,7). Still, our extrapolated annual predictions for SSc and SS ($12,501 and $14,092, respectively) are similar to those for a Canadian study of SSc ($15,232 converted to 2015 Canadian dollars) (7) and a UK study of SS ($16,392)

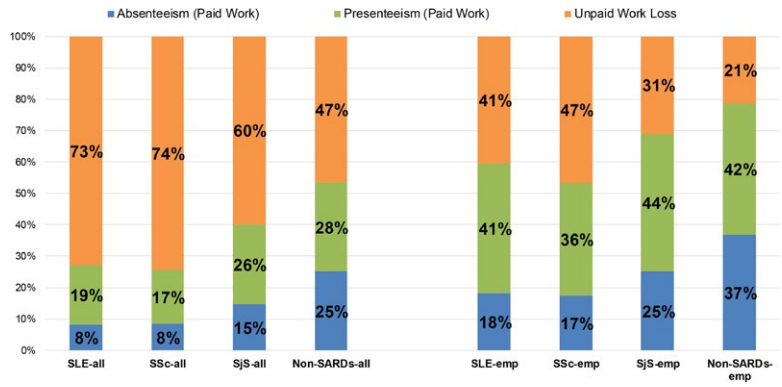

Figure 1. Breakdown of lost productivity costs by component, among all participants (**left**) and employed participants (**right**). SLE = systemic lupus erythematosus; SSc = systemic sclerosis; SjS = Sjögren's syndrome; SARDs = systemic autoimmune rheumatic diseases; emp = employed.

(8). There is disagreement about whether to include, for work-disabled individuals, the costs of potential time loss from paid work. From a societal perspective, including work-disabled individuals may overestimate costs, since that person's job will eventually be filled (and their productivity will be replaced) by someone previously unemployed (24). When costs associated with potential productivity losses of work-disabled individuals were included (based on a conservative 22.28 lost hours of paid work each week), unadjusted annual costs rose to $23,774 for SLE and $11,144 for non-SARDs.

Estimates of presenteeism and unpaid work loss can vary depending on their operationalization. In a comparison of 4 presenteeism instruments in Canadians with rheumatoid arthritis or osteoarthritis (34), the one we used (WPAI) had the least amount of missing data (our main reason for selecting it), but produced the highest estimates. We measured unpaid productivity losses using a VOLP question (originally from the Health and Labor Questionnaire) on hours of paid or unpaid help received due to health (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23573/abstract). This more conservative approach aims to measure time lost only from essential tasks, not all time available for unpaid work, and assumes individuals experiencing health impairments will not obtain extra help for tasks that are optional or can be put off (11). Thus, we may have overestimated presenteeism, and underestimated time loss from unpaid work. However, we do not believe the degree of over- or underestimation would differ between SARDs and non-SARDs.

Clearly, more research is needed to address the considerable productivity burden of SARDs. Productivity costs/gains are not usually considered by health care payers but are important to patients (35) and workplace stakeholders. The determinants of productivity costs that we identified among SARDs patients included pain, fatigue, smoking, low education, and being overweight. While these were unadjusted, cross-sectional associations, they are consistent with findings from adjusted analyses (2,36–39). Thus, with encouragement from clinicians, modifications in these factors may attenuate future productivity losses, especially among newly diagnosed individuals, as may educational supports. Nonpharmacologic interventions have been effective at reducing fatigue in SLE (40) and SS (41), and vocational programs have been developed to prevent work loss and maintain (or improve) at-work productivity in patients with arthritis. Their long-term effectiveness and cost-effectiveness are still being evaluated, but some efficacy has been demonstrated (42,43). In addition to health status, evidence suggests that work context factors such as increased job strain and psychosocial demands, and decreased control, are also key determinants of work limitations (4) and work loss (33). Although some patients do not wish to disclose their diagnosis at work, having increased access to, and uptake of, accommodations such as flexibility in work hours/location (5,44), pacing tasks (4), training for a different position (44), or software to reduce time spent keyboarding (5), may help ameliorate these factors and preserve individuals' productivity and ability to work. Preservation of individuals' productivity and ability to work, in turn, could reduce costs to patients, employers, disability insurers, and society.

Our recruiting both SARDs patients and non-SARDs participants from population-based cohorts was novel; the process eliminated the complex task (45) of deciding whether productivity losses were due to a SARD and enhanced generalizability, since clinic-based cohorts may have more severe disease and higher levels of productivity loss than other individuals with SARDs. Cohorts recruited exclusively online tend to have higher-than-average levels of education (46,47), while friend controls, used in other studies (36,48), may not be fully representative of the general population. Privacy regulations limited comparisons of who did or did not consent or participate, but we know our participants were somewhat younger, on average, than the initial survey sample as a whole (mean age 57.8 versus approximately 61 years), and more were women. Nonetheless, the same

Table 3. Results of regression analysis of productivity loss for patients with systemic lupus erythematosus (SLE)*

	All			Employed			Not employed		
	SLE (n = 167)	Non-SARDs (n = 375)	Difference	SLE (n = 63)	Non-SARDs (n = 160)	Difference	SLE (n = 104)	Non-SARDs (n = 215)	Difference
Work disabled (Y/N)†	2.4 (1.4, 4.1)‡	–	–	–	–	–	–	–	–
Any absenteeism (Y/N)§	–	–	–	1.7 (0.78, 3.7)	–	–	–	–	–
Costs of absenteeism, $¶	–	–	–	58 (2, 139)	93 (3, 233)	−35 (−97, −1)‡	–	–	–
Any presenteeism (Y/N)§	–	–	–	1.3 (0.66, 2.4)	–	–	–	–	–
Costs of presenteeism, $¶	–	–	–	134 (57, 266)	102 (41, 207)	32 (16, 59)‡	–	–	–
Any paid work loss (Y/N)#	–	–	–	1.2 (0.63, 2.4)	–	–	–	–	–
Costs of paid work loss, $¶	–	–	–	175 (54, 348)	206 (60, 419)	−31 (−71, −6)‡	–	–	–
Any unpaid work loss (Y/N)§	2.7 (1.8, 4.1)‡	–	–	2.3 (1.1, 4.7)‡	–	–	3.0 (1.8, 5.1)‡	–	–
Costs of unpaid work loss, $¶	203 (26, 530)	76 (7, 217)	127 (19, 310)‡	141 (7, 399)	54 (2, 175)	87 (5, 228)‡	248 (42, 653)	92 (11, 251)	156 (30, 418)‡
Any paid or unpaid productivity loss (Y/N)§	2.0 (1.3, 3.0)‡	–	–	1.6 (0.78, 3.1)	–	–	3.0 (1.8, 5.1)‡	–	–
Hours of productivity loss¶	9.68 (3.09, 18.92)	6.17 (1.55, 13.79)	3.51 (1.54, 5.87)‡	11.04 (3.61, 20.57)	9.39 (2.71, 18.15)	1.65 (0.72, 2.56)‡	9.66 (1.67, 25.22)	3.60 (0.44, 9.41)	6.06 (1.20, 15.65)‡
Costs of productivity loss, $¶	254 (75, 535)	167 (39, 392)	86 (36, 154)‡	299 (91, 616)	262 (73, 563)	36 (16, 59)‡	248 (42, 653)	92 (11, 251)	156 (30, 418)‡

* Values are the regression analysis (95% confidence/credible interval). For hours and costs, we report 95% credible intervals. For odds of work disability or any loss (Y/N), we report 95% confidence intervals. SLE = systemic lupus erythematosus; SARDs = systemic autoimmune rheumatic diseases.
† Ages <65 years.
‡ Significant.
§ From the first part of the 2-part model: logistic regression (expressed as odds ratio) with occurrence of productivity loss as the dependent variable.
¶ From the second part of the 2-part model: generalized linear model (log-link and gamma distribution) with hours of productivity loss (or costs) as the dependent variable.
# Absenteeism or presenteeism. From the first part of the 2-part model: logistic regression (expressed as odds ratio) with occurrence of productivity loss as the dependent variable.

Table 4. Results of regression analysis of productivity loss for Sjögren's Syndrome (SS)*

	All			Employed			Not employed		
	SS (n = 90)	Non-SARDs (n = 375)	Difference	SS (n = 33)	Non-SARDs (n = 160)	Difference	SS (n = 57)	Non-SARDs (n = 215)	Difference
Work disabled (Y/N)†	1.8 (0.85, 3.6)	–	–	–	–	–	–	–	–
Any absenteeism (Y/N)‡	–	–	–	2.1 (0.86, 5.2)	–	–	–	–	–
Costs of absenteeism, $§	–	–	–	88 (16, 229)	99 (15, 257)	−11 (−61, 1)	–	–	–
Any presenteeism (Y/N)‡	–	–	–	2.9 (1.2, 7.0)¶	–	–	–	–	–
Costs of presenteeism, $§	–	–	–	188 (88, 424)	98 (37, 247)	90 (51, 168)¶	–	–	–
Any paid work loss (Y/N)#	–	–	–	3.2 (1.2, 8.6)¶	–	–	–	–	–
Costs of paid work loss, $§	–	–	–	258 (110, 460)	196 (71, 408)	61 (18, 113)¶	–	–	–
Any unpaid work loss (Y/N)‡	2.0 (1.2, 3.3)¶	–	–	3.5 (1.5, 8.1)¶	–	–	1.5 (0.78, 2.9)	–	–
Costs of unpaid work loss, $§	152 (30, 345)	70 (12, 172)	82 (18, 185)¶	120 (3, 392)	55 (1, 205)	65 (2, 179)¶	183 (30, 477)	82 (12, 212)	101 (18, 266)¶
Any paid or unpaid productivity loss (Y/N)‡	1.8 (1.1, 3.1)¶	–	–	4.8 (1.6, 14.7)¶	–	–	1.5 (0.78, 2.9)	–	–
Hours of productivity loss§	9.16 (3.44, 15.62)	5.74 (1.77, 11.02)	3.42 (1.69, 4.81)¶	14.24 (6.20, 21.83)	8.98 (3.59, 15.80)	5.26 (1.87, 7.65)¶	7.09 (1.23, 17.45)	3.16 (0.49, 7.79)	3.92 (0.74, 9.73)¶
Costs of productivity loss, $§	239 (82, 434)	155 (43, 317)	84 (39, 124)¶	378 (160, 600)	248 (89, 457)	130 (42, 204)¶	183 (30, 477)	82 (12, 212)	101 (18, 266)¶

* Values are the regression analysis (95% confidence/credible interval). For hours and costs, we report 95% credible intervals. For odds of work disability or any loss (Y/N), we report 95% confidence intervals. SS = Sjögren's syndrome; SARDs = systemic autoimmune rheumatic diseases.

† Ages <65 years.

‡ From the first part of the 2-part model: logistic regression (expressed as odds ratio) with occurrence of productivity loss as the dependent variable.

§ From the second part of the 2-part model: generalized linear model (log-link and gamma distribution) with hours of productivity loss (or costs) as the dependent variable.

¶ Significant.

Absenteeism or presenteeism, from the first part of the 2-part model: logistic regression (expressed as odds ratio) with occurrence of productivity loss as the dependent variable.

Table 5. Results of regression analysis of productivity loss for systemic sclerosis (SSc)*

	All			Employed			Not employed		
	SSc (n = 42)	Non-SARDs (n = 375)	Difference	SSc (n = 16)	Non-SARDs (n = 160)	Difference	SSc (n = 26)	Non-SARDs (n = 215)	Difference
Work disabled (Y/N)†	2.6 (0.94, 6.9)	–	–	–	–	–	–	–	–
Any absenteeism (Y/N)‡	–	–	–	2.3 (0.70, 7.3)	–	–	–	–	–
Costs of absenteeism, $§	–	–	–	81 (7, 226)	86 (6, 239)	−5 (−33, 4)	–	–	–
Any presenteeism (Y/N)‡	–	–	–	1.7 (0.56, 5.2)	–	–	–	–	–
Costs of presenteeism, $§	–	–	–	115 (44, 289)	98 (32, 256)	17 (8, 35)¶	–	–	–
Any paid work loss (Y/N)#	–	–	–	1.8 (0.56, 5.7)	–	–	–	–	–
Costs of paid work loss, $§	–	–	–	169 (72, 302)	186 (65, 355)	−17 (−65, 10)¶	–	–	–
Any unpaid work loss (Y/N)‡	3.0 (1.5, 5.8)¶ 2.7 (1.4, 5.3)**	–	–	5.1 (1.6, 15.7)¶	–	–	2.4 (0.98, 5.9) 2.0 (0.82, 5.1)††	–	–
Costs of unpaid work loss, $§	260 (63, 902) 169 (33, 411)††	73 (14, 245) 69 (10, 190)††	187 (48, 660)¶ 100 (22, 235)**	100 (5, 332)	58 (2, 220)	42 (3, 99)¶	389 (73, 1,413) 239 (37, 648)††	86 (12, 292) 80 (10, 248)††	303 (62, 1,071)¶ 159 (27, 432)**
Any paid or unpaid productivity loss (Y/N)‡	2.8 (1.4, 5.5)¶ 2.6 (1.3, 5.2)**	–	–	5.7 (1.2, 27.1)¶	–	–	2.4 (0.98, 5.9) 2.0 (0.82, 5.1)††	–	–
Hours of productivity loss§	12.72 (5.89, 19.50) 8.76 (3.46, 14.43)††	5.61 (1.82, 10.15) 5.57 (1.55, 11.03)††	7.11 (4.07, 10.37)¶ 3.19 (1.79, 4.35)**	11.62 (5.77, 17.65)	8.58 (3.56, 15.49)	3.04 (0.47, 5.48)¶	15.19 (3.01, 52.00) 9.31 (1.35, 23.98)††	3.30 (0.48, 10.67) 3.11 (0.36, 8.12)††	11.88 (2.54, 38.55)¶ 6.20 (1.01, 15.94)**
Costs of productivity loss, $§	329 (142, 520) 220 (80, 399)††	151 (45, 292) 151 (39, 317)††	178 (97, 260)¶ 69 (30, 102)¶	288 (118, 465)	238 (83, 417)	51 (−19, 130)	389 (73, 1,413) 239 (37, 648)††	86 (12, 292) 80 (10, 248)††	303 (62, 1,071)¶ 159 (27, 432)**

* Values are the regression analysis (95% confidence/credible interval). For hours and costs, we report 95% credible intervals. For odds of work disability or any loss (Y/N), we report 95% confidence intervals. Cells with two sets of values report those determined both excluding and including an outlier response (one unemployed person with SSc who reported very high unpaid productivity losses). SSc = systemic sclerosis; SARDs = systemic autoimmune rheumatic diseases.
† Ages <65 years.
‡ From the first part of the 2-part model: logistic regression (expressed as odds ratio) with occurrence of productivity loss as the dependent variable.
§ From the second part of the 2-part model: generalized linear model (log-link and gamma distribution) with hours of productivity loss (or costs) as the dependent variable.
¶ Significant.
# Absenteeism or presenteeism. From the first part of the 2-part model: logistic regression (expressed as odds ratio) with occurrence of productivity loss as the dependent variable.
** Estimates after the removal of the outlier. Significant.
†† Estimates after the removal of the outlier.

differences were observed for those with and without a SARD diagnosis.

As mentioned, participants had established disease, so our findings may not represent the productivity impact on newly diagnosed patients at present. Small sample sizes, and even smaller numbers of employed participants (especially for SSc), limited our assessment of productivity losses from paid work and determinants of costs among SARDs patients. Though beyond the scope of this cost analysis, we nevertheless acknowledge that data were not collected on items such as workplace accommodations, discrimination, job security, career advancement, reduced hours, or job changes. Data were self-reported, and SARD diagnoses were not clinically confirmed, but participants were asked to only report diagnoses from a health professional. Instead of sampling from the community at large (where the prevalence of SARDs is low), we recruited from population-based cohorts that met a validated case definition. The productivity questionnaires have been used and validated in SLE (46,49), SSc (50), and rheumatoid arthritis (23).

Despite these limitations, our study makes several unique contributions in highlighting the societal burden of SARDs, relative to the general population. To the best of our knowledge, it is the first known analysis of the excess productivity costs of SSc, the first population-level analysis of productivity costs in SS, and one of the few SLE estimates to include presenteeism in paid work and unpaid work loss. Furthermore, we minimized equity concerns by including paid and unpaid work, using opportunity costs to value unpaid work losses, and applying sector-specific instead of sex-specific wages.

These comprehensive, more generalizable estimates should provide incentive for, and help evaluating, interventions and accommodations to improve health and productivity outcomes in SARDs. Finally, our work underscores the need for clinicians, researchers, and policymakers to look beyond paid work absences when evaluating the impact of these little known disorders on patients and society.

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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. 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.

Study conception and design. Marra, Kopec, Aviña-Zubieta.

Acquisition of data. Aviña-Zubieta.

Analysis and interpretation of data. McCormick, Marra, Sadatsafavi, Kopec, Aviña-Zubieta.

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All-Cause and Cause-Specific Mortality in Patients With Granulomatosis With Polyangiitis: A Population-Based Study

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Objective. To investigate all-cause and cause-specific mortality in patients with newly diagnosed granulomatosis with polyangiitis (GPA) between 2 calendar time periods, 1997–2004 and 2005–2012.

Methods. Using an administrative health database, we compared all patients with incident GPA with non-GPA controls matched for sex, age, and time of entry into the study. The study cohorts were divided into 2 subgroups based on the year of diagnosis ("early cohort [1997–2004] and "late cohort" [2005–2012]). The outcome was death (all-cause, cardiovascular disease [CVD]–related cancer-related, renal disease–related, and infection-related) during the follow-up period. Hazard ratios (HR) were estimated using Cox proportional hazards models, first adjusted for age, sex, and time of entry and then adjusted for selected covariates based on a purposeful selection algorithm.

Results. Three hundred seventy patients with GPA and 3,700 non-GPA controls were included in this study, contributing 1,624.8 and 1,8671.3 person-years of follow-up, respectively. Sixty-eight deaths occurred in the GPA cohort, and 310 deaths occurred in the non-GPA cohort. Overall, the age-, sex-, and entry time–adjusted all-cause mortality HR in the GPA cohort was 3.12 (95% confidence interval CI 2.35–4.14). There was excess mortality due to CVD-related causes, but not cancer, in the GPA cohort. Reports of death due to infection or renal disease was not permitted, because the numbers of death were insufficient (<6 deaths for each outcome). All-cause mortality significantly improved between the early cohort and late cohort time periods (HR 5.61 and 2.33, respectively; *P* for interaction = 0.017).

Conclusion. This population-based study showed increased all-cause and CVD-related mortality risks in patients with GPA. There was significant improvement in the all-cause mortality risk over time, but the risk remained increased compared with that in the general population.

INTRODUCTION

Granulomatosis with polyangiitis (GPA), a rare form of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis, is characterized by necrotizing and granulomatous inflammation of small vessels (1). It was initially a disease with a poor prognosis, because 80% of patients did not survive beyond the first year without treatment (2). Over time, the use of cyclophosphamides and glucocorticoids has dramatically improved survival. Current 1-year and 5-year survival rates are estimated to range from 81% to 95% and from 73% to 83%, respectively (3–11). Studies of mortality in GPA patients compared with that in the general population showed variable standardized mortality ratios (SMRs) ranging from 1.77 to 4.69 (7,11–16).

With improved patient care, mortality in GPA patients is expected to decline, as evident from a recent report on GPA in-hospital mortality rates in the US (17). However, longitudinal data on secular trends in GPA mortality are scarce. Such data were derived mostly from studies in selected populations (12,14), and although one study was performed in a general population setting, it identified GPA patients who were seen by primary care physicians (18).

Once an immediately life-threatening disease, GPA has evolved into a chronic disease with a considerable burden of

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SIGNIFICANCE & INNOVATIONS

- Patients with granulomatosis with polyangiitis (GPA) have a 3-fold increased risk of dying compared with the general population.
- The risk of death from cardiovascular-related causes in GPA patients is twice that in the general population
- The all-cause mortality risk has significantly improved over time, but the mortality gap between GPA patients and the general population still exists.

accrued complications (8,19), including cardiovascular disease (CVD), infections, cancer, and renal failure. There is a limited number of studies evaluating cause-specific mortality in patients with GPA. To the best of our knowledge, cancer-related mortality has been evaluated in only 2 studies, 1 of which demonstrated a 2-fold increased risk of mortality in GPA patients compared with that in the general population (15), while the other showed no excess mortality attributable to cancer (14). We are not aware of any study evaluating CVD-, infection-, or renal disease–related mortality risks in patients with GPA at the general population level.

To address these knowledge gaps regarding GPA mortality, we conducted a population-based study to investigate all-cause and cause-specific mortality in patients with newly diagnosed GPA. We also evaluated whether all-cause and cause-specific mortality risks differed between 2 calendar time periods, 1997–2004 and 2005–2012. The procedures used were in compliance with the British Columbia Freedom of Information and Privacy Protection Act. Ethics approval was obtained from the University of British Columbia.

PATIENTS AND METHODS

Data sources. Universal health care coverage is available for all residents of British Columbia, Canada (population ~4.6 million). Population Data BC captures all provincially funded health care services from 1990, including all outpatient medical visits (20), hospital admissions and discharges (21), interventions (20), investigations (20), demographic data (22), cancer registry (23), and vital statistics (24). Furthermore, Population Data BC encompasses the comprehensive prescription drug database PharmaNet (25), which includes all dispensed medications for all British Columbia residents since 1996 regardless of the source of funding. Several other studies have been successfully conducted using Population Data BC databases (26–29). All accessible data have been de-identified by the data providers, and each subject received a unique identification number to protect his/her privacy.

Study design and cohort definition. Using Population Data BC, we conducted a matched cohort analysis comparing patients with newly diagnosed GPA (GPA cohort) with age-, sex-, and entry time–matched individuals without GPA (non-GPA cohort). We identified an incident cohort of patients (>18 years of age) in whom GPA was diagnosed between January 1, 1997 and December 31, 2012.

GPA definitions for inclusion into the cohort were 2 International Classification of Diseases (ICD), codes for GPA from outpatient medical visits (ICD, Ninth Revision [ICD-9] code 446.4) or from hospitalization (ICD-9 code 446.4 or ICD, Tenth Revision [ICD-10] code M31.3), at least 2 months apart and within a 2-year period; and a least 1 prescription for oral glucocorticoids, methotrexate, cyclophosphamide, leflunomide, azathioprine, cyclosporine, mycophenolate mofetil, or rituximab during the period 1 month before and 6 months after the index date. The latter of the 2 ICD codes was considered the index date. Individuals were excluded if there was less than a 7-year run-in time between the start of follow-up and the first diagnostic code for GPA in that individual (earliest health data from 1990 onward), to ensure patients with incident GPA. The validity of ICD codes to identify GPA cases in administrative databases was demonstrated in previous studies, with up to 89% of identified patients fulfilling the American College of Rheumatology (ACR) diagnostic criteria (30), based on chart review (15,31).

To assess time trends, we divided the cohorts into an "early cohort" (GPA diagnosed between January 1997 and December 2004) and a "late cohort" (GPA diagnosed between January 2005 and December 2012). To allow equal observation time for both cohorts, follow-up for the early GPA cohort was right-censored on December 31, 2004. Therefore, person-time and events occurring after this time point did not contribute to early GPA cohort–related analyses. This may result in a discrepancy between total events in the overall cohort and summation of events in both the early cohort and the late cohort. The specific time intervals were selected because it was the midpoint of the time range for the entire cohort and also because it corresponded to a treatment shift toward a reduced cumulative dose of cyclophosphamide and introduction of newer immunosuppressive agents such as mycophenolate mofetil and rituximab (32–34).

For each patient with GPA, we matched 10 individuals without GPA who were randomly selected from the general population based on age, sex, and calendar year of study entry (i.e., index date).

Assessment of outcome. The outcome of this study was death (all-cause and cause-specific) during the follow-up period. Causes of death were collected from death certificates, using ICD-9 and ICD-10 codes. Cause-specific mortality events include CVD (ICD-9 codes 390–459 and ICD-10 codes I00–I99), infections (ICD-9 codes 001–139, 460–466, 480–488, 680–686, 449, 590, 670, 566, 567, 730, 321.8, 321.2, 320.9, 321.1, 320.7, 790.7, 999.3, 322.1–322.9, 599.0, 595.0, 639.0, 569.5, 572.0, 711.9, 711.4, 711.0, 995.91, 995.92, and 996.64 and ICD-10 codes A00–A99, B00–B99, J00–J06, J09–J18, J20–J22, K61,

K65, K67, L00–L08, M00–M01, M86, O85–O86, G01, G00, G07, K750, O080, O753, G020, G021, G028, G042, G050–G052, G060–G062, and K630), cancer (ICD-9 codes 140–209 23–234 and ICD-10 codes C00–C97 D37–D48), and renal disease (ICD-9 codes 584–586 and ICD-10 codes N17–N19).

Assessment of covariates. We assessed covariates that were potential risk factors for mortality, during the 1-year time period prior to the index date. These covariates included health care resource utilization (outpatient medical and hospital visits), dispensing of medication during an outpatient visit (e.g., hormone replacement therapy, oral contraceptives, glucocorticoids, cyclooxygenase 2 inhibitors, nonsteroidal antiinflammatory drugs [NSAIDs], cardiovascular medications [antianginal drugs, antihypertensive drugs, cardiac glycosides, diuretics, antiarrhythmic agents, and nitrates], antidiabetic medications [oral hypoglycemic agents and insulin], aspirin, statins, fibrates, dipyridamole), and comorbidities (hypertension, angina, chronic obstructive pulmonary disease, obesity, and alcoholic liver disease). We also assessed socioeconomic status (SES), using census-derived

Table 1. Baseline characteristics of the GPA and non-GPA early and late cohorts*

Variable	Early cohort (1997–2004)			Late cohort (2005–2012)		
	GPA (n = 91)	Non-GPA (n = 910)	*P*	GPA (n = 279)	Non-GPA (n = 2,790)	*P*
Female sex	49 (53.8)	490 (53.8)	NS	163 (58.4)	1630 (58.4)	NS
Age, mean ± SD years	56.8 ± 16.9	56.8 ± 16.9	NS	54.9 ± 15.6	54.8 ± 15.5	NS
Hospitalizations	45 (49.5)	136 (14.9)	<0.001	148 (53.0)	429 (15.4)	<0.001
No. of outpatient visits, mean ± SD	24 ± 20.2	9 ± 9.4	<0.001	25 ± 18.0	9 ± 10.5	<0.001
Medications						
Cardiovascular drugs	26 (28.6)	237 (26.0)	NS	92 (33.0)	723 (25.9)	0.013
Antidiabetic drugs	7 (7.7)	47 (5.2)	NS	24 (8.6)	200 (7.2)	NS
Hormone replacement therapy	7 (7.7)	54 (5.9)	NS	14 (5.0)	120 (4.3)	NS
Glucocorticoids	47 (51.6)	40 (4.4)	<0.001	163 (58.4)	108 (3.9)	<0.001
NSAIDs	26 (28.6)	134 (14.7)	0.001	78 (28.0)	392 (14.1)	<0.001
COX-2 inhibitors	10 (11.0)	32 (3.5)	0.003	12 (4.3)	72 (2.6)	NS
Aspirin	<6†	13 (1.4)	NA	<6†	47 (1.7)	NA
Dipyridamole	0	0	NA	0	0	NA
Oral contraceptives	<6	41 (4.5)	NA	<6	91 (3.3)	NA
Fibrates	<6	13 (1.4)	NA	<6	17 (0.6)	NA
Statins	<6	99 (10.9)	NA	<6	392 (14.1)	NA
CCI, mean ± SD	1.41 ± 1.99	0.28 ± 0.89	<0.001	1.36 ± 1.6	0.32 ± 0.95	<0.001
Comorbidity						
Angina	11 (12.1)	55 (6.0)	0.042	13 (4.7)	85 (3.0)	NS
CHF	6 (6.6)	19 (2.1)	0.02	15 (5.4)	50 (1.8)	0.001
Obesity	<6	<6	NA	<6	<6	NA
Hypertension	10 (11.0)	192 (21.1)	0.020	79 (28.3)	655 (23.5)	0.077
Alcoholic liver disease	<6	<6	NA	<6	<6	NA
COPD	19 (20.9)	64 (7.0)	<0.001	70 (25.1)	191 (6.8)	<0.001
Socioeconomic status						
Quintile 1	15 (16.5)	198 (21.8)	NS	41 (14.7)	548 (19.6)	0.046
Quintile 2	22 (24.2)	181 (19.9)	NS	66 (23.7)	514 (18.4)	0.037
Quintile 3	14 (15.4)	166 (18.2)	NS	64 (22.9)	609 (21.8)	NS
Quintile 4	19 (20.9)	190 (20.9)	NS	52 (18.6)	541 (19.4)	NS
Quintile 5	21 (23.1)	175 (19.2)	NS	56 (20.1)	578 (20.7)	NS

* Except where indicated otherwise, values are the number (%). GPA = granulomatosis with polyangiitis; NS = not significant; NSAIDs = nonsteroidal antiinflammatory drugs; COX-2 = cyclooxygenase 2; NA = not applicable (because cell size <6); CCI = Charlson Comorbidity Index; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease.
† Cell size <6 in either the early *or* late cohort is listed as <6 in both the early *and* late cohorts, to prevent residual disclosure.

neighborhood income quintiles, with quintile 1 representing the lowest SES and quintile 5 representing the highest quintile. In addition, we calculated the Romano modified Charlson Comorbidity Index score from the year before the index date (35,36).

Statistical analysis. We compared the baseline characteristics of the GPA and non-GPA cohorts. All subjects were followed up from the index date until death, until they moved out of the province, or until the end of the follow-up period (December 31, 2004 for the early cohort and December 31, 2012 for the late cohort), whichever occurred first. Approximately 2% of patients and 4% of controls moved out of the province during the follow-up period.

Follow-up was computed in person-years contributed per subject. We calculated all-cause and cause-specific mortality rates per 1,000 person-years for each cohort. Survival curves were constructed using the Kaplan-Meier method. Differences in survival between the GPA and non-GPA cohorts were tested using nonparametric log rank tests (37).

Cox proportional hazards regression models were used to assess the relationship between GPA and all-cause as well as cause-specific mortality (38). Effect size was reported as the hazard ratio (HR), first adjusted for age, sex, and entry time (univariable analysis) and then adjusted for selected covariates (multivariable analysis). Selected covariates were computed into the Cox models in a forward selection based on a purposeful selection algorithm (39). The minimum accepted effect was a change in estimate of ≥5% in the HR. An interaction term was included to determine whether the relationship between GPA and mortality changes over time (i.e., calendar time cohort × disease status). To assess the effect of competing risks between specific causes of death on cause-specific mortality, sensitivity analyses using proportional hazard models for subdistribution HRs were performed. To evaluate the impact of duration of GPA (i.e., time after diagnosis), we estimated HRs for various time periods: <1, <2, <3, <4, <5, and ≥5 years. Testing of the proportional hazards assumption was performed by graphically plotting $\log(-\log_{survival})$ versus $\log_{time}$.

All statistical analyses were performed using SAS version 9.4. For all HRs, we calculated 95% confidence intervals (95% CIs). All *P* values were 2-sided, with a significance threshold of 0.05.

RESULTS

A total of 370 patients with newly diagnosed GPA and 3,700 individuals without GPA were included in this study, contributing 1,624.8 and 1,8671.3 person-years of follow-up, respectively. The age- and sex-standardized incidence rates of GPA were $2.7/10^6$ for the early cohort (1997–2004) and $7.9/10^6$ for the late cohort (2005–2012), consistent with previous reports of an increase in incidence rates over time (40,41). Over the entire time period, 68 deaths occurred in the GPA cohort, and 310 deaths occurred in the non-GPA cohort.

The baseline characteristics of the GPA and non-GPA cohorts are shown in Table 1. As expected, GPA patients had more comorbidities at baseline compared with their matched control subjects without GPA, with higher rates of hospitalizations and outpatient visits, preexisting comorbidities, and use of glucocorticoids and NSAIDs. Furthermore, the Charlson Comorbidity Index scores were significantly higher in the GPA cohorts compared with those in the non-GPA cohorts but was similar between the early and late GPA cohorts.

There were some notable observations regarding the rates of dispensing of immunosuppressive medications in our study cohorts (Table 2). Cyclophosphamide and rituximab were dispensed in 45.5% and 9.0% of the GPA patients, respectively, cumulatively over the follow-up period. These medications are normally reserved for use as induction–remission therapy in patients with severe disease, which indicates that the majority of patients in the GPA cohort had significant vital organ involvement. There was also an increase in the rate of azathioprine

Table 2. Comparison of the cumulative proportion of drugs dispensed in the GPA and non-GPA cohorts*

Drugs dispensed during follow-up	Overall cohort		Early cohort (1997–2004)		Late cohort (2005–2012)		
	GPA (n = 366)	Non-GPA (n = 3,420)	GPA (n = 88)	Non-GPA (n = 894)	GPA (n = 278)	Non-GPA (n = 2,526)	*P*†
Cyclophosphamide	166 (45.4)	7 (0.2)	62 (70.5)	0 (0)	104 (37.4)	7 (0.3)	<0.001
Rituximab	33 (9.0)	<6	<6	0 (0)	29 (10.4)	<6	NS
Methotrexate	124 (33.9)	36 (0.1)	25 (28.4)	9 (1.0)	99 (35.6)	27 (1.1)	NS
Azathioprine	147 (40.2)	NA	24 (27.3)	<6	123 (44.2)	11 (0.4)	0.005
Mycophenolate mofetil	38 (10.4)	<6	9 (10.2)	0 (0)	29 (10.4)	<6	NS
Leflunomide	<6	<6	<6	<6	<6	<6	NS
Cyclosporine	NA	<6	6 (6.8)	<6	<6	<6	0.027

* Values are the number (%). GPA = granulomatosis polyangiitis; NS = not significant; NA = not available (because a component cell size in either the early or late cohort was <6).
† Early cohort vs. late cohort.

dispensing between the early and late GPA cohorts (27.3% versus 44.2%) and a concomitant decrease in cyclophosphamide use (70.5% versus 37.4%). These dispensing rates were solely outpatient-based.

Cumulative GPA patient survival rates at 1, 5, and 10 years were estimated to be 93.1%, 83.1%, and 68.5%, respectively, and were significantly lower than those in subjects without GPA ($P < 0.001$, by log rank test). However, survival in the GPA patients significantly improved between the periods of time representing the early cohort (1997–2004) and the late cohort (2005–2012) ($P = 0.002$), thus reducing the magnitude of the survival difference between the GPA and non-GPA cohorts (Figure 1).

The mortality risks in the GPA cohort compared with those in the non-GPA cohort are shown in Table 3. Overall, the age-, sex-, and entry time–adjusted all-cause mortality risk in the GPA cohort was >3-fold compared with that in the non-GPA cohort (HR 3.12, 95% CI 2.35–4.14). Even after adjustment for selected covariates including SES quintiles, outpatient visits, Charlson Comorbidity Index score, and presence of hypertension, the risk remained significant. There was also excess mortality attributable to CVD in the GPA cohort relative to the non-GPA cohort (age-, sex-, and entry time–adjusted HR 2.41, 95% CI 1.35–4.29), which persisted in the fully adjusted model. Cancer-related mortality was not significantly increased. As a consequence of the residual disclosure policy of Population Data BC to ensure patient confidentiality, we are not allowed to report on the deaths due to infection or renal disease, because <6 deaths were associated with each outcome.

The mortality risk in the GPA cohort improved over time (Table 3). In the age-, sex-, and entry time–adjusted models, we observed a significant improvement in all-cause mortality between 1997–2004 (early cohort) and 2005–2012 (late cohort) (HR 5.61 [95% CI, 3.14–10.04] versus 2.33 [95% CI 1.53–3.55]; P for interaction = 0.017). This improvement remained significant after full adjustment ($P = 0.033$). There was a trend toward improvement in CVD-related mortality, although this trend did not reach statistical significance (P for interaction = 0.188 in the fully adjusted model).

Analyses stratified by year since GPA diagnosis showed persistently elevated mortality risks for each year of disease duration (Table 4). The all-cause mortality risk in the GPA cohort remained >2-fold compared with the non-GPA cohort even after 5 years. CVD mortality risks stratified by year of disease duration were not significantly increased, likely due to small numbers of CVD-related deaths in each year. Cancer-related mortality risks in the GPA cohort were not different from the risks in the general population for any year of disease duration (data not shown).

Sensitivity analyses performed to determine the effect of competing risks between specific causes of death did not reveal significant differences between the subdistribution HRs and the original HRs (see Supplementary Table, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23587/abstract).

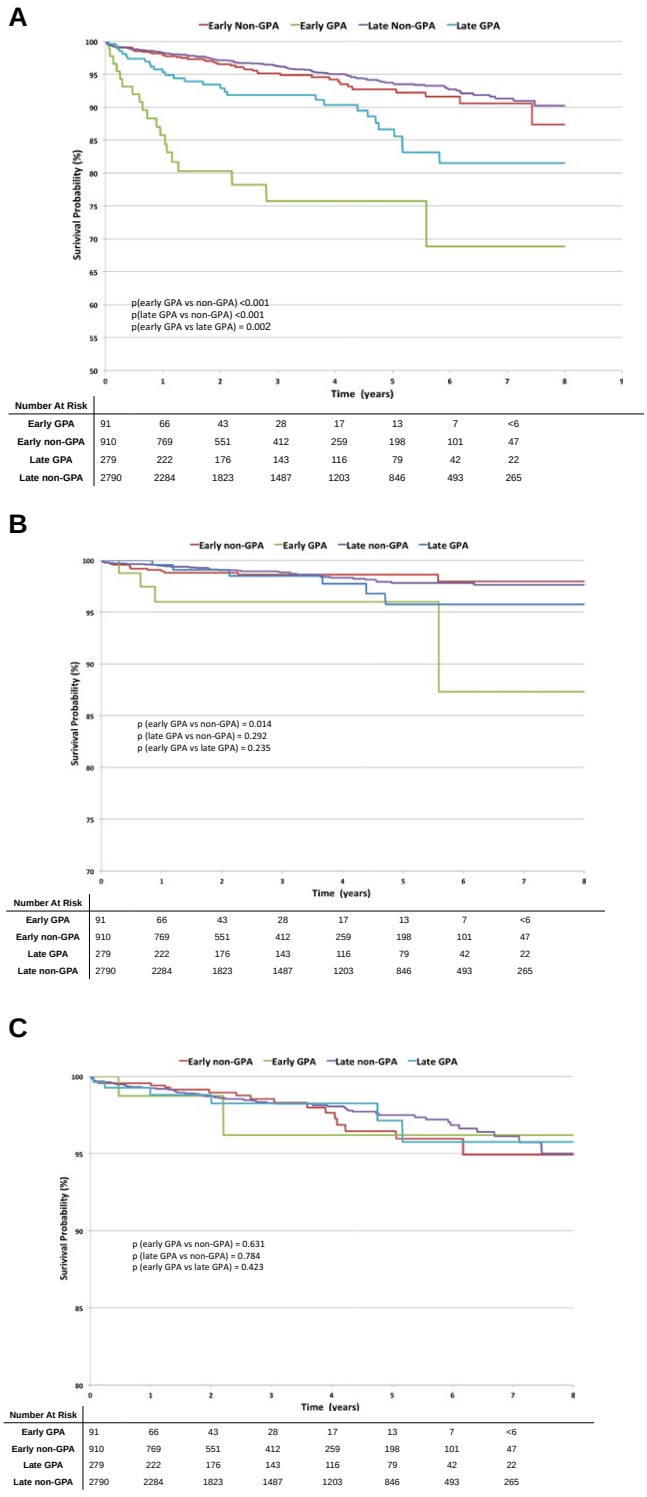

Figure 1. Probability of survival from all-cause (**A**), cardiovascular disease (**B**) and cancer (**C**) deaths in the granulomatosis polyangiitis (GPA) and non-GPA cohorts (early GPA vs. non-GPA) = P value for early GPA vs. non-GPA.

Table 3. Summary of all-cause and cause-specific mortality risks in the overall, early, and late GPA and non-GPA cohorts*

Variables	Overall cohort		Early cohort (1997–2004)		Late cohort (2005–2012)	
	GPA (n = 370)	Non-GPA (n = 3,700)	GPA (n = 91)	Non-GPA (n = 910)	GPA (n = 279)	Non-GPA (n = 2,790)
Total follow-up, person-years	1,624.8	18,671.3	217.8	2,783.0	939.0	9802.4
Mean follow-up, years	4.39	5.05	2.39	3.06	3.37	3.51
All-cause mortality						
No. of deaths†	68	310	19	45	29	130
MR, cases per 1,000 person-years	41.9	16.6	87.2	16.2	30.9	13.3
Age-, sex-, and entry time–adjusted HR (95% CI)	3.12 (2.35–4.14)	1.00	5.61 (3.14–10.04)	1.00	2.33 (1.53-3.55)	1.00
Fully adjusted HR (95% CI)‡	2.02 (1.47–2.78)	1.00	3.58 (1.91–6.73)	1.00	1.60 (1.02–2.48)	1.00
CVD mortality						
No. of deaths†	16	92	<6	<6	6	39
MR (cases per 1,000 person-years)	9.8	4.9	NR	NR	6.4	4.0
Age-, sex-, and entry time–adjusted HR (95% CI)	2.41 (1.35–4.29)	1.00	4.37 (1.24–15.44)	1.00	1.65 (0.68–4.01)	1.00
Fully adjusted HR (95% CI)§	1.99 (1.03–3.85)	1.00	5.50 (1.42–21.27)	1.00	1.89 (0.70–5.14)	1.00
Cancer mortality						
No. of deaths†	12	112	<6	<6	6	56
MR (deaths per 1,000 person-years)	7.4	6.0	NR	NR	6.4	5.7
Age-, sex-, and entry time–adjusted HR (95% CI)	1.33 (0.72–2.46)	1.00	1.33 (0.30–5.91)	1.00	1.02 (0.43–2.43)	1.00
Fully adjusted HR (95% CI)¶	0.96 (0.50–1.85)	1.00	1.00 (0.21–4.75)	1.00	0.73 (0.29–1.79)	1.00

* GPA = granulomatosis polyangiitis; MR = mortality rate; HR = hazard ratio; 95% CI = 95% confidence interval; CVD = cardiovascular disease; NR = not reported (due to restrictions on death counts <6).
† The sum of the respective numbers of death in the early and late cohorts is not equal to the overall numbers (observations were right-censored in the early cohort).
‡ Adjusted for socioeconomic status (SES) quintile, outpatient visits, Charlson Comorbidity Index (CCI), and hypertension.
§ Adjusted for SES quintile, outpatient visits, use of CVD drugs and statins, hypertension, and angina.
¶ Adjusted for SES quintile, CCI, and use of nonsteroidal antiinflammatory drugs.

Table 4. All-cause mortality risks in the GPA cohort from the time of diagnosis*

Years since GPA diagnosis	HR (95% CI)	*P*
<1	2.26 (1.31–3.89)	0.003
<2	2.15 (1.36–3.41)	0.001
<3	2.15 (1.42–3.25)	<0.001
<4	2.07 (1.41–3.03)	<0.001
<5	2.00 (1.39–2.88)	<0.001
≥5	2.33 (1.20–4.51)	0.012
Overall	2.02 (1.47–2.78)	<0.001

* GPA = granulomatosis with polyangiitis; HR = hazard ratio; 95% CI = 95% confidence interval.

DISCUSSION

In this population-based study, all-cause as well as cause-specific mortality risks in patients with GPA were assessed. We observed a 3-fold increased risk for all-cause mortality in GPA patients relative to the general population. However, there was significant improvement in the all-cause mortality risk between 1997–2004 (early cohort) and 2005–2012 (late cohort) (HR 5.61 [95% CI, 3.14–10.04] and HR 2.33 [95% CI 1.53–3.55], respectively). Overall, there was excess mortality due to cardiovascular disease but not cancer. All-cause mortality risk persisted for every year of disease duration, up to and beyond 5 years.

Our observation of an increased all-cause mortality risk in GPA patients was consistent with the recent findings of a large general practice–based cohort study in the UK (18). A total of 465 GPA patients were included in that study, with an overall comorbidity and medication-adjusted mortality HR of 2.52 (95% CI 1.91–3.32). Those investigators observed an improvement in mortality between 2 time periods (for 1992–2002, HR 4.34; for 2003–2013, HR 2.41 [P = 0.04]). Our results are almost identical. Improvement in treatment practices may be a factor, and in our cohort we observed a decrease in outpatient dispensing rates of cyclophosphamide between 1997–2004 (early cohort) and 2005–2012 (late cohort) but unfortunately did not capture data on inpatient practices. The authors of the UK study hypothesized that there was a shift toward less cyclophosphamide exposure as well as improved management of long-term comorbidities such as CVD-, cancer-, and vasculitis-related complications in GPA patients. Nevertheless, they did not have data on cause-specific deaths, and thus their reasons for the observed improvement remained speculative.

Our study suggests that the improved mortality in GPA may have been partially driven by the diminishing CVD mortality risk between 1997–2004 (early cohort) and 2005–2012 (late cohort). The significantly increased CVD-related mortality risk observed in the early cohort was no longer present in the late cohort, because it approached the population-level risk. This trend in improvement could be attributed to the increasing recognition of CVD as a major contributor to late morbidity and mortality in GPA patients (11,13). As widely reported in other population studies, recent advances in medical therapies and reduction in risk factors have led to the steady decline in the number of deaths related to coronary heart disease in the general population (42,43). Patterns of alcohol consumption and tobacco use were important risk factors to consider, but these data were not captured in the administrative health database.

In 2 previous studies, the investigators assessed secular trends in GPA mortality (11,14). We confirmed the results of a study conducted in Germany, in which declining mortality risks over 3 time periods from 1966 to 2002 (14) were reported. In fact, the risk in that GPA cohort was equivalent to that in the general population during the latest time period (1999–2002). However, the German cohort was derived from an academic hospital unit specializing in rheumatology, whereas our cohort is population-based, rendering our results generalizable to the population at large. The second study was a retrospective cohort study using hospital discharge records for GPA patients in Finland, comparing the time periods 1981–1990 and 1991–2000 (11). Those investigators reported no significant improvement in mortality. We noted that this particular study included hospitalized patients, i.e., those whose disease was more likely to be in the acute stage of disease. Therefore, these findings suggest that the early mortality risk component (within 1 year of disease) had not improved during the study period.

In our overall GPA cohort, we observed an approximately 2-fold increase in the CVD-related mortality risk (age-, sex-, and entry time–adjusted HR 2.41 [95% CI 1.35–4.29]), which was confirmed even after adjustment for selected covariates. There is a lack of reported CVD-related mortality risks in the literature to allow for comparisons. A previous estimate of the CVD mortality rate ratio in patients with GPA and those with microscopic polyangiitis enrolled in clinical trials was >3-fold that in the general population (age-standardized mortality rate ratio 3.68) (44). Furthermore, in that study only the first 5 years after GPA diagnosis were assessed.

We did not observe any excess mortality risk attributable to cancer. Our results differed from those from a Swedish population-based study in which an all-cancer SMR of 2.2 (95% CI 1.7–2.8) was noted in GPA patients (n = 1,065) (15). Compared with the mortality rate observed in that larger study, the rate of cancer mortality in our study was also lower (7.4 cases per 1,000 person-years versus 11.9 cases per 1,000 person-years in the Swedish study). This difference may be attributable to inadequate follow-up time in our study (mean 4.4 years). A recent study showed increased incidences of bladder cancer and myeloid leukemia after the fifth year of follow-up in GPA patients (45).

We were unable to further analyze the remaining specific causes (i.e., infection and renal), because we were restricted by the residual disclosure clause in Population Data BC, which prevents reporting of event counts of <6. This restriction applied to infection or renal failure specifically as a primary cause of death, which may explain the low number of events. When we analyzed for infection as any cause of death along the death axis coding, there were 19 listed cases (28% of 68) of all deaths. This would suggest that a substantial number of admitted cases may have been complicated by infections but ultimately was not recorded as the primary cause of death.

The all-cause mortality risk in GPA patients remained elevated for every year of disease, up to and beyond 5 years. The increased risk remained stable (~2-fold higher than that in the general population). Other studies that have evaluated similar risk patterns demonstrated a markedly increased risk during the early stage of disease (<1 year), which gradually declined over subsequent years (18,46). The results of our study suggest that disease duration had minimal or no impact on all-cause mortality in our patient population. Reasons for the dissimilarities in our findings include possible difference in disease severity at the time of presentation (i.e., proportion of localized to systemic disease), although our data did not allow us to analyze specific clinical features.

We presented data on outpatient drug dispensing in our GPA cohort, and although the data did not capture inpatient prescriptions (especially rituximab or cyclophosphamide given in infusion form), they provided an indication that the majority of GPA patients had severe disease. We also noted an increase in

the dispensing of azathioprine between the time periods representing the early and late cohorts. This may be due to changes in our clinical practice, in which azathioprine was increasingly used as maintenance therapy, notably as a result of a number of landmark trials published during the same time period as that for our late cohort (47,48). The other possible explanation is that more patients survived the acute stage of disease and developed chronic limited disease. Less-severe relapses are known to occur more frequently than severe relapses (49), and azathioprine may be a drug of choice for re-induction of treatment.

There are some limitations to this study. Because it was an observational study utilizing administrative data, there were potential inaccuracies in the coding of GPA cases. To improve the identification of GPA cases, we imposed a minimum of 2 months between 2 ICD codes and assigned the date of the latter code as the index date, which would affect the duration of follow-up and disease exposure; however, patients in both the early and late cohorts would have been affected equally. Furthermore, to improve the specificity of the case definition, we included a criterion for medication prescriptions, and this approach has a reported positive predictive value of 83.9–90.8% (50). We were confident that we identified true cases with minimal margins of error using our case definition algorithm, because the incidence rates of GPA in our cohort were consistent with data from studies in the UK (51) and Sweden (31). We speculate that the increasing incidence rate between the periods 1997–2004 and 2005–2012 were possibly attributable to increasing availability of ANCA testing, improved classification, and heightened awareness among medical professionals.

The current study was also limited because the number of cause-specific death events, in particular deaths related to infection or renal disease, was insufficient to power the analysis. Therefore, we were unable to report on infection- or renal disease–related mortality risks. Moreover, the relatively few numbers of cancer- and CVD-related deaths also limit interpretation of the Kaplan-Meier survival curves. Further studies in this area with longer follow-up will be necessary to address these issues.

Our study has several strengths. Because it is a population-based study, the external validity of our results is increased. Furthermore, we included only incident GPA cases by definition. We also imposed a minimum lead-in period of 7 years to minimize underestimation of mortality risks, because prevalent cases would potentially include patients who had survived beyond the first year of untreated GPA to enter the cohort (i.e., survival bias). Finally, due to the longitudinal nature of our cohort, we were able to demonstrate the mortality trends in patients with GPA, all of which adds to the body of evidence from previous studies showing improvements in GPA mortality risks over time (12,14).

In conclusion, our population-based study showed increased all-cause and CVD-related mortality risks in patients with GPA. There was a significant improvement in all-cause mortality risks over time. However, reasons for this improvement, such as evidence-based medical treatment, warrant further study. There is an ongoing need to develop strategies to bridge the mortality gap between patients with GPA and 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. 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.

Study conception and design. Tan, Choi, Xie, Esdaile, Aviña-Zubieta.
Acquisition of data. Tan, Sayre, Aviña-Zubieta.
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ARP Announcements

Association of Rheumatology Professionals
2200 Lake Boulevard NE, Atlanta, Georgia 30319
www.rheumatology.org

ACR/ARP Annual Meeting

November 8–13, 2019, Atlanta

New Division Name

Rheumatology is truly a people specialty: We often develop lifelong relationships with our patients as well as our colleagues. We increasingly recognize that providing the best rheumatologic care requires a team effort. The collegial nature of our specialty is reflected in the ACR's mission statement: To empower rheumatology professionals to excel in their specialty.

In keeping with this mission, we are pleased to announce that our health professionals' membership division is changing its name to Association of Rheumatology Professionals (ARP). This name change highlights the dedication of the ACR to serve the entire rheumatology community. It also reflects our broadened base of interprofessional members (administrators, advanced practice nurses, health educators, nurses, occupational therapists, pharmacists, physical therapists, physician assistants, research teams, and more).

The name is new, but our commitment and promise remain the same: We are here for you, so you can be there for your patients.

ARP Membership

The Association of Rheumatology Professionals (ARP), a division of the American College of Rheumatology, appreciates your continued membership and looks forward to serving you another year. Membership costs range from $30 to $140. ARP welcomes nurse practitioners, nurses, physician assistants, office staff, researchers, physical therapists, occupational therapists, assistants, and students. Student membership is complimentary; the Annual Meeting registration fee is waived for students who submit the required student verification letter. For information, go to www.rheumatology.org and select "Membership" or call 404-633-3777 and ask for an ARP staff member.

***ACR Open Rheumatology* Accepting Submissions**

The American College of Rheumatology will be publishing the first issue of its third official journal, *ACR Open Rheumatology (ACROR)*, in early 2019. Editors-in-Chief Drs. Patricia P. Katz and Edward H. Yelin, and Clinical and Basic Science Deputy Editors Drs. David I. Daikh and Bruce N. Cronstein, will be heading *ACROR*'s editorial team.

ACROR will publish manuscripts describing potentially important findings of rigorously conducted studies in all aspects of rheumatology. As an open access journal, immediate access to full content of *ACROR* will be available to all readers. The electronic-only format of the journal, as well as other aspects of the review and production processes, will allow for faster review and publication, and liberal sharing of articles. The projected article publication fee (APC) for *ACROR* will be $2,500 with a discounted rate of $2,000 for articles in which the first or corresponding author is an ACR/ARP member. In addition, there will be waivers of the APC for all articles submitted through March 31, 2019.

New Year and New Product Launches

The Association of Rheumatology Professionals (ARP) has launched its newly-designed comprehensive Advanced Rheumatology Course, which is designed to expand the knowledge of providers in rheumatology. ARP is also premiering 11 newly-created Advanced Rheumatology eBytes (bite-size education offerings) that are free to ALL members. For information on pricing, credits hours, and registration go to www.rheumatology.org, click the drop down box "I AM A" next to the Membership tab and select "Health Professional Education."