ARP Announcements

Association of Rheumatology Professionals
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ACR/ARP Annual Meeting

November 8–13, 2019, Atlanta

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The brand-new ACR Publications app can be downloaded for free from the Apple store or Google Play. ACR members can log in for full-text access to all articles in A*rthritis Care & Research* and *Arthritis & Rheumatology*. Nonmembers can access abstracts of all *AC&R* and *A&R* articles, the full text of articles published more than one year ago, and select open-access articles published recently, as well as the full text of all articles from *ACR Open Rheumatology* and *The Rheumatologist*.

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.

New ACR Journal Twitter Account (@ACR_Journals) and Social Media Editor

The ACR journals are heightening our focus on social media, to benefit authors and readers. Among our first activities is the introduction of an official ACR Journals Twitter account: @ACR_Journals. Followers will enjoy special features and the opportunity to engage with authors and other fellow professionals about studies published in *Arthritis Care & Research, Arthritis & Rheumatology,* and *ACR Open Rheumatology*. Authors of published articles will have the opportunity to use @ACR_Journals to share their work and engage in dialogue with others interested in the research. The journals welcome Dr. Paul Sufka of Minneapolis as our first Social Media Editor.

Arthritis Care & Research

Aims and Scope

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

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Special Articles

Rheumatoid Arthritis

Osteoarthritis

Psoriatic Arthritis

Letters

Cover image: The figure on the cover (from Herath et al, page 1313) is bone marrow aspirate with acid-fast stain demonstrating rare acid-fast bacilli (original magnification × 40).

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American College of Rheumatology
Empowering Rheumatology Professionals

SPECIAL ARTICLE

2019 Update of the American College of Rheumatology/ Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the 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 update evidence-based recommendations for the treatment of patients with ankylosing spondylitis (AS) and nonradiographic axial spondyloarthritis (SpA).

Methods. We conducted updated systematic literature reviews for 20 clinical questions on pharmacologic treatment addressed in the 2015 guidelines, and for 26 new questions on pharmacologic treatment, treat-to-target strategy, and use of imaging. New questions addressed the use of secukinumab, ixekizumab, tofacitinib, tumor necrosis factor inhibitor (TNFi) biosimilars, and biologic tapering/discontinuation, among others. We used the Grading of Recommendations, Assessment, Development and Evaluation methodology to assess the quality of evidence and formulate recommendations and required at least 70% agreement among the voting panel.

Results. Recommendations for AS and nonradiographic axial SpA are similar. TNFi are recommended over secukinumab or ixekizumab as the first biologic to be used. Secukinumab or ixekizumab is recommended over the use of a second TNFi in patients with primary nonresponse to the first TNFi. TNFi, secukinumab, and ixekizumab are favored over tofacitinib. Co-administration of low-dose methotrexate with TNFi is not recommended, nor is a strict treat-to-target strategy or discontinuation or tapering of biologics in patients with stable disease. Sulfasalazine is recommended only for persistent peripheral arthritis when TNFi are contraindicated. For patients with unclear disease activity, spine or pelvis magnetic resonance imaging could aid assessment. Routine monitoring of radiographic changes with serial spine radiographs is not recommended.

Conclusion. These recommendations provide updated guidance regarding use of new medications and imaging of the axial skeleton in the management of AS and nonradiographic axial SpA.

INTRODUCTION

Axial spondyloarthritis (SpA), comprising ankylosing spondylitis (AS) and nonradiographic axial SpA, is the main form of chronic inflammatory arthritis affecting the axial skeleton (1). AS affects 0.1–0.5% of the population, and is characterized by inflammatory back pain, radiographic sacroiliitis, excess spinal bone formation, and a high prevalence of HLA–B27 (2,3). Although nonradiographic axial SpA shares several features with AS, advanced sacroiliac joint damage and spine ankylosis are absent (4). The severity of arthralgia, stiffness, and limited flexibility varies widely among patients and over the course of axial SpA. Skeletal disease may be accompanied by uveitis, psoriasis, and inflammatory bowel disease (IBD). Axial SpA can impose substantial physical and social burdens on patients, and can interfere with work and schooling (5,6). The goals of treatment are to alleviate symptoms, improve functioning, maintain the ability to work, decrease disease complications, and forestall skeletal damage as much as possible.

In 2015, the American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) published recommendations for the treatment of adults with AS and those with nonradiographic axial SpA (7). Recommendations were provided for pharmacologic treatment, rehabilitation, use of surgery, management of selected comorbidities, disease monitoring, patient education, and preventive care. The recommendations were tailored to patients with either active or stable disease and focused on the most common decisions confronting clinicians when treating these patients.

The advent of new medications to treat axial SpA warranted this update. We did not reexamine all of the 2015 recommendations, but rather focused on those questions for which consequential new evidence was present. We added several new recommendations on how the newly available medications should fit in treatment strategies and on the use of imaging. The target populations are adults with AS or nonradiographic axial SpA. The target users of these recommendations are rheumatologists, primary care clinicians, physiatrists, physical therapists, and others providing care to patients with axial SpA.

METHODS

These recommendations followed ACR and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology (8,9), as described in Supplementary Appendix 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract. Briefly, systematic literature reviews were done for prespecified clinical population, intervention, comparator, outcomes (PICO) questions. The resulting evidence was reviewed, and recommendations formulated and voted on, by an expert voting panel (see Supplementary Appendices 2–5 at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract). Key definitions, including ones for active and stable disease, are provided in Table 1. Clinical trials of ixekizumab became available during the time the manuscript was in preparation, after the voting panel had met (10,11). The data from these trials were provided to the voting panel, and revised recommendations that included ixekizumab were reviewed and voted on by the panel.

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

The views expressed herein do not necessarily represent those of the National Institutes of Health or the United States Department of Veterans Affairs.

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Table 1. Definitions of key terms*

Term	Definition
Active disease	Disease causing symptoms at an unacceptably bothersome level to the patient and judged by the examining clinician to be due to inflammation.
Stable disease	Disease that was asymptomatic or causing symptoms but at an acceptable level as reported by the patient. A minimum of 6 months was required to qualify as clinically stable.
Primary nonresponse	Absence of a clinically meaningful improvement in disease activity over the 3 to 6 months after treatment initiation, not related to toxicity or poor adherence.
Secondary nonresponse	Recurrence of ankylosing spondylitis activity, not due to treatment interruption or poor adherence, after having a sustained clinically meaningful improvement on treatment (generally, beyond the initial 6 months of treatment).
Conventional synthetic antirheumatic drug	Sulfasalazine, methotrexate, leflunomide, apremilast, thalidomide, pamidronate.
Biosimilar	Biopharmaceuticals that are copies of an original biologic medication and tested to be of the same purity and potency as the original. In these recommendations, we refer only to TNFi biosimilars. Examples include infliximab-dyyb, etanercept-szzs, and adalimumab-atto.
TNFi	Infliximab, etanercept, adalimumab, certolizumab, golimumab, and their biosimilars.
TNFi monoclonal antibodies	Infliximab, adalimumab, certolizumab, golimumab.
Biologics	TNFi, abatacept, rituximab, sarilumab, tocilizumab, ustekinumab, secukinumab, ixekizumab.**
High-quality evidence	Studies that provide high confidence in the effect estimate, and new data from future studies are thought unlikely to change the effect.
Moderate-quality evidence	Studies that provide confidence that the true effect is likely to be close to the estimate but could be substantially different.
Low-quality evidence	Studies that provide limited confidence about the effect, and the true effect may be substantially different from the estimate.
Very low-quality evidence	Studies that provide very little certainty about the effect, and the true effect may be quite different from the estimate.
Strong recommendation	Action should be favored in almost all patients, usually requiring high-quality evidence, high confidence that future research will not alter the conclusion, AND an assessment that the desirable effects of the intervention outweigh the undesirable effects. Should not be taken to imply that the intervention has large clinical benefits.
Conditional recommendation	Action should be followed in only selected cases, often limited by low-quality evidence, OR when the desirable and undesirable consequences of an intervention are more balanced, OR if patients' preferences for the intervention are thought to vary widely.
Patient preferences	Beliefs and expectations regarding potential benefits and harms of treatment and how these relate to an individual's goals for health and life.
Shared decision-making	The process by which a patient and clinician arrive at an individualized treatment decision based on an understanding of the potential benefits and risks of available treatment options and of a patient's values and preferences.

* TNFi = tumor necrosis factor inhibitor.

RESULTS

Here we present the recommendations that were reviewed in this update, whether it was a new recommendation (designated "new") or reevaluation of an existing recommendation. Table 2 and Table 3 provide all current recommendations, including those from the 2015 report that were not newly reviewed. The order of recommendations presented here does not imply priority for use or recommended sequencing of different interventions. PICO numbers following each recommendation can be used to locate related evidence in Supplementary Appendix 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract.

**Correction added on 26 September 2019, after first online publication: Secukinumab and ixekizumab were omitted in Table 1. They have been restored in this version of the article.

A. Recommendations for the treatment of patients with active AS

In adults with active AS, we conditionally recommend continuous treatment with nonsteroidal antiinflammatory drugs (NSAIDs) over on-demand treatment with NSAIDs (PICO 1).

The efficacy of NSAIDs for symptom improvement in active AS has been established in many controlled trials. Evidence that continuous NSAID use results in slower rates of spinal fusion on radiographs over 2 years compared to on-demand NSAID use is inconsistent, with results of one trial of celecoxib suggesting less progression with continuous use, and one trial of diclofenac indicating no difference in progression (12,13) (See Supplementary Appendix 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract). Despite the

Table 2. Recommendations for the treatment of adults with AS*

Recommendation	Level of evidence	PICO
RECOMMENDATIONS FOR ADULTS WITH ACTIVE AS		
1. We strongly recommend treatment with NSAIDs over no treatment with NSAIDs.†	Low	2
2. We conditionally recommend continuous treatment with NSAIDs over on-demand treatment with NSAIDs.	Low to moderate	1
3. We do not recommend any particular NSAID as the preferred choice.†	Low to moderate	3
4. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications. Sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNFi are not available.	Very low to moderate	7
5. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with tofacitinib.	Very low	60
6. In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with TNFi over no treatment with TNFi.	High	6
7. We do not recommend any particular TNFi as the preferred choice.	Moderate	5
8. In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab.	High	58
9. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab.	Very low	59
10. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib.	Very low	61
11. In adults with active AS despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib.	Low	8
12. In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with a different TNFi in patients with primary nonresponse to TNFi.	Very low	10
13. In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with a different TNFi over treatment with a non-TNFi biologic in patients with secondary nonresponse to TNFi.	Very low	10
14. In adults with active AS despite treatment with the first TNFi used, we strongly recommend against switching to treatment with a biosimilar of the first TNFi.	Very low	62
15. In adults with active AS despite treatment with the first TNFi used, we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of treatment with a new biologic.	Very low	9
16. We strongly recommend against treatment with systemic glucocorticoids.†	Very low	4
17. In adults with isolated active sacroiliitis despite treatment with NSAIDs, we conditionally recommend treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids.†	Very low	13
18. In adults with stable axial disease and active enthesitis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids. Peri-tendon injections of Achilles, patellar, and quadriceps tendons should be avoided.†	Very low	14
19. In adults with stable axial disease and active peripheral arthritis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids.†	Very low	15
20. We strongly recommend treatment with physical therapy over no treatment with physical therapy.†	Moderate	16
21. We conditionally recommend active physical therapy interventions (supervised exercise) over passive physical therapy interventions (massage, ultrasound, heat).†	Very low	17
22. We conditionally recommend land-based physical therapy interventions over aquatic therapy interventions.†	Moderate	18
RECOMMENDATIONS FOR ADULTS WITH STABLE AS		
23. We conditionally recommend on-demand treatment with NSAIDs over continuous treatment with NSAIDs.	Low to moderate	1
24. In adults receiving treatment with TNFi and NSAIDs, we conditionally recommend continuing treatment with TNFi alone compared to continuing both treatments.	Very low	11
25. In adults receiving treatment with TNFi and a conventional synthetic antirheumatic drug, we conditionally recommend continuing treatment with TNFi alone over continuing both treatments.	Very low	12
26. In adults receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic.	Very low to low	66

(Continued)

Table 2. (*Cont'd*)

Recommendation	Level of evidence	PICO
27. In adults receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach.	Very low to low	65
28. In adults receiving treatment with an originator TNFi, we strongly recommend continuing treatment with the originator TNFi over mandated switching to its biosimilar.	Very low	63
29. We strongly recommend treatment with physical therapy over no treatment with physical therapy.†	Low	19
RECOMMENDATIONS FOR ADULTS WITH ACTIVE OR STABLE AS		
30. In adults receiving treatment with TNFi, we conditionally recommend against co-treatment with low-dose methotrexate.	Low	64
31. We conditionally recommend advising unsupervised back exercises.†	Moderate	20
32. We conditionally recommend fall evaluation and counseling.†	Very low	51
33. We conditionally recommend participation in formal group or individual self-management education.†	Moderate	48
34. In adults with spinal fusion or advanced spinal osteoporosis, we strongly recommend against treatment with spinal manipulation.†	Very low	21
35. In adults with advanced hip arthritis, we strongly recommend treatment with total hip arthroplasty over no surgery.†	Very low	25
36. In adults with severe kyphosis, we conditionally recommend against elective spinal osteotomy.†	Very low	26
RECOMMENDATIONS FOR ADULTS WITH AS-RELATED COMORBIDITIES		
37. In adults with acute iritis, we strongly recommend treatment by an ophthalmologist to decrease the severity, duration, or complications of episodes.†	Very low	27
38. In adults with recurrent iritis, we conditionally recommend prescription of topical glucocorticoids over no prescription for prompt at-home use in the event of eye symptoms to decrease the severity or duration of iritis episodes.†	Very low	28
39. In adults with recurrent iritis, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics.	Low	29
40. In adults with inflammatory bowel disease, we do not recommend any particular NSAID as the preferred choice to decrease the risk of worsening of inflammatory bowel disease symptoms.†	Very low	31
41. In adults with inflammatory bowel disease, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics.	Very low	32
DISEASE ACTIVITY ASSESSMENT, IMAGING, AND SCREENING		
42. We conditionally recommend the regular-interval use and monitoring of a validated AS disease activity measure.†	Very low	54
43. We conditionally recommend regular-interval use and monitoring of CRP concentrations or ESR over usual care without regular CRP or ESR monitoring.†	Very low	55
44. In adults with active AS, we conditionally recommend against using a treat-to-target strategy using a target of ASDAS <1.3 (or 2.1) over a treatment strategy based on physician assessment.	Low	67
45. We conditionally recommend screening for osteopenia/osteoporosis with DXA scan over no screening.†	Very low	49
46. In adults with syndesmophytes or spinal fusion, we conditionally recommend screening for osteoporosis/osteopenia with DXA scan of the spine as well as the hips, compared to DXA scan solely of the hip or other non-spine sites.†	Very low	50
47. We strongly recommend against screening for cardiac conduction defects with electrocardiograms.†	Very low	52
48. We strongly recommend against screening for valvular heart disease with echocardiograms.†	Very low	53
49. In adults with AS of unclear activity while on a biologic, we conditionally recommend obtaining a spinal or pelvis MRI to assess activity.	Very low	68
50. In adults with stable AS, we conditionally recommend against obtaining a spinal or pelvis MRI to confirm inactivity.	Very low	69
51. In adults with active or stable AS on any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach.	Very low	70

* AS = ankylosing spondylitis; PICO = population, intervention, comparison, and outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; TNFi = tumor necrosis factor inhibitor; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ASDAS = Ankylosing Spondylitis Disease Activity Score; DXA = dual x-ray absorptiometry; MRI = magnetic resonance imaging.
† These recommendations were from 2015 and were not reviewed in this update. The number preceding the recommendation is the recommendation number and is referenced as bracketed numbers in Figure 1.

Table 3. Recommendations for the treatment of adults with nonradiographic axial SpA*

Recommendation	Level of evidence	PICO
RECOMMENDATIONS FOR ADULTS WITH ACTIVE NONRADIOGRAPHIC AXIAL SpA		
52. We strongly recommend treatment with NSAIDs over no treatment with NSAIDs.†	Very low	34
53. We conditionally recommend continuous treatment with NSAIDs over on-demand treatment with NSAIDs.	Very low	33
54. We do not recommend any particular NSAID as the preferred choice.†	Very low	35
55. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications.	Very low	39
56. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we strongly recommend treatment with TNFi over no treatment with TNFi.	High	38
57. We do not recommend any particular TNFi as the preferred choice.	Very low	37
58. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with tofacitinib.	Very low	73
59. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab.	Very low	71
60. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab.	Very low	72
61. In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib.	Very low	74
62. In adults with active nonradiographic axial SpA despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib.	Very low	40
63. In adults with active nonradiographic axial SpA and primary nonresponse to the first TNFi used, we conditionally recommend switching to secukinumab or ixekizumab over switching to a different TNFi.	Very low	42
64. In adults with active nonradiographic axial SpA and secondary nonresponse to the first TNFi used, we conditionally recommend switching to a different TNFi over switching to a non-TNFi biologic.	Very low	42
65. In adults with active nonradiographic axial SpA despite treatment with the first TNFi used, we strongly recommend against switching to the biosimilar of the first TNFi.	Very low	75
66. In adults with active nonradiographic axial SpA despite treatment with the first TNFi used, we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of treatment with a different biologic.	Very low	41
67. We strongly recommend against treatment with systemic glucocorticoids.†	Very low	36
68. In adults with isolated active sacroiliitis despite treatment with NSAIDs, we conditionally recommend treatment with local glucocorticoids over no treatment with local glucocorticoids.†	Very low	45
69. In adults with active enthesitis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids. Peri-tendon injections of Achilles, patellar, and quadriceps tendons should be avoided.†	Very low	46
70. In adults with active peripheral arthritis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids.†	Very low	47
71. We strongly recommend treatment with physical therapy over no treatment with physical therapy.†	Low	22
72. We conditionally recommend active physical therapy interventions (supervised exercise) over passive physical therapy interventions (massage, ultrasound, heat).†	Very low	23
73. We conditionally recommend land-based physical therapy interventions over aquatic therapy interventions.†	Very low	24
RECOMMENDATIONS FOR ADULTS WITH STABLE NONRADIOGRAPHIC AXIAL SpA		
74. We conditionally recommend on-demand treatment with NSAIDs over continuous treatment with NSAIDs.	Very low	33
75. In adults receiving treatment with TNFi and NSAIDs, we conditionally recommend continuing treatment with TNFi alone compared to continuing both medications.	Very low	43
76. In adults receiving treatment with TNFi and a conventional synthetic antirheumatic drug, we conditionally recommend continuing treatment with TNFi alone over continuing treatment with both medications.	Very low	44
77. In adults receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic.	Low	79
78. In adults receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach.	Very low	78
79. In adults receiving treatment with an originator TNFi, we strongly recommend continuation of treatment with the originator TNFi over mandated switching to its biosimilar.	Very low	76

(Continued)

Table 3. (*Cont'd*)

Recommendation	Level of evidence	PICO
RECOMMENDATIONS FOR ADULTS WITH ACTIVE OR STABLE NONRADIOGRAPHIC AXIAL SpA		
80. In adults receiving treatment with TNFi, we conditionally recommend against co-treatment with low-dose methotrexate.	Low	77
DISEASE ACTIVITY ASSESSMENT AND IMAGING		
81. We conditionally recommend the regular-interval use and monitoring of a validated AS disease activity measure.†	Very low	56
82. We conditionally recommend regular-interval use and monitoring of the CRP concentrations or ESR over usual care without regular CRP or ESR monitoring.†	Very low	57
83. In adults with active nonradiographic axial SpA, we conditionally recommend against using a treat-to-target strategy using a target of ASDAS <1.3 (or 2.1) over a treatment strategy based on physician assessment.	Very low	80
84. In adults with nonradiographic axial SpA of unclear activity while on a biologic, we conditionally recommend obtaining a pelvis MRI to assess activity.	Very low	81
85. In adults with stable nonradiographic axial SpA, we conditionally recommend against obtaining a spinal or pelvis MRI to confirm inactivity.	Very low	82
86. In adults with active or stable nonradiographic axial SpA on any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach.	Very low	83

* SpA = spondyloarthritis; PICO = population, intervention, comparison, and outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; TNFi = tumor necrosis factor inhibitor; AS = ankylosing spondylitis; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ASDAS = Ankylosing Spondylitis Disease Activity Score; MRI = magnetic resonance imaging.
† These recommendations were from 2015 and were not reviewed in this update. The number preceding the recommendation is the recommendation number and is referenced as bracketed numbers in Figure 1.

uncertainty regarding potential disease-modifying effects, the committee conditionally favored continuous use of NSAIDs in patients with active AS, primarily for controlling disease activity. The decision to use NSAIDs continuously may vary depending on the severity of symptoms, patient preferences, and comorbidities, particularly gastrointestinal and kidney comorbidities, and cardiovascular disease.

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications (new, PICO 7). Sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when tumor necrosis factor inhibitors (TNFi) are not available.

Treatment with sulfasalazine is recommended primarily for patients with prominent peripheral arthritis and few or no axial symptoms. However, TNFi may provide a better option for these patients. Evidence for the efficacy of sulfasalazine is based on 8 older controlled trials that showed benefit for peripheral arthritis (see Supplementary Appendix 6, on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract). Although a recent placebo-controlled trial of sulfasalazine demonstrated improvement in axial symptoms, and modest clinical and imaging responses were seen in a second trial, the preponderance of evidence indicates that sulfasalazine has little benefit for axial symptoms (14,15). Sulfasalazine may have a role in treating patients who have contraindications to TNFi, those who decline treatment with TNFi, or those with limited access to TNFi.

Three trials of methotrexate with negative results tested doses of ≤10 mg weekly, and the lack of benefit may reflect the low doses used (16–18). One uncontrolled study of methotrexate 20 mg weekly showed no improvement in axial symptoms, but a decrease in swollen joint count (19). Treatment with methotrexate may be considered for patients with predominately peripheral arthritis, although among nonbiologics, there is more evidence supporting the use of sulfasalazine.

A phase II study of tofacitinib showed benefit in both clinical and imaging outcomes of axial disease over 12 weeks (20). Use of tofacitinib could be another option, although the results of phase III trials are not available. Leflunomide, apremilast, thalidomide, and pamidronate are not recommended (See Supplementary Appendix 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract).

In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with TNFi over no treatment with TNFi (PICO 6).

In adults with active AS despite treatment with NSAIDs, we do not recommend any particular TNFi as the preferred choice (PICO 5).

The efficacy of TNFi in patients with active AS has been demonstrated in 24 randomized controlled trials, most of which were short-term (6 months or shorter) placebo-controlled studies. Improvements were shown in patient-reported outcomes, composite response criteria, and spine and sacroiliac inflammation on magnetic resonance imaging (MRI) (see Supplementary Appendix 6, on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract). The panel judged that the evidence justified a strong recommendation

for use of TNFi in patients whose AS remained active (as defined in Table 1) despite treatment with NSAIDs. The panel recommended that lack of response (or intolerance) to at least 2 different NSAIDs at maximal doses over 1 month, or incomplete responses to at least 2 different NSAIDs over 2 months, would be adequate trials with which to judge NSAID responsiveness prior to escalating to treatment with TNFi.

Indirect comparisons in network meta-analyses of clinical trials have not showed clinically meaningful differences in short-term efficacy among TNFi in the treatment of active AS (see Supplementary Appendix 6, at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract) (21). Direct comparisons among these medications are limited to a trial of infliximab versus its biosimilar, and a very small open-label trial of infliximab versus etanercept (22,23). The panel judged that the evidence did not support preference of 1 TNFi over any other for the typical patient. Important exceptions apply to patients with recurrent uveitis or coexistent IBD (see PICO 29 and PICO 32 below). Patients treated with infliximab may have increased risks of tuberculosis and of infections generally (24,25). TNFi other than infliximab should be considered for patients at higher risk of tuberculosis exposure (either through travel or household contacts) or with a history of recurrent infections. Patient preferences regarding the frequency of dosing and route of administration should be weighed when selecting a specific TNFi.

In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab (new, PICO 58).

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab (new, PICO 59).

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with tofacitinib (new, PICO 60).

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib (new, PICO 61).

The use of secukinumab and ixekizumab in patients with active AS is supported by data from large placebo-controlled trials (see Supplementary Appendix 6, on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract). The panel recommended use of TNFi over secukinumab or ixekizumab based on greater experience with TNFi and familiarity with their long-term safety and toxicity. Similarly, the panel judged that TNFi, secukinumab, or ixekizumab should be used over tofacitinib, given the larger evidence base for TNFi, secukinumab, and ixekizumab. In patients with coexisting ulcerative colitis, if treatment with TNFi is not an option, tofacitinib should be considered over secukinumab or ixekizumab. Interleukin-17 (IL-17) inhibitors have not been shown to be efficacious in IBD, although tofacitinib is an approved treatment for ulcerative colitis (26,27).

In adults with active AS despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib (new, PICO 8).

No studies have directly compared the risks and benefits of treatment alternatives in patients who have contraindications to treatment with TNFi. The panel favored treatment with secukinumab or ixekizumab over treatment with sulfasalazine or methotrexate based on a higher likelihood of benefit, but this recommendation was conditional on the specific contraindication. If the contraindication to TNFi use was the presence of congestive heart failure or demyelinating disease, secukinumab or ixekizumab was preferred, since these medications have not been shown to worsen these conditions. If the contraindication to TNFi use was tuberculosis, other chronic infection, or a high risk of recurrent infections, sulfasalazine was preferred over secukinumab, izekizumab, and tofacitinib. In these cases, efforts to mitigate the infections should be undertaken so that TNFi might safely be used. Treatment with rituximab, abatacept, ustekinumab, or IL-6 inhibitors is not recommended, even in patients with contraindications to TNFi, due to lack of effectiveness.

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with a different TNFi in patients with primary nonresponse to TNFi (new, PICO 10).

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with a different TNFi over treatment with a non-TNFi biologic in patients with secondary nonresponse to TNFi (new, PICO 10).

In adults with active AS despite treatment with the first TNFi used, we strongly recommend against switching to treatment with a biosimilar of the first TNFi (new, PICO 62).

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of switching to a new biologic (PICO 9).

Direct comparisons of treatment strategies for patients who do not have or sustain adequate responses to their first TNFi have not been reported, and the recommendations are based on the panel's consideration of indirect comparisons among the available treatment options (see Supplementary Appendix 6, at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract). Data from observational studies suggest that 25–40% of patients who switch from one TNFi to another will have a meaningful response (e.g.,

50% improvement in Bath AS Disease Activity Index) to the second TNFi (28–30). However, not all patients in these studies switched TNFi because of ineffectiveness.

The panel judged that treatment should differ for patients who had a primary nonresponse to TNFi and those with secondary nonresponse to TNFi. Switching to secukinumab or ixekizumab was recommended in most patients who had a primary nonresponse to the first TNFi, under the assumption that TNF was not the key inflammatory mediator in these patients. Continuing treatment with the first TNFi could be considered if additional time was believed important to assess the response fully, or if a higher dose or shorter dosing interval was thought to be beneficial.

In patients who relapse after an initial response (i.e., secondary nonresponse), the panel judged that treatment with a different TNFi held a reasonable prospect of benefit and should be used in most patients, rather than immediately switching to a different class of biologics. Although ixekizumab is efficacious among TNFi nonresponders, trials have not directly compared responses to ixekizumab (or secukinumab) to responses to a second TNFi in patients with a secondary nonresponse to the first TNFi (11). Given that options for biologics are limited, treatment with a second TNFi was recommended in these patients.

In cases of nonresponse (primary or secondary), the panel recommended against switching to the biosimilar of the first TNFi (e.g., switching from originator infliximab to infliximab-dyyb), as the clinical response would not be expected to be different. The panel also recommended against the addition of sulfasalazine or methotrexate to TNFi in cases of nonresponse to TNFi, judging any benefit would likely be marginal. The addition of sulfasalazine could be considered in the rare patient whose axial symptoms are well-controlled with TNFi but who has active peripheral arthritis.

In adults with either active or stable AS on treatment with TNFi, we conditionally recommend against co-treatment with low-dose methotrexate (new, PICO 64).

In rheumatoid arthritis, the likelihood of TNFi discontinuation is lower among patients who receive co-treatment with methotrexate, perhaps by reducing the development of antidrug antibodies (31). In AS, it is less clear whether the duration of TNFi use, and by inference their effectiveness, is similarly prolonged (32). Data from observational studies are conflicting, although some studies, primarily of infliximab, showed longer TNFi treatment when methotrexate was co-administered (see Supplementary Appendix 6 at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract). Clinical responses were not greater among patients who received co-treatment with methotrexate. In the absence of convincing evidence of benefit, and due to greater burden for patients, the panel recommended against routine co-administration of methotrexate with TNFi, although its use could be considered in patients treated with infliximab.

B. Recommendations for the treatment of patients with stable AS

In adults with stable AS, we conditionally recommend on-demand treatment with NSAIDs over continuous treatment with NSAIDs (PICO 1).

This recommendation applies to patients whose AS has been stable while not receiving any pharmacologic treatment. In this group, the panel considered that the potential toxicities of continuous NSAID treatment outweighed the uncertain benefit of less radiographic progression. On-demand treatment should be considered for short-term symptom recurrences (flares).

In adults with stable AS receiving treatment with TNFi and NSAIDs, we conditionally recommend continuing treatment with TNFi alone over continuing both medications (PICO 11).

In adults with stable AS receiving treatment with TNFi and a conventional synthetic antirheumatic drug, we conditionally recommend continuing treatment with TNFi alone over continuing both medications (PICO 12).

No new studies have directly compared outcomes between patients who continued combination treatment and those who discontinued either NSAIDs or a conventional synthetic antirheumatic drug (csARD). The NSAID-sparing potential of etanercept was demonstrated in a recent trial (33). The panel judged these recommendations primarily based on symptom control, rather than on any potential effect of combination therapy on future spinal fusion. In stable patients, a trial of withdrawing either the NSAIDs or the csARD should be considered, due to the likelihood of greater toxicity with the long-term use of more than one medication. However, on-demand NSAID treatment for control of intermittent symptoms is recommended for patients with good responses to previous courses of NSAIDs.

In adults with stable AS receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic (new, PICO 66).

In adults with stable AS receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach (new, PICO 65).

Data from several observational studies suggest that discontinuation of TNFi after achieving either remission or low disease activity results in relapses in 60–74% of patients, occasionally within a few weeks to months from discontinuation (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract). Although the data only concerned TNFi discontinuation, the panel judged that a similar recommendation would also apply to other biologics. In general, treatment with a biologic should be planned to be

continued long-term, barring toxicities. Discontinuation might be considered in patients in sustained remission (i.e., several years), with the anticipation that only one-third of patients would not experience relapse. Patient preferences should help guide this decision.

Tapering of TNFi could entail a change in either the dose or frequency of administration. Two controlled unblinded trials of tapering etanercept to 25 mg weekly versus maintaining the dose at 50 mg weekly in patients with stable AS showed that remission or partial remission was somewhat less likely among those in whom etanercept was tapered (34,35). In small observational studies, 53–70% of patients were still receiving their reduced dose at 2 years, but there is little evidence regarding maintenance of long-term remission after tapering of TNFi (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract). Therefore, the panel recommended against tapering of biologics as a standard approach. One condition in which tapering could be considered would be in patients with prolonged stable AS, if the patient and provider engage in shared decision-making.

In adults with stable AS receiving an originator TNFi, we strongly recommend continuing treatment with the originator TNFi over mandated switching to its biosimilar (new, PICO 63).

While the efficacy of originator and biosimilar TNFi is comparable, and although either could be chosen to initiate new courses of TNFi treatment, it was the opinion of the panel to recommend against mandated switching to a biosimilar during the course of treatment, in the absence of evidence of interchangability. Medication changes can increase the risk of destabilizing a patient's condition, and the panel judged that additional data were needed to understand the frequency of potential problems and concerns associated with switching patients who were stable on an originator TNFi to its biosimilar. Given these concerns, the panel judged that there should be a compelling rationale for switching medications, particularly in light of the marginal cost savings apparent for US patients (36).

C. Recommendations for adults with AS-related comorbidities

In adults with AS and recurrent uveitis, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics (PICO 29).

Evidence for this recommendation is limited to indirect comparisons of the rates of acute uveitis episodes in clinical trials or observational studies, rather than from direct comparisons (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract). Many reports showed overall rates of uveitis without separately reporting recurrences as opposed to incident episodes (37). The rates were generally lower for adalimumab and infliximab compared to etanercept. For example, a large observational study demonstrated rates of uveitis (per 100 patient-years) in patients receiving adalimumab, infliximab, and etanercept of 13.6, 27.5, and 60.3, respectively, compared to pretreatment rates of 36.8, 45.5, and 41.6, respectively (38). Adalimumab or infliximab are preferred over etanercept for the treatment of AS in patients with recurrent uveitis. Certolizumab or golimumab may also be considered, although supporting data are less substantial (39,40). Data from clinical trials suggest that rates of uveitis flares were not different between patients with AS treated with secukinumab and those treated with placebo, but more evidence is needed. Secukinumab was not efficacious in the treatment of panuveitis or posterior uveitis (41). Rates of uveitis flares among patients treated with ixekizumab have not been well-defined.

In adults with AS and IBD, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics (PICO 32).

This recommendation was based on limited indirect evidence on the risks of flares or new onset of IBD among patients with AS during treatment with biologics, and the much larger literature on the treatment of IBD in general. Patients with AS treated with infliximab or adalimumab have lower risks of IBD exacerbations than those treated with etanercept (see Supplementary Appendix 6, on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract). Infliximab, adalimumab, and certolizumab are approved for the treatment of Crohn's disease, and infliximab, adalimumab, and golimumab are approved for the treatment of ulcerative colitis, while etanercept is not approved for either condition (42,43). This evidence is the basis for the recommendation favoring TNFi monoclonal antibody use in patients with AS and coexisting IBD. The choice of the particular TNFi monoclonal antibody should be made in consultation with the patient's gastroenterologist. Secukinumab has been associated with the new onset, or exacerbation, of Crohn's disease (44–46). Increased risks of IBD exacerbation appear to also occur with ixekizumab (47).

D. Recommendations for the treatment of patients with either active or stable nonradiographic axial spondyloarthritis

Parallel questions on pharmacologic treatment were investigated for patients with nonradiographic axial SpA. There were no relevant published data for 19 questions. There was high-quality evidence only for the use of TNFi in nonradiographic axial SpA, which was examined in several clinical trials. Low-quality or very low-quality evidence from single studies suggested no differences in outcomes among different TNFi in nonradiographic axial SpA, high likelihood of relapse following discontinuation of TNFi, and no association between co-treatment with nonbiologics and TNFi persistence (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract).

Therefore, the recommendations for nonradiographic axial SpA were largely extrapolated from evidence in AS (Table 3). The recommendations were identical in both patient groups with 1 notable exception: treatment with secukinumab or ixekizumab was strongly recommended over no treatment with secukinumab or ixekizumab in patients with AS, while use of these medications was conditionally recommended in patients with nonradiographic axial SPA, because trials in nonradiographic axial SPA have not been reported. Evidence on tofacitinib in nonradiographic axial SpA has not been reported.

E. Disease activity assessment and imaging

In adults with active AS, we conditionally recommend against using the treat-to-target strategy, which aims at a target of an Ankylosing Spondylitis Disease Activity Score <1.3 (or 2.1), over a treatment strategy based on physician assessment (new, PICO 67).

The concept of treat-to-target strategies is well-founded in chronic disease management for conditions that have an accurate measure of disease activity (often one that is asymptomatic, as in blood pressure or glycosylated hemoglobin), a tight link between this disease activity measure and future health outcomes, and evidence that maintaining a particular target in the disease activity measure is closely associated with better long-term health (48). The treat-to-target approach in AS is indirectly supported by associations between levels of AS activity and future radiographic progression but lacks robust direct evidence. Because adoption of this strategy would place additional burdens on patients and providers, the panel judged that more convincing evidence of benefit should be present before endorsing this change in practice. There was also concern that focus on a specific target could lead to rapid cycling through all currently available treatments in some patients. As reflected in the 2015 guidelines, quantifying disease activity is important to help guide treatment decisions.

In adults with AS of unclear activity while receiving a biologic, we conditionally recommend obtaining a spinal or pelvis MRI to assess activity (new, PICO 68).

In adults with nonradiographic axial SpA of unclear activity while receiving a biologic, we conditionally recommend obtaining a pelvis MRI to assess activity (new, PICO 81).

Because physical and laboratory measures are often normal despite active axial SpA, and because symptoms may be nonspecific, it may be difficult to know whether a patient is experiencing inflammation that warrants a change in treatment. Limited evidence suggests that knowledge of MRI findings in the spine and sacroiliac joints may alter treatment recommendations. However, the degree of inflammatory change on MRI may not correlate with treatment responses, and the location of inflammation on MRI may not correlate with the location of pain (49) (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract). The panel judged that MRI could provide useful information in cases where the level of disease activity was unclear and where this information would influence treatment decisions. For patients with nonradiographic axial SpA, the imaging should focus on the sacroiliac joints. In interpreting MRI results, it is important to keep in mind the range and frequency of abnormalities, including bone marrow edema lesions, that may occur in individuals without axial SpA and that may not represent inflammation due to axial SpA (50,51). MRI is not recommended in patients in whom disease activity is either clearly clinically active or clinically stable, or when the results of MRI would not be expected to change treatment.

In adults with stable AS, we conditionally recommend against obtaining a spinal or pelvis MRI to confirm inactivity (new, PICO 69).

In adults with stable nonradiographic axial SpA, we conditionally recommend against obtaining a spine or pelvis MRI to confirm inactivity (new, PICO 82).

Because the clinical assessment of inflammation in axial SpA has many limitations, questions may arise about whether subclinical inflammation that could be detected by MRI is being "missed" by either the physical examination, symptoms, or laboratory studies. Given the lack of evidence that obtaining an MRI in stable patients improves clinical outcomes, the only moderate sensitivity and specificity of MRI-defined abnormalities for measurement of activity in axial SpA, the burden of testing, and concern for possible overtreatment, the panel recommended against obtaining an MRI in this setting. MRI could be considered in circumstances where the clinician and patient differ in their assessment of whether the disease is stable.

In adults with active or stable AS receiving any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach (new, PICO 70).

In adults with active or stable nonradiographic axial SpA on any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach (new, PICO 83).

Spine radiographs are useful for the diagnosis of axial SpA, in evaluating the extent of spinal fusion, and for investigating new spinal pain in patients with established AS. In research studies, small changes in the extent of spine damage can be detected in 20–35% of patients with AS over a 2-year interval (see Supplementary Appendix 6, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24025/abstract). There is no evidence that monitoring serial changes in

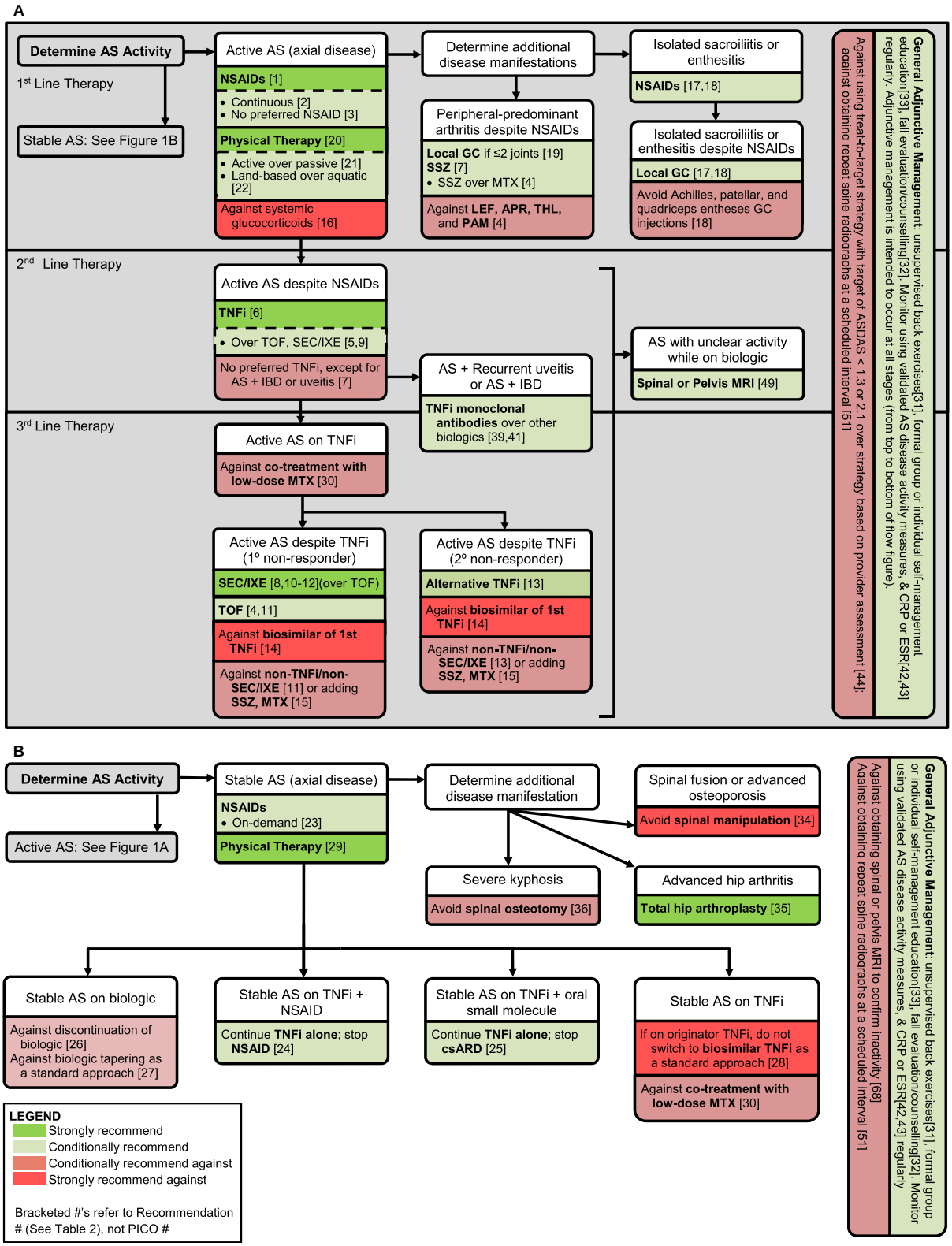

Figure 1. Summary of the main recommendations for the treatment of patients with **A,** active ankylosing spondylitis and **B,** stable ankylosing spondylitis. AS = ankylosing spondylitis; NSAIDs = nonsteroidal antiinflammatory drugs; GC = glucocorticoid; SSZ = sulfasalazine; MTX = methotrexate; LEF = leflunomide; APR = apremilast; THL = thalidomide; PAM = pamidronate; TNFi = tumor necrosis factor inhibitor; TOF = tofacitinib; SEC = secukinumab; IXE = ixekizumab; IBD = inflammatory bowel disease; csARD = conventional synthetic antirheumatic drugs; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein level; ASDAS = Ankylosing Spondylitis Disease Activity Score; MRI = magnetic resonance imaging; PICO = population, intervention, comparison, and outcomes.

spine radiographs at a regular interval leads to better patient outcomes, and data balancing a clinical benefit with the risk of radiation exposure are absent. Therefore, the panel recommended against repeating spine radiographs as a standard approach. In the absence of clinical indications, repeat spine radiographs could be considered on an ad hoc basis for counseling patients on the progression of their disease, which may help in career and life planning.

F. Summary of recommendations

Figure 1 presents a diagram of the main treatment recommendations for active and stable AS, integrating the new recommendations with the 2015 recommendations that were not updated in this review.

DISCUSSION

This update was primarily motivated by the availability of new treatment options, notably secukinumab, ixekizumab, tofacitinib, and TNFi biosimilars, for patients with axial SpA. Providers and patients have questions on where these new medications fit in the pharmacologic strategy, and how originator TNFi, sulfasalazine, and NSAIDs should be used given these new options. Based on the current evidence and the considerations of the panel, NSAIDs and TNFi remain the primary classes of medications for the treatment of AS and nonradiographic axial SpA. Secukinumab or ixekizumab is recommended for patients with active disease who have heart failure or demyelinating disease as a contraindication to TNFi, and in primary nonresponders to TNFi. Secukinumab and ixekizumab are not recommended in patients with IBD or recurrent uveitis, as TNFi monoclonal antibodies are better options. Tofacitinib is a potential second-line option for patients with contraindications to TNFi other than infections. Recommendations regarding tofacitinib may change pending the results of larger clinical trials.

Several of the 2015 recommendations were modified in this update. The current recommendation is conditionally in favor of use of sulfasalazine in limited clinical circumstances, whereas the 2015 recommendations had this as an exception to the general recommendation against the use of conventional synthetic antirheumatic drugs. In the 2015 recommendations, sulfasalazine and pamidronate were suggested as alternatives for the treatment of patients with active disease and contraindications to TNFi, while the current recommendations suggest use of secukinumab or ixekizumab in most of these cases (except patients with high risk of infections). In cases of failure of TNFi, the 2015 guidelines included a conditional recommendation for a trial of a second TNFi and against use of a non-TNFi biologic, whereas the current guidelines differentiate treatment recommendations based on whether there was primary or secondary nonresponse to the TNFi. For the treatment of patients with recurrent uveitis, the previous guidelines specified conditional use of infliximab or adalimumab, while the update broadened this recommendation to include TNFi monoclonal antibodies generally. Similarly, for patients with coexisting IBD, the update includes a conditional recommendation for TNFi monoclonal antibodies over other biologics, rather than over only etanercept. Finally, the recommendation for use of TNFi in patients with active nonradiographic axial SpA was changed from conditional to strong.

New questions on the treatment of patients with stable disease were addressed in this update. Discontinuation of biologics is not recommended due to the likelihood for symptom recurrence. If tapering is considered, patients should be counseled regarding the potential for increased disease activity. Co-treatment with low-dose methotrexate is not generally recommended, but ongoing studies will shed further light on this question. Switching to a biosimilar during the course of treatment with TNFi is also not recommended, echoing the concerns previously expressed by the ACR (52).

Imaging remains a central tool in the diagnosis of axial SpA, but its role in monitoring patients is less well-defined. Spine and/or pelvis MRI could aid in the evaluation of patients in whom the degree of active inflammation is uncertain, and especially in those for whom the findings would change management. MRI is not recommended to seek subclinical inflammation in patients with stable disease (as defined in Table 1). However, MRI could be considered in circumstances where it may inform shared decision-making. We recommend against obtaining spine radiographs on scheduled intervals to monitor progression. This practice entails radiation exposure and would not alter treatment in most cases.

We used the GRADE method to develop these treatment recommendations in a way that was transparent, systematic, and explicit, and that was informed by the medical evidence as well as patient preferences. The major limitation of these guidelines is the very low quality of evidence for many recommendations, which necessitated reliance on the clinical expertise of the panel. For nonradiographic axial SpA, most recommendations were based on extrapolation of results from studies in AS. We tried to identify the most common and consequential treatment questions, so that the recommendations would be useful in guiding clinical decision-making. The low quality of evidence for many questions is an indication that research has not yet tackled many of the most important treatment questions. As more treatment options become available, this problem will grow. Importantly, failure to recommend a particular medication does not imply that it is contraindicated. Key evidence gaps include the comparative effectiveness and safety of different biologics, the optimal sequencing of treatments, and the role of NSAIDs.

This update addressed only a subset of treatment questions. The 2015 recommendations that were not reexamined are to be considered extant. Recommendations are meant to describe the approach to treatment of the typical patient and cannot anticipate all possible clinical scenarios. Application of these recommendations must be individualized, and requires

careful assessment, sound clinical judgment of each patient's circumstances, and consideration of a patient's preferences.

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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. Ward 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. Ward, Deodhar, Turner, Caplan.

Acquisition of data. Ward, Deodhar, Shah, Sullivan, Turgunbaev, Oristaglio, Caplan.

Analysis and interpretation of data. Ward, Deodhar, Gensler, Dubreuil, Yu, Khan, Haroon, Borenstein, Wang, Biehl, Fang, Louie, Majithia, Ng, Bigham, Pianin, Shah, Sullivan, Turgunbaev, Oristaglio, Maksymowych, Caplan.

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EDITORIAL

Is It Time to Banish Composite Measures for Remission in Rheumatoid Arthritis?

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In this issue of *Arthritis Care & Research*, Ferreira et al have reported a study on how the patient's global assessment (PtGA) impacts remission in rheumatoid arthritis (RA) (1). This study calls into question the use of certain components within the American College of Rheumatology (ACR)/European League Against Rheumatism Boolean definition for RA remission (2) . The authors analyzed RA patients in the large Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology (METEOR) database with >27,000 patients. METEOR is a longitudinal database, recruiting patients who have RA from multiple countries within routine practice and following them over time. The authors wanted to determine the effect of the PtGA on disease activity and especially on remission status. Boolean remission occurred in approximately 6% of patients, but that number more than doubled if the PtGA was removed (a remission rate of approximately 6% increased to 16%). The PtGA was related more to pain and function and less to inflammation or active disease. Interestingly, eliminating the PtGA in patients with near-remission boosts the proportion in remission in various ways, depending on the country, with India only increasing remission by <2% and The Netherlands and some other countries by nearly 14% (1). The swollen joint count (SJC) score also affected near-remission overall by 5%, and this result had virtually no variation by country. One might think that the components of remission with higher variability (such as the PtGA) may, by definition, be less reliable. The results of the SJC, tender joint count (TJC), PtGA, and C-reactive protein (CRP) level used to determine remission are shown to have modest correlations. The correlations between PtGA are lowest with CRP level and highest with pain and function (such as the Health Assessment Questionnaire disability index) and intermediate with joint counts (1). The authors found that for patients meeting other components of remission, there was no correlation between the PtGA and disease activity. Overall, the PtGA could have an impact with respect to misclassification of RA disease activity if a patient is not in remission due solely to a high PtGA.

In RA, we have had a large problem with determining remission, probably due to our concept of remission that takes into account both pathologic factors (swollen joints) and patient-reported outcomes (PROs). Ideally, RA remission requires a universal definition that is easy to use in clinical practice and has face validity.

Remission varies depending on what definition is used. Boolean remission is defined as 0 or 1 swollen joints, 0 or 1 tender joints, PtGA ≤1 and CRP level ≤1 mg/dl for clinical trials and removal of the CRP level for clinical practice (2). The Clinical Disease Activity Index (CDAI; composed of the physician global assessment + PtGA + SJC + TJC) defines remission as ≤2.8, and the Simple Disease Activity Index (CDAI + CRP level in mg/dl) defines remission as ≤3.3 (3). The global scales are from 0 to 10, and SJC and TJC range from 0 to 28. The Disease Activity Score in 28 joints (DAS28) using the erythrocyte sedimentation rate remission is ≤2.6 (4). DAS28 remission occurs more frequently than the stricter definitions of remission, which is problematic, because all of these methods define remission. These various remission values are correlated to each other (often only modestly) and are predictive of less radiographic progression (2,5). However, the definitions are a construct and may exclude patients with inactive RA (who may be considered to be in remission). For instance, a patient with no swollen joints may still have pain and/or tender joints, and this circumstance could exclude remission in all of the composite scores. The correlation between patients and physicians with respect to RA disease activity is often poor to modest (6,7). This discrepancy implies that patients are defining their RA activity very differently from their rheumatologist. When Boolean criteria were developed, there were many stakeholders involved, with several strongly held beliefs, and multiple constructs were studied (2). For instance, the SJC and CRP level in clinical trials were most predictive of radiographic progression from trials where patients had active RA at onset (5).

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The PtGA is not requested or collected in a standardized fashion and may have more to do with patient satisfaction and overall health than with RA activity. A small mean difference of 1.25 on a 0–10 scale for PtGA can separate patients who are satisfied with their health compared to those who are not (8).

Residual pain is common in RA and affects the PtGA, causing less remission in composite scores. The mean pain score is 4 of 10 for patients with RA seen in follow-up visits with their rheumatologist (9). Thus, many patients in routine care would not meet any remission criteria that contain a PtGA. Chronic pain is part of this disease in some patients, even with inactive RA. Physician's global assessments are also not necessarily comparable between rheumatologists (10). A case might be made for trying to simplify RA remission by using the definition of no swollen joints with the absence of other RA disease-related comorbidity, such as interstitial lung disease or vasculitis (both of which are not common in RA) and possibly accelerated cardiovascular disease that is more frequent in RA than in the age- and sex-matched population (11). Fibromyalgia is more prevalent in RA than in the matched population, and the incidence is markedly increased in the first 2 years of RA onset (12). Fibromyalgia will affect PtGA, giving a higher score. Sjogren's syndrome can occur in RA, especially in seropositive older patients with long disease duration, and there is no consensus whether this occurrence would be considered a factor when rating overall RA disease activity from the patient's and physician's perspective.

The PtGA also may reflect age- and sex-matched background population norms. At a certain age, a proportion of individuals may rate their overall health as not perfect. This rating can be due to comorbidities, chronic pain, and noninflammatory musculoskeletal symptoms. PtGA and pain in RA are tightly linked, so how the question is asked may not matter regarding global health or RA disease activity, because the correlation is strong between patient-reported pain and global assessment (1).

We do not treat to target, maybe because we do not believe the target signifies active RA. Study of the treat-to-target strategy has shown that many times when a patient is not in a low disease state, no change in treatment is made (13). There are many reasons for this finding, but the lack of face validity of a composite score and physician global assessment or SJC is a major reason. For instance, if the RA is thought to be inactive, but the patient has not obtained the outcome of low disease activity or remission due to reasons such as a high PtGA, there is often no change made in RA treatment. In the ACR's Rheumatology Informatics System for Effectiveness registry, in most patients a composite measure was not performed serially (including SJC), and only half the patients considered to have moderate or high disease activity did not change treatment over the following year (12,14).

The SJC may be problematic in some patients. The SJC often uses a 28-joint count that misses the ankles, midfoot, and toes, which are sometimes very important active joints in patients with RA. Also, should no swollen joints exclude pannus, exclude nontender joints, and/or have mandatory power Doppler negative findings on ultrasound? Patients with damage may be more difficult to examine for the absence of swollen joints. Additionally, recent research has shown that the TJC performed on patients with RA may not reflect inflammatory arthritis (15).

All nonlaboratory variables have subjectivity. Even the SJC can vary between observers (16). There is good within-rheumatologist agreement for the SJC but only moderate concordance between rheumatologists (16). Another problem is attribution, when a patient with RA and concomitant erosive OA may have very swollen and tender proximal interphalangeal joints but not from RA. In addition, studies have shown that patients with a SJC of 0 still have activity measurable by ultrasound and magnetic resonance imaging.

Perhaps if defining remission in RA as 0 swollen joints is too difficult, then a biomarker could be a surrogate instead, such as the multibiomarker disease activity score (MBDA) or 14-3-3η protein (17,18). These measures correlate well with disease activity, and the MBDA may perform better than the CRP level or DAS28 score for radiograph progression (17), and even if in Simplified Disease Activity Index remission the 14-3-3η enzyme-linked immunosorbent assay levels can predict radiographic progression (18), they are expensive and have not been tested to determine whether they provide added value to the physician global assessment or the actual SJC. The subspecialty of rheumatology should continue to use the joint assessment with the physical examination to define active RA and remission in RA.

Comparing remission in RA to other diseases. Would remission in cancer use a PRO as a component within the definition? No. For example, remission in cancer is the absence of tumor, sometimes based on a time point. For Crohn's disease there is a definition for endoscopic remission (19) that does not take into account any PRO. Many diseases define remission as a biologic state. Psoriasis has remission when there are no active skin lesions present (i.e., 100% clearing of the skin). The target for diabetes mellitus is a blood test (glycated hemoglobin in the normal range) and not PROs. In vasculitis, the Birmingham Vasculitis Activity Score works very well for defining disease activity and can go to 0 for activity despite having damage, irrespective of how a patient feels, because patients may have residual fatigue or chronic pain from previous vasculitis activity or damage. We do not want to say that the patient's opinion is not important in RA, because in fact PROs are important predictors of long-term outcomes (20), but they are often related to many factors beyond disease activity that is not related to inflammation, such as joint damage and hypersensitization and even the influence of culture, as the current article suggests. PROs tell us about a patient's experience and perspective but not necessarily about disease activity.

The study by Ferreira et al used SJC, TJC, and the CRP level for a modified Boolean definition (1). The reliability of intraobserver and interobserver variability from the literature for swollen and tender joints actually showed that the reliability was better for tender joints than swollen joints (16), and tender joints have early responsivity to change with active treatment but may not be better than either PtGA or physician global assessment (21). We can have high reliability, so that the patient is consistent on test–retest for their TJC, and the test is sensitive to change in active RA treatment trials, but it could lack face validity in patients thought to be in remission by the SJC who have a high discrepant TJC.

However, in an ideal world, there should be a single standardized outcome that measures remission in RA. Having an elevated CRP level from RA if there are no swollen joints is very unusual (and if there are no other causes such as infection), except due to extraarticular activity such as interstitial lung disease or vasculitis. Therefore, remission in RA should be the absence of RA disease activity, which could be based on the physician global assessment of RA disease activity or the SJC. The former would take into consideration joints beyond the 28-joint count (such as metatarsophalangeal joints and ankles) and extraarticular RA manifestations, and the latter would be the lack of swollen joints (from RA) in the joints that were examined.

The physician global assessment is more predictive of remission in early RA than other outcomes, including composite scores. Data from an incident cohort of early RA demonstrated that the physician global assessment score of 0 at 3 months was more predictive of remission at 1 year than composite scores, even if the DAS28 score was the definition of remission (which does not contain the physician global assessment) (22). Therefore, having a definition of remission that does not take into consideration the physician's assessment of RA disease activity may miss true remission. A study comparing scenarios of patients with RA over the spectrum of disease activity and having the physicians rate the disease activity showed that the physician global assessment had poor agreement in moderate disease activity but had better agreement in extremes of disease activity (such as low or 0 SJC or very high SJC) (10).

There is a need to redefine remission in RA. The next steps to redefining remission may be using multiple data sources, with statistical analyses of what are the most appropriate measures of remission and with a consensus exercise among leaders in the field. For now, we think that remission in RA is the absence of swollen joints (including joints beyond the traditional 28) and the absence of extraarticular disease activity.

AUTHOR CONTRIBUTIONS

Drs. Pope and Michaud drafted the editorial, revised it critically for important intellectual content, and approved the final version for publication.

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REVIEW

Using Questions to Enhance Rheumatology Education

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Introduction

Musculoskeletal disorders are among the most common causes of disability worldwide (1). In the US, the prevalence of these conditions will increase with the aging population and, as a result, so will the demand for rheumatology services (2). However, changes in the workforce are expected to decrease the supply of rheumatologists, creating a substantial shortage. Meeting this increased need will require a comprehensive approach that should include recruitment and training of additional rheumatology providers as well as improving rheumatology education for those who deliver primary care (3). Enhancing rheumatology education in medical school and residency programs may encourage trainees to pursue rheumatology careers and may improve the ability of primary care providers to recognize and treat the growing number of patients with musculoskeletal conditions.

A challenge of teaching rheumatology is the uncertainty that surrounds the etiology, diagnosis, and treatment of many conditions that we treat (4), as definitive answers to the questions we ask are often lacking. These features distinguish rheumatology from most specialties. Thus, approaches to education that encourage learners to continuously ask themselves questions about what they know, how they know it, what they do not know, and where uncertainty lies, may help in teaching this complex specialty while at the same time fostering critical thinking skills and metacognition that may enhance clinical care. As in the training of scientists (5), we believe that training learners to ask questions is an essential ingredient for learning rheumatology.

In addition, by asking our learners questions, we model the behavior we want our learners to achieve. Nevertheless, studies have shown that clinical faculty should ask more questions of their learners (6), especially those that enhance a learner's critical thinking skills (7). Otherwise, questioning can lead to an emphasis on memorization of facts rather than thinking, as well as to "pimping," in which questions are aimed to reinforce hierarchy and humiliate the student (8). This may demoralize the learner, and cause a deterioration in the learning environment that inhibits motivation and curiosity (9).

While previously published recommendations on teaching rheumatology have focused on the content of rheumatology and musculoskeletal education (10), the present review focuses on how this material can be taught. We are separating this review into 3 categories: 1) questions and their relationship to learning theory, 2) questions in different teaching venues, and 3) techniques for effective questioning.

Each section will start with a succinct "tip" followed by the educational rationale supporting the technique. Tips were derived from research in the science of teaching, learning, and human cognition, which has provided us with a greater understanding of how science could be taught more effectively. This review will be useful for faculty who teach rheumatology at all levels, including those who engage in undergraduate, graduate, and continuing medical education as well as the allied health professions.

Questions and learning theory

Questions and Bloom's taxonomy. *Ask questions that begin with "how" or "why."* Questions can assess different levels of knowledge possessed by the learner. Bloom's taxonomy is a hierarchical model originally designed to classify educational learning objectives for curricula (11,12) that has been recently adapted to examine the cognitive skills required to answer questions (7,13). Questions lower on the taxonomy ("remembering," "understanding"), known as lower-order thinking questions, are close-ended, usually begin with "what is…," and often ask for facts that can be answered with a quick search on a smartphone. Higher-ordered questions, on the other hand, are open-ended and require a deeper comprehension of concepts, frameworks that link knowledge, and critical thinking skills to interpret and analyze information. They support a culture of inquiry, as opposed to one of memorization.

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Table 1. Using Bloom's taxonomy to teach rheumatology

Bloom's Category	Description	Question stems	Examples
Higher-order thinking			
Creating	Developing new ideas or theories, or combining elements into new patterns	How would you improve___? How could you create ___?	Based on your understanding of the pathophysiology of RA, how would you design a new drug to treat it?
Evaluating	Making judgments of processes or outcomes based on criteria and standards	How was ___ managed? What is the evidence to support your treatment plan?	How has the patient's rheumatoid arthritis been treated over the last 10 years, in light of recommendations by the ACR?
Analyzing	Interpreting data and selecting the best conclusion, making a diagnosis	How does ___ and ___ differ? How would the treatment differ if the patient were___?	Given the history, physical exam, and laboratory work on this patient, what is the most likely diagnosis?
Applying	Carrying out a procedure in a given situation, predicting an outcome given a perturbation in the system	Calculate___ What would happen if___?	What would happen to this patient with gout if we increased his allopurinol dose?
Lower-order thinking			
Understanding	Determining the meaning of facts by building connections between new and prior knowledge	How does __ work? Explain why___? Describe how___?	Explain why a patient with rheumatoid arthritis has more stiffness in the morning than later in the day.
Remembering	Retrieving, recalling, or recognizing factual information from long-term memory	What is___? What are the most common causes of___? Where is___located?	What percentage of patients with rheumatoid arthritis have a positive rheumatoid factor?

Although most teachers hope to improve their learner's ability to think critically and apply learned material to solve new problems (14), 70–90% of questions asked by teachers in the classroom are lower-order thinking questions (15,16). By being aware of this taxonomy and deliberately asking questions from each of the categories of the taxonomy (Table 1), faculty can guide their learners to a deeper comprehension of the material.

Questions to diagnose your learner. *Ask open-ended questions to probe for understanding and knowledge gaps.* Diagnosing the learner is the process by which a teacher identifies what a learner knows, what she can do with her knowledge, and where her deficiencies lie. This process is essential for discussing topics at a level that is appropriate to meet a learner's needs. Asking "exploratory questions," a type of Socratic questioning designed to assess what learners know about a specific topic, can help reveal biases and misunderstandings and explore whether learners can assimilate past knowledge into present behavior (17). These questions are intentionally broad and aimed to integrate several topics ("How do you think about autoimmunity?" "How would you describe the differences between autoimmune and autoinflammatory diseases?").

Clinical experiences can also be leveraged to provide information about what the learner knows. The questions based on the Five Microskills of Clinical Teaching (18) (Table 2), have been shown to improve faculty's ability to diagnose a learner's knowledge gaps, as compared to the traditional preceptor model in which questions are focused on diagnosing the patient (19). Also, the questions that a learner asks about a topic provides significant insights into her knowledge base and allows the teacher to assess the learner's comprehension of the subject (20).

Questions as a form of retrieval practice. *Use questions to reinforce prior learning.* Research has shown the potent effects of testing and asking questions to enhance learning and the retention of previously-learned material (the "testing effect") (21,22). While testing is often used to assess knowledge, the act of retrieving information from memory strengthens the neural connections for that information and enhances durable or long-term learning. Testing may also enhance clinical reasoning skills, which require the ability to apply learned knowledge to a new clinical situation, generate a hypothesis about the clinical condition, test the hypothesis among other possibilities, and assess the appropriateness of tests and treatments (23). Asking questions through testing has been shown to help learners consolidate content and improve their clinical reasoning skills (24). Further benefits can be gained if the material is retested over time, a method called "distributive practice" (25).

"Production tests," in which the learner is asked to construct a response, produce more powerful learning than "recognition tests," which ask the learner to identify a correct response from various alternatives (22). This finding stems from the constructivist theory of learning, which states that learners benefit from "constructing" their own knowledge based on what they already know (26).

Questions to enhance metacognition and critical thinking. *Ask questions that probe the learner's assumptions and provide insight into how she is thinking.* Questions are an ideal method to encourage learners to think about their thought process, i.e., to practice metacognition. Through questions, learners can be guided to reflect on their knowledge, identify gaps in their learning, and to recognize biases and emotions that may lead to errors in decision-making (27). Table 2 lists questions that may help learners identify their learning needs through metacognition.

Table 2. Purposeful questioning

Purpose	Questions
Questions to diagnose your learner (18)	What do you think is going on with this patient? What were the major findings that led to your diagnosis or decision? What else did you consider?
Questions to enhance metacognition (27)	Does anything surprise me about the situation? Do I have the information or skills to deal with this situation? Do I need to have further information or skills to deal with this situation, either now or in the future? Is the lack of information due to an absence of information or an inability to search appropriately for it? What is the underlying reason why the identified issue was not resolved?
Questions to enhance critical thinking (14)	Why do you think that? How does this relate to what you already know? How is it different? How does this explain the results? What do you expect to see? What would you predict if…? How do you assess the arguments? Was there a reason for that? What data are going to actually help you? What's difficult for you about this subject?
Questions to overcome cognitive biases (31)	Why can't this be something else? One month from now we find out that our diagnosis was wrong, what did we miss, what else should we have considered? What diagnosis can't I miss? Why did this happen? How does the patient make me feel? What can't we explain? Was I comprehensive? Did I consider inherent flaws in heuristic thinking? Was my judgment affected by bias? Do I need to make the diagnosis, or can I wait? What is the worst-case scenario? Are there data that don't fit with my hypothesis?
Four-question technique (40)	What one important concept, research finding, theory, or idea did you learn while completing this activity? Why do you believe that this concept, research finding, theory, or idea is important? How can you apply what you have learned from this activity to some aspect of your life? What questions has the activity raised for you? What are you still wondering about?

Questions are also essential to promote the critical thinking skills required for patient care. Critical thinking is often defined as the ability to apply higher-order cognitive skills (e.g., those higher on Bloom's taxonomy) that lead to logical and appropriate actions. A study by Huang et al (14) demonstrated that experienced clinical faculty frequently use purposeful questioning as a tool to teach critical thinking skills. Questions that faculty can use during clinical scenarios to promote the critical thinking skills of their trainees are shown in Table 2.

Questions to overcome cognitive biases. *Ask questions to highlight thinking errors due to cognitive biases.* Cognitive biases often lead to medical errors (28), a leading cause of death in the US (29). Cognitive biases arise from systematic errors in thinking from shortcuts, or heuristics, that people unconsciously employ (30). For instance, clinical situations that seem familiar may cause physicians to become overconfident and ignore alternative diagnoses (31). This type of fast, reflexive thinking is referred to as "System 1."

In contrast, "System 2" thinking is slower, effortful, and deliberate. Checklists have been implemented in many industries, including in medicine, to encourage the focused attention that is demanded by System 2, and have been shown to improve outcomes (32). Habitually using a checklist of standard questions after evaluating patients may be helpful in reducing cognitive biases by decreasing reliance on memory, broadening the differential diagnosis, examining the thought processes of others to avoid framing biases, and acknowledging how mood and sleep deprivation influence cognition (31). Table 2 shows questions that assist learners in avoiding cognitive biases.

Questions to stimulate curiosity. *Ask questions that may not have an answer.* Highlighting the limits of our knowledge—the questions that remain to be answered—can stimulate curiosity. Curiosity arises when a person perceives gaps in knowledge, leading to feelings of deprivation and the desire to learn (33). Curiosity activates the brain's reward system and enhances memory for new information (34). Faculty should be encouraged to discuss the questions that remain to be answered within rheumatology and should stimulate their learners to formulate the questions that will advance the field (35).

By fostering an environment of inquiry and curiosity, rather than the memorization of facts, rheumatology education may become more exciting and enjoyable. Time spent between faculty and students should focus on celebrating good questions rather than on memorizing correct answers; the transfer of facts should be increasingly delegated to home study.

Teaching venues

Questions in the classroom and during didactics. *Make questions a standard part of classroom teaching to stimulate learners to apply knowledge in new settings.* Asking questions at the beginning of a lecture can stimulate curiosity and prime the learner to learn (36). The answers to these questions help the teacher assess learners' preparation for the session and comprehension of the material, reveal common misconceptions, and highlight topics of interest that should be addressed during the talk.

Incorporating questions during lectures allows learners to apply acquired knowledge to new settings. This can be done with audience response systems (e.g., online software such as http://www.polleverywhere.com), think-pair-share (a strategy in which the teacher poses a question to learners who think of the answer on their own, then pair up with their peers to share their responses), or by asking learners to work on their own. Applying learned material to new situations is an essential aspect of learning—it challenges the learner to transfer knowledge to a different context. Engaging in any of these activities during a lecture also changes the pace of the lecture, which helps to re-engage learners (37).

After lectures, learners should receive questions to reinforce important themes. Prior studies have shown that a brief quiz after a lecture significantly improved retention of lecture material compared to no intervention when tested 1 month later (38). With the use of questions as part of assignments or lectures, learners test their knowledge of learned material and avoid the illusion of mastery, the mistaken belief that what they have just heard or read is fully understood (39).

Questions at the bedside and in the examination room. *Use questions during clinical interactions to focus the learner on critical issues.* Asking questions at the bedside can be challenging due to the presence of learners at different levels in their education and to time pressures due to the exigencies of patient care. Asking too many recall-based questions that have obscure answers may be interpreted as "pimping." In contrast, asking open-ended questions has the potential to allow both the teacher and learner to engage in new discovery (6).

Before asking a question, you should think about the purpose of the question. Questions should not be asked at random; they work best when they are organized and follow a specific pattern. For instance, questions may build in complexity from lower-ordered ("What is an antibody?") to higher-ordered thinking questions ("How do environmental factors affect the development of autoimmunity?"). Alternatively, questions can first address a broad topic ("How do you evaluate patients with arthralgias?"), and then narrow down to specifics ("How will we manage this patient's gout?").

It is important to be mindful of the individual to whom a question is being directed. If a senior resident is unable to answer a question, avoid asking the medical student or intern to respond for fear of embarrassing the resident. It is often best to start questioning medical students and work your way up if the answer is not known.

Questioning techniques

The Four-Question Technique. *Ask questions that foster reflection.* The Four Question Technique (40), promotes deep thinking and active learning. These questions (Table 2) can be applied after any educational session in any venue. At the end of the activity, learners write down the answers to the 4 questions. These questions encourage learners to analyze the material, reflect on the activity, relate the activity to their personal lives, and promote further questioning of the material. In the study by Dietz-Uhler et al (40), learners who were asked these questions were better able to recall presented material and had improved performance on a quiz than learners who were not asked these questions.

Learner-generated questions. *Ask learners to generate their own questions and answers.* Physicians spend large parts of their education answering examination questions during their training. To become critical thinkers and self-directed learners, however, they need the skills to generate and answer their own questions (engage in self-testing). Several studies have shown that having learners generate their own questions and answers is an effective metacognitive strategy that enhances comprehension of written assignments (41,42) and lecture (43) material. In addition, learner-generated questions encourage the learner to make connections between topics and to extend and construct new knowledge (20). Generating questions and answers is also one of the most effective study strategies known (25). Sharing these learner-generated questions with others can further enhance learning and serves as a type of peer-to-peer teaching (43). While this technique can be applied with the use of index cards, we also created a free, open-source web platform called AskUp (http://www.askup.net), which establishes learning communities that encourage users to create and share questions with their peers. Training learners in the generation of questions may help them to employ one of the most effective, yet underused (44), study strategies in medical education.

Foster an environment for learning. *Ask questions in a way that does not penalize incorrect responses.* When using questions as an educational strategy, it is essential to create an environment appropriate for learning, one that is receptive to innovative thinking and fosters hypothesis testing. Establishing relationships with learners can positively impact motivation and learning (13). This is one reason why learning communities (intentionally created groups of students and faculty who actively engage in teaching and learning from each other) have become increasingly popular in medical schools (45). Allowing team members to voice their opinion without feeling embarrassed or punished enhances team learning behavior (46).

In addition to providing a safe space, it is essential to ensure sufficient time for learners to respond to questions. Most teachers allow learners less than 1 second to answer a question, and when a learner does answer the question in time, teachers respond or ask a new question almost immediately (47). Waiting longer (7 seconds or more) after asking a question and after hearing a learner's response allows learners to process the information better, ultimately producing better discussions and improving learner comprehension of the material.

In conclusion, to meet the increased demand for rheumatology care in the future, it will be necessary to attract more trainees into the field as well as to improve the abilities of physicians in primary care to recognize and treat many musculoskeletal conditions. Enhancing rheumatology education may deliver on both of these fronts, but doing so will require overcoming the challenges of teaching a specialty fraught with uncertainty. Uncertainty may stem from 3 sources, including limitations in medical knowledge, an incomplete or imperfect understanding of available knowledge, and by a physician's ability to differentiate between the first 2 sources (4). The use of questioning may help to mitigate these sources of uncertainty through encouragement of curiosity, generation of new knowledge, and enhancement of critical thinking skills and metacognition. Leaning in and embracing uncertainty with trainees may kindle in them the "intellectual interest" that has steered most rheumatologists into the field (48).

By mastering the art of asking questions, faculty can improve a learner's ability to comprehend and remember material, apply knowledge in new settings, overcome cognitive biases, and develop metacognition. Faculty development workshops can provide the theories underlying these strategies, as discussed above, while peer observation sessions can help faculty incorporate these tools into their teaching. By asking better questions, it may be possible to reveal the beautiful mysteries of the specialty to a much broader audience.

AUTHOR CONTRIBUTIONS

Both authors were involved in drafting the article or revising it critically for important intellectual content, and both authors approved the final version to be published.

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CLINICOPATHOLOGIC CONFERENCE

A Case of Unremitting Fevers

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CASE PRESENTATION

Chief symptoms

The patient, a 44-year-old man who was originally from India and had a history of Crohn's disease presented with a 12-day history of fevers and rectal drainage.

History of present illness

The patient had been feeling well and was in his usual state of health, when he first noticed increasing rectal drainage. This symptom was followed several days later by malaise and fevers up to 40.5°C. He was evaluated at an emergency department, where computed tomography (CT) imaging of the abdomen and pelvis demonstrated sigmoid colon wall thickening, left perianal inflammation, and sinus tract formation, possibly indicative of active Crohn's disease. The patient declined admission and was prescribed amoxicillin-clavulanate. The patient was also advised to withhold the adalimumab he had been taking for 5 months to treat his Crohn's disease, due to concerns for concomitant intestinal infection.

The patient's high fevers and malaise continued despite antibiotic treatment, and the patient requested hospital admission 2 days later. New-onset hypoxia was discovered, which required 3 liters/minute of supplemental oxygen to maintain normal oxygen saturation. The initial blood culture results were negative, and the chest radiography results were unremarkable. Systemic inflammatory response syndrome secondary to a sigmoid or anal abscess was suspected, and the patient underwent surgical debridement of the perianal fistula on day 2 of hospitalization; however, no tissue sample was obtained. Meropenem was started empirically, but the fevers and hypoxia continued. A chest CT was obtained on day 3, and demonstrated diffuse nodular lung densities and mediastinal and hilar adenopathy. The interferon gamma release assay result was indeterminate, and the results of testing for HIV, rapid plasma reagin, cytomegalovirus, and Epstein-Barr virus were negative. Video-assisted thoracoscopic surgery was performed, and a histopathologic review of the biopsy specimens from the right upper and lower lobes revealed caseating and noncaseating granulomas, which were concerning for tuberculosis (TB). Acid-fast bacilli (AFB) and fungal staining were negative.

On Day 9 of hospitalization, RIPE therapy (rifampin, isoniazid, pyrazinamide, and ethambutol) was empirically started for treatment of TB, with a rapid initial resolution of his fevers and improvement in malaise. The patient was transferred to our facility for further management. At the time of transfer, the diagnosis of TB had not been confirmed microbiologically. Although the patient was afebrile for 1 day before his arrival at our hospital, he developed a temperature of 38.9°C immediately after transfer to our facility. The rheumatology service was consulted for evaluation of persistent fevers and evidence of granulomatous inflammation on the lung biopsy sample in the absence of a definitive TB diagnosis.

Medical, social, and family history

The patient had been diagnosed with Crohn's disease in 2012 by a colonoscopy and biopsy results. The Crohn's disease had been well-controlled until the patient developed recurrent perianal abscesses 5 months prior to the current presentation. Treatment with adalimumab was started at that time. Notably, a tuberculin skin test (TST) administered 2 months prior to the initiation of adalimumab was negative. The patient was not receiving steroids or other immunosuppressants at the time of the TST. The patient's medical history was otherwise significant for hypothyroidism and iron deficiency anemia requiring iron infusions. Prior surgeries included an appendectomy and 2 incision and drainage procedures for the perianal abscesses.

The patient's medications included bifidobacterium-lactobacillus (1 capsule/day), budesonide (9 mg/day), levothyroxine (37.5 mcg/day), mesalamine (3.6 gm/day), adalimumab,

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(which had been withheld due to concerns for infection), and a daily multivitamin.

The patient had previously lived in India until he moved to the US in 2001. He had last visited India 2 years prior to his current presentation. He is married and works in finance. He had smoked for several years but quit smoking 10 years prior to the current admission. He denied any alcohol or drug use and had no history of incarcerations or homelessness.

The patient's mother had died of an unknown type of cancer at approximately 40 years of age. His father had died at age 73 from coronary artery disease.

Review of systems

The patient reported fevers, chills, malaise, weakness, and fatigue. He also described increased shortness of breath and nonproductive cough. He denied any rashes, sicca symptoms, abdominal pain, nausea/vomiting, diarrhea, dysuria, hematuria, or paresthesias.

Physical examination

Upon evaluation, the patient was febrile (38.9°C) and tachycardic (122 beats per minute). His respiration rate was 21 breaths per minute, and he had normal oxygen saturation levels (measured by pulse oximetry) while using 3 liters per minute of supplemental oxygen. The patient was an ill-appearing, thin, diaphoretic man lying in bed in moderate distress. He had anicteric sclerae, no oral or nasal ulcerations, and no palpable lymphadenopathy. The lung examination was significant with bilateral basal crackles. The cardiovascular examination revealed no murmurs, rubs, or gallops, and 1+ bilateral pitting edema was present in his legs. A complete skin examination revealed no rashes or other lesions. The abdominal examination revealed hypoactive bowel sounds with no rebound tenderness or guarding, or organomegaly. No synovitis was apparent during the musculoskeletal examination. The neurologic examination was remarkable for generalized weakness with no focality. The rectal examination was deferred by the patient.

Laboratory evaluation

The laboratory evaluation results are presented in Table 1. Laboratory results prior to the patient's transfer to our facility were similar to those results obtained at our hospital on the day of transfer.

CASE SUMMARY

This is a 44-year-old man originally from India with a history of biopsy-confirmed Crohn's disease, who presented with sev-

Table 1. Laboratory values prior to and after hospitalization*

Laboratory test	Normal range	5 weeks before admission	On day of transfer	At discharge	3 days after discharge
WBC cells $\times 10^9$	3.8–10.6	8.4	1.3	2.3	2.8
Hemoglobin, gm/dl	12.9–16.9	9.3	7.9	8.1	8.2
Hematocrit, %	38.0–48.8	30.3	25.6	24.8	25
Platelet count, $\times 10^9/mm^3$	156–369	549	78	167	67
Sodium, mmoles/liter	136–146		127	129	
Chloride, mmoles/liter	98–107		98	99	
Potassium, mmoles/liter	3.5–5.0		3.5	4.7	
Bicarbonate, mEq/liter	21–31		22	24	
BUN, mg/dl	8–26		15	5	
Creatinine, mg/dl	0.5–1.4		0.8	0.6	
Alkaline phosphatase, units/liter	38–126		578	564	553
AST, units/liter	15–41		104	42	28
ALT, units/liter	17–63		54	44	37
Total bilirubin, mg/dl	0.3–1.5		2.1	0.9	1.4
ESR, mm/hour	0–23		22	22	36
CRP, mg/dl	<0.748		24.089	1.952	5.9
Ferritin, ng/ml	10–282		9,334	1,412	1,247
Triglycerides, mg/dl	<150		362	143	
LDH, units/liter	<171		746	385	318
Haptoglobin, mg/dl	36–195		284		
ANCA			Negative		
Cryoglobulins			Negative		
ACE, units/liter	9–67		87		
Fungal cultures			Negative		
Blood cultures			Negative		
Histoplasma/cryptococcus cultures			Negative		

* WBC = white blood cells; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; LDH = lactate dehydrogenase; ANCA = antineutrophil cytoplasmic antibodies; ACE = angiotensin-converting enzyme.

eral weeks of perirectal drainage, 2 weeks of fevers (≤40.5°C), and new-onset hypoxia with lung biopsy samples revealing caseating and noncaseating granulomas and negative initial AFB and fungal staining. Physical examination revealed fever, hypoxia, tachycardia, and crackles on lung examination. Laboratory values were remarkable for pancytopenia, elevated lactate dehydrogenase (LDH), triglycerides, and C-reactive protein (CRP) level, but a normal erythrocyte sedimentation rate (ESR).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included TB, co-infection, sarcoidosis, vasculitis, malignancy, combined variable immune deficiency, and macrophage activation syndrome.

TB. Disseminated TB from reactivation of latent TB infection (LTBI) was first on our differential diagnosis list. Pancytopenia may be caused by infiltration of TB into the bone marrow, and TB may also cause high fevers and elevated LDH, transaminases, and CRP levels. Caseating, or necrotizing granulomas seen on lung biopsy samples are also fairly specific for infections, including mycobacterial infections (1). In addition, the patient had clinical risk factors for TB, including a childhood in an endemic area.

Tumor necrosis factor inhibitors (TNFi) increase the risk of reactivation of LTBI (2). The risk of reactivation of LTBI may be higher with the use of monoclonal anti-TNF antibodies (e.g., infliximab, adalimumab) than with soluble receptor anti-TNF therapy (i.e., etanercept) (3). A recent meta-analysis described the risk of TB in patients treated with TNFi as 1.92 times higher than in control patients, and 2.39 times higher if prescribed in an endemic area (4). The median time between initiation of adalimumab and reactivation of LTBI is 4 to 6 months (2); notably, our patient had started adalimumab 5 months prior to presentation. Factors that do not support the diagnosis of TB in this case included 1) the absence of microbiologic confirmation of the diagnosis at the time of our evaluation (initial AFB stains of the lung specimen were negative), 2) the negative TST that was obtained 2 months prior to starting adalimumab, and 3) an "indeterminate" interferon gamma release assay result rather than a positive result.

Secondary infection. A secondary, non-TB infectious etiology was initially considered; the patient was immunosuppressed from the use of TNFi therapy and seemed to worsen clinically after a brief initial improvement while receiving RIPE therapy. HIV is the most common co-infection with TB, but the patient's HIV testing result was negative. Blood, viral, and fungal cultures were also negative at both the initial treating hospital and at our institution, and fungal elements were not seen on the pathologic lung specimen.

Sarcoidosis. Sarcoidosis is associated with the pathologic development of granulomas that infiltrate organs and cause inflammation and fibrosis (5). The patient's fevers, chest CT findings of mediastinal and hilar adenopathy, pathologic evidence of noncaseating granulomas, and elevated angiotensin converting enzyme (ACE) level were concerning for sarcoidosis. Similar to TB, pancytopenia in sarcoidosis may result from bone marrow infiltration. However, although the granulomas in sarcoidosis have no unique or distinguishing features from other granulomatous diseases, they are generally noncaseating in contrast to TB (5). In addition, the patient received a TNFi, which is a treatment for sarcoidosis (although not a US Food and Drug Adminstration approved indication) (6); while cases of a sarcoid-like response to TNFi therapy have been reported, this reaction appears to be rare (7,8). Furthermore, as ACE levels are nonspecific, the patient's elevated ACE level did not help us to clarify his diagnosis; in addition to sarcoidosis, high ACE levels are associated with Crohn's disease, miliary TB infection, other infectious granulomatous diseases (e.g., leprosy), diabetes mellitus, alcoholic liver disease, and hyperthyroidism (9–11). Finally, Crohn's disease was unlikely to independently increase this patient's risk for sarcoidosis; while a pathologic relationship between Crohn's disease and sarcoidosis has been postulated, the diseases appear to follow distinct clinical pathways (4).

Vasculitis. Vasculitis, particularly granulomatosis with polyangiitis (GPA), was considered given the lung biopsy findings of noncaseating granulomas. GPA and TB may be difficult to differentiate because the radiographic lung opacities and constitutional symptoms may be similar (e.g., fevers, arthritis) (12), and antineutrophil cytoplasmic antibody (ANCA) titers may also be elevated in patients with TB (13). Concomitant GPA and TB have also been reported, albeit rarely (14). In our case, GPA was considered less likely than other diagnoses because ANCA serum testing was negative and pancytopenia is rare in GPA.

Malignancy. Malignancy, particularly lymphoma, was considered given the patient's high fevers, adenopathy, cytopenia, elevated LDH and inflammatory markers. Inflammatory bowel disease (IBD) has inconsistently been associated with various types of lymphoma, although an increased risk of non-Hodgkin's lymphoma has been reported (15). TNFi have also been independently associated with a small increase in lymphoma risk among patients with IBD (16), although it is unclear how much of this association is related to the underlying inflammatory condition for which the TNFi are used.

Common variable immune deficiency (CVID). CVID is a heterogeneous disorder in which impaired B-cell differentiation leads to decreased serum immunoglobulins and antibody formation (17). Noncaseating granulomas occur in 8–22% of patients with CVID and are most commonly found in the lung with or without lymphocytic interstitial infiltrates (18). Although CVID may mimic sarcoidosis in that the clinical presentations may involve

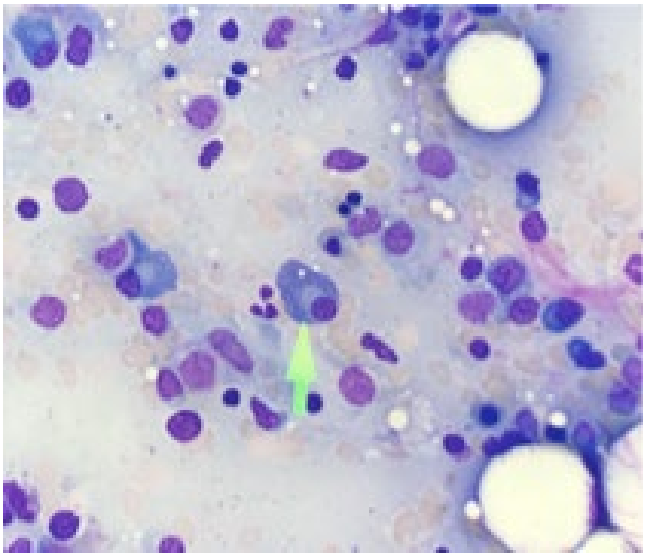

Figure 1. Bone marrow aspirate demonstrates a histiocyte with phagocytized erythrocyte and a nucleated cell (**arrow**). Wright-Giemsa stained; original magnification ×100.

both granulomas and adenopathy, the underlying pathogeneses differ. CVID is associated with decreased immunoglobulins, and more commonly with recurrent sinopulmonary infections, splenic involvement, and thrombocytopenia, as compared to sarcoidosis (19). Of particular interest to this case, CVID is also associated with gastrointestinal manifestations in 10–20% of patients, including IBD-like symptoms that may mimic Crohn's disease (20). To our knowledge, immunoglobulins had not been checked as part of this patient's previous medical care and were not checked during the current hospitalization; they could have been low in the setting of possible infection and thus may not have been immediately helpful in diagnosing CVID. Furthermore, the patient denied any history of recurrent infections, and noncaseating granulomas were not observed on pathologic specimens from the patient's initial outpatient intestinal biopsy. Finally, the presence of caseating granulomas on lung biopsy was inconsistent with CVID.

Macrophage activation syndrome (MAS). MAS is a potentially fatal clinical syndrome caused by activation and expansion of macrophages and predominately CD8+ T lymphocytes that exhibit hemophagocytic activity. MAS belongs to a group of disorders classified as hemophagocytic lymphohistiocytosis (HLH). MAS may be differentiated from other causes of HLH because this particular entity occurs in patients with underlying inflammatory or rheumatic diseases. The pathophysiology of MAS is still unclear; several genetic mutations have been identified that may increase the likelihood of MAS in rheumatic disease patients. However, the final pathway of MAS is shared with the other causes of HLH and involves a massive release of inflammatory cytokines (i.e., cytokine storm), including interferon gamma, interleukin-1 (IL-1), IL-2, IL6, IL-18, and TNF (21).

Diagnostic criteria for HLH/MAS include 5 of the 8 following: 1) fever ≥38.5ºC, 2) splenomegaly, 3) cytopenias affecting ≥2 cell lines, 4) hypertriglyceridemia (fasting triglycerides >265 mg/dl) or hypofibrinogenemia of <150 mg/dl, 5) ferritin >500 ng/ml, 6) hemophagocytosis in bone marrow, spleen, lymph nodes, or liver, 7) low/absent natural killer cell activity, and 8) elevated soluble CD25 (soluble IL-2 receptor α) (22). Clinical features may also include encephalopathy, hypoxia, rash, hepatomegaly, and liver transaminitis. An important pattern to recognize in MAS is persistent fever, decline in platelet counts and ESR, and elevation in CRP and d-dimer levels. Diagnosis may be further supported by presence of hemophagocytic macrophages on bone marrow biopsy. Poor prognostic factors include elevated ferritin, disseminated intravascular coagulation, age older than 30 years, and increased β2-microglobulin levels (23). In our case, the patient had a predisposing inflammatory condition (Crohn's disease), and high persistent fevers, elevated CRP, normal ESR, ferritin level of nearly 10,000 ng/ml, cytopenias in 3 blood cell lines, and elevated triglycerides and LDH.

DIAGNOSIS

Given the patient's profound pancytopenia, a bone marrow biopsy was completed. Histologic evaluation demonstrated scattered hemophagocytic histiocytes (Figure 1 and Figure 2);

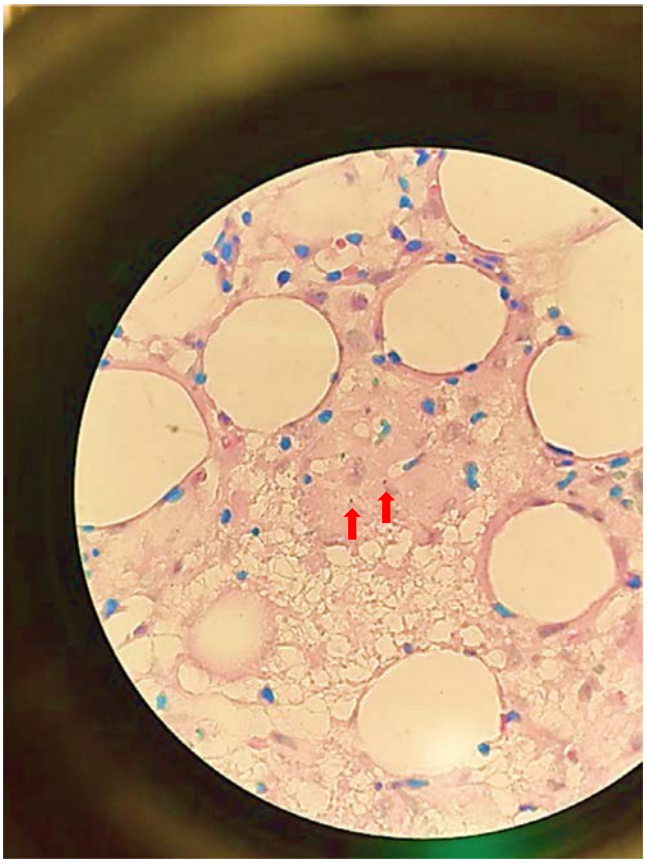

Figure 2. Bone marrow aspirate with acid-fast stain demonstrates rare acid-fast bacilli (**arrows**). Original magnification ×40.

acid-fast stain performed on the core biopsy confirmed the presence of rare acid-fast bacilli. The pathologic impression was HLH/MAS in the setting of miliary TB.

CLINICAL COURSE

Treatment for HLH/MAS was initiated with anakinra, an IL-1 inhibitor, at a dosage of 100 mg every 12 hours via subcutaneous route. Steroids and cytotoxic agents were avoided given that the patient had an active TB infection. The patient's fevers and malaise resolved after 2 doses of anakinra. Laboratory values also improved, as shown in Table 1. After 2 days of anakinra therapy, the dose was decreased to a once daily administration for 4 days and then discontinued due to the patient's clinical stability. The patient's hypoxia improved, and he was weaned off supplemental oxygen. He was discharged from the hospital and RIPE therapy was continued.

The patient completed 6 months of RIPE therapy without recurrence of clinical symptoms or laboratory abnormalities. TNFi therapy was not restarted. The patient's Crohn's disease remained active, and he was prescribed ustekinumab by his gastroenterologist, which resulted in resolution of his perirectal drainage.

DISCUSSION

Clinicopathologic correlation led to the diagnosis of MAS in the setting of acute TB infection. To our knowledge, this is the first case reported of MAS precipitated by TB in a patient with Crohn's disease who was receiving adalimumab. This patient had several independent risk factors for MAS, including TB and a history of IBD.

TB associated with MAS has been rarely reported except in endemic areas, in which it has an overall mortality of 50% (24). A case review (25) presented treatment regimens used in TB-associated MAS; these include antibacterial medications alone or in combination with immunosuppressive medications and/or immunomodulators, including corticosteroids, cyclosporine, etoposide, vincristine, chlorambucil, fludarabine, or IL-1 receptor antagonists. In a literature review of 36 causes of TB-associated MAS, 12 of 20 patients who received a combination of immunosuppressive treatments and antibacillary treatment recovered, whereas 7 of 9 patients who received only antibacillary treatment survived (24). Immunosuppressive therapy must be used with great caution in the setting of disseminated TB, and future work must be done to identify a safer treatment regimen for MAS in the setting of bacterial infections. In our case, we elected to use anakinra to treat this patient's MAS because it has a relatively short half-life and could be discontinued quickly if the patient experienced a clinical decline.

IBD is another independent risk factor for MAS, with a mortality rate of approximately 30% (26). A prior review described 50 cases of MAS in patients with IBD. Infections were the primary trigger of MAS in 78% of these patients, particularly viral infections such as Epstein-Barr virus and cytotomegalovirus. Three cases of TB in patients with IBD were reported (all in patients who had received infliximab), and death occurred in 2 of the 3 cases. There are no randomized control trials comparing the effectiveness of treatments for IBD-associated MAS. Case reports and reviews describe successful treatments with immunomodulators and/or immunosuppressants (20).

This case underscores several additional clinical points about TB testing in patients from endemic areas prior to initiating treatment with TNFi. Approximately two-thirds of active TB cases in the US are in foreign-born individuals, and in 2015, over 50% of TB cases in foreign-born patients were cumulatively from India (9.1%), Mexico (19.7%), the Phillippines (12.9%), Vietnam (8.1%), and China (6.7%) (27). In our patient, we had a higher suspicion for LTBI reactivation rather than acute infection because the patient was originally from India and had not recently had any new TB exposure risk factors, such as recent contact with actively infected people, foreign travel, or incarceration. Despite receiving TB screening prior to initiation of TNFi treatment as per current recommendations (28), the patient developed reactivated TB, underscoring the potential limitations of TB screening tests in individuals with an elevated risk of LTBI.

TSTs use purified protein derivative to induce a localized skin reaction; an induration ≥15mm is universally recognized as positive for LTBI, whereas 5–10 mm of induration may indicate LTBI in certain subgroups. Our patient had a "negative" TST result prior to starting TNFi therapy (the amount of induration was not recorded by his outpatient practice). TST tests cannot distinguish between active infection and LTBI. False-negative TST reactions may occur when patients have cutaneous anergy caused by a weakened immune system (e.g., HIV, high-dose prednisone use, or other immunosuppressants), new TB infection occurring within 8 weeks of the TST, very old TB infection, a recent live-virus vaccination (e.g., shingles), overwhelming TB, or viral illness (29). In contrast, false-positive TST readings may occur in individuals who have previously received the BCG vaccine (30), and TST is not a preferred screening method in areas where BCG vaccination is common (31).

T-cell interferon-γ–release assays (IGRAs) are an alternative method of screening for TB; similar to TSTs, these blood tests do not differentiate between LTBI and active TB. A positive result is strongly suggestive of TB infection, whereas a negative result suggests that infection is unlikely. Several studies suggest that IGRA may be more sensitive than TST in detecting LTBI (32–34); both have high specificity in countries with low TB burden (34). IGRA testing has some benefits as compared to TST, including that it can be obtained in a single visit, and BCG vaccination status does not affect results. In our case, the patient had an indeterminate IGRA result, which connotes uncertain likelihood of *Mycobacterium tuberculosis* infection even though this patient had active, disseminated TB. He had several risk factors for indeterminate IGRA, including use of TNFi therapy, cytopenia, and hypoalbuminemia; other risk factors for indeterminate IGRA

include anergy, systemic lupus erythematosus, and sulfasalazine use (25).

A recent consensus statement from the American Thoracic Society, Infectious Diseases Society of America, and the Centers for Disease Control and Prevention has updated clinical practice guidelines for screening and diagnosing TB (36). The consensus panel does not state a preference for TST or IGRA as the initial diagnostic test for individuals who are at high risk of TB infection because of lack of evidence. The panel does recommend routine screening with either TST and IGRA, but these tests may be used in combination when: 1) the IGRA is indeterminate, 2) the initial TB test is negative but there is high clinical suspicion for TB, or 3) the patient is likely to be infected with TB. Combination TST and IGRA testing appear to increase sensitivity for detecting TB (37), and this approach should be considered in individuals who come from regions with a moderate or higher prevalence of TB (31). If a TST or IGRA is positive, chest radiography should follow, and treatment for LTBI should be considered in consultation with an infectious diseases specialist.

An alternative series of guidelines for TB screening was published in 2012 by the American College of Rheumatology (ACR) for patients with rheumatoid arthritis (RA) (28). Many RA patients who are screened for TB—often in anticipation of initiating treatment with a TNFi or other biologic—use immunosuppressive therapies concomitantly; this increases their risk for a false-negative TST or IGRA. The ACR recommends that in patients with an increased risk of LTBI but with negative initial screening tests, health care providers should consider repeating TST or IGRA 1–3 weeks after the initial negative screening test (2-step testing). Although for RA patients, these recommendations could certainly be used to screen any patients who are at elevated risk for LTBI in advance of initiating TNFi therapy.

It is unclear if dual or 2-step TST and IGRA testing would have revealed this patient's LTBI, although his IGRA may have been positive if performed prior to his development of MAS since the cytologic abnormalities may cause a false-negative IGRA test. However, even the chest radiograph at this patient's initial hospital admission was negative despite active pulmonary TB, which underscores the limitations of any of these TB screening methods. Future work is needed to clarify specific recommendations for TB screening in individuals from endemic areas who are initiating treatment with TNFi.

In summary, this patient developed MAS in the setting of TB, Crohn's disease, and treatment with a TNFi. MAS should be considered in any patient with unremitting fevers, specific clinical and laboratory features, and risk factors for MAS, such as an underlying inflammatory disease or infection. Treatment for TB-associated MAS should be started promptly due to its high mortality rate, and antibacterial regimens are a particularly important component of care. Treatment recommendations for MAS in the setting of TB or other overwhelming bacterial infections must be clarified, in addition to TB screening recommendations for individuals from endemic areas prior to the initiation of TNFi therapy.

FINAL DIAGNOSIS

Concomitant MAS and reactivated TB in a patient with Crohn's disease who received adalimumab.

AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, approved the final version to be published, and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Impact of Patient's Global Assessment on Achieving Remission in Patients With Rheumatoid Arthritis: A Multinational Study Using the METEOR Database

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Objective. There is an ongoing debate about excluding patient's global assessment (PtGA) from composite and Boolean-based definitions of rheumatoid arthritis (RA) remission. This study aimed at determining the influence of PtGA on RA disease states, exploring differences across countries, and understanding the association between PtGA, measures of disease impact (symptoms), and markers of disease activity (inflammation).

Methods. Cross-sectional data from the Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology international database were used. We calculated the proportion of patients failing American College of Rheumatology/European League Against Rheumatism Boolean-based remission (4-variable remission) solely due to PtGA (PtGA-near-remission) in the overall sample and in the most representative countries (i.e., those with >3,000 patients in the database). Multivariable linear regression models were used to identify the main determinants of PtGA, grouped in predominantly inflammatory impact factors (28 tender joint counts, 28 swollen joint counts, and C-reactive protein level) and disease impact factors (pain and function).

Results. This study included 27,768 patients. Excluding PtGA from the Boolean-based definition (3-variable remission) increased the remission rate from 5.8% to 15.8%. The rate of PtGA-near-remission varied considerably between countries, from 1.7% in India to 17.9% in Portugal. One-third of the patients in PtGA-near-remission group scored PtGA >4 of 10. Pain and function were the main correlates of PtGA, with inflammation-related variables contributing less to the model (R^2 = 0.57).

Conclusion. PtGA is moderately related to joint inflammation overall, but only weakly so in low levels of disease activity. A considerable proportion of patients otherwise in biologic remission still perceive high PtGA, putting them at risk of excessive immunosuppressive treatment.

INTRODUCTION

Remission is now the target of treatment in rheumatoid arthritis (RA) (1,2). However, the percentage of patients achieving remission is strongly influenced by the remission definition used (3), and there is currently no consensus on which definition is the most appropriate to support a treat-to-target approach (4). The most authoritative definition, adopted jointly by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) (5), provides 2 alternative definitions: either a Boolean-based definition (28 swollen joint count [SJC28], 28 tender joint count [TJC28], C-reactive protein [CRP; mg/dl] level, and patient's global assessment [PtGA; 0–10-cm scale], all ≤1), or a Simplified Disease Activity Index (SDAI) ≤3.3. The SDAI is calculated from the simple sum of the 4 Boolean components and the physician global assessment (0–10-cm scale). Two other commonly used

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SIGNIFICANCE & INNOVATIONS

- Among 27,799 patients with rheumatoid arthritis from a large number of countries, 10% failed to reach American College of Rheumatology/European League Against Rheumatism Boolean-based remission only due to a patient's global assessment (PtGA) >1, and among these, approximately 1 of 3 scored the PtGA >4 (0–10 scale).
- PtGA showed a moderate-to-poor relationship with disease activity, especially at levels close to defined treatment targets.
- The inclusion of PtGA in definitions of remission may lead to overtreatment with immunosuppressive drugs.
- The patient's perspective remains essential to patient care. However, a separation between inflammatory and disease impact targets will probably improve safety and outcomes from the patients' perspective.

definitions are based on the 28-joint count Disease Activity Score (DAS28), either with 4 or 3 variables (i.e., with or without PtGA), (6) or the Clinical Disease Activity Index (CDAI; with the same formula as the SDAI, but without the CRP level) (7,8).

PtGA is included in all these definitions, except in the 3-variable DAS28, but there is an ongoing debate regarding whether the PtGA should remain in the definition. Its inclusion has been justified because PtGA tends to accompany disease activity (inflammation control) in clinical trials of RA (5) and because it conveys the patient perspective, which is obviously core to the objectives of treatment (9). However, a growing concern has emerged as to whether PtGA reflects disease activity at the biologic inflammatory process close enough to make it an appropriate instrument to define the target for immunosuppressive therapies (10–12), namely in long-term follow-up and in low–disease activity populations followed in clinical practice. Support for this idea has been demonstrated by a low correlation of PtGA with joint counts and acute-phase reactants (10,13,14), and by PtGA being unrelated to structural damage or other important outcomes (15,16) that treat-to-target aims to prevent. PtGA is highly affected by comorbidities and by other musculoskeletal and psychological conditions (e.g., osteoarthritis, fibromyalgia, depression) that cannot be improved by therapies targeting the inflammatory process, which makes it inappropriate to guide the readjustment of such therapies (11,17,18). Additionally, concerns have been raised regarding the variety of formulations used to ask this question (18), which have been shown to influence remission rates by 4.7% to 6.3% (19). The patient's health literacy also affects the validity and reliability of PtGA: approximately 40% of patients find the concept of PtGA confusing and the instruments difficult to mark (20).

The importance of understanding how PtGA influences disease activity classification became especially important with the new ACR/EULAR remission criteria, given that a PtGA score >1 excludes remission, even if all the other 3 criteria are ≤1 (a condition referred to as PtGA-near-remission state). Several independent studies have shown that 14% to 38% of patients with RA, in different settings, are in PtGA-near-remission (10,21–25), although these proportions need to be confirmed in larger international samples. The main issue is that following current treatment recommendations (1,2), this state of PtGA-near-remission would justify intensification of immunosuppressive treatment, after considering "other patient factors, such as progression of structural damage, comorbidities, and safety issues" (1), or the "patient's individual circumstances" (2). Treatment decisions have been regarded as more nuanced and most rheumatologists would be unlikely to base a treatment escalation decision on the value of the PtGA alone (26). The question remains: if it is acceptable that rheumatologists ignore PtGA for treatment decisions, then why should it be kept in target definitions? Other researchers have proposed the increase of the cutoff point of PtGA to approximately 2.5 or 3 cm (27,28), but this suggestion does not solve the problems of validity and reliability mentioned above.

Members of our group (10,29) have proposed the dual-target concept, involving concomitant and obligatory use of 2 different targets: a measure of inflammatory disease activity (biologic remission or 3-variable remission) and a measure of patient-reported impact of the disease (symptom remission). The latter should be based on patient-reported outcomes (PROs) that are better than PtGA at discriminating disease impact and thus help to guide adjunctive therapy (10,29). This proposal has ignited controversy (12,26). The concepts being addressed are of crucial importance in defining management strategies, supporting the need for further studies to enlighten the ongoing debate (30). Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology (METEOR), a large international longitudinal database, reflecting current clinical practice, provides a valuable opportunity to take into account the variability of clinical settings of care provision, including differences in cultural background, as well as treatment accessibility and standards.

The objectives of the current study were to determine the influence of PtGA on the classification of patients according to disease activity states, particularly remission, and explore differences across countries, to explore the range of PtGA values among patients in remission by DAS28 and in PtGA-near-remission, and to determine the associations of PtGA with markers of inflammation and of impact of disease.

PATIENTS AND METHODS

Patients and study design. This study used data from the METEOR database, an ongoing prospective international register of patients with RA founded in 2006 (31,32). The METEOR is a free web-based tool available worldwide, containing >45,000 patients,

>33 countries, and >270,000 visits, corresponding to a mean ± SD of 3.1 ± 3.1 person-years of follow-up. Data regarding patients' sociodemographics, diagnosis, treatment, and follow-up, according to usual care, are collected anonymously in a central database. Data can also be uploaded from local electronic health record systems or registries, which is the case in The Netherlands, Portugal, India, and other countries (31,32). All data in METEOR are fully anonymized and all follow-up visits, measurements, and medication are based on daily clinical practice; therefore, medical ethics approval is not required. For this study, the first visits of patients registered in METEOR, from adult patients with no missing data in the variables used to determine ACR/EULAR Boolean-based remission status, were selected. The database included visits from June 1985 until December 2017.

Assessments. PtGA of the current disease activity was measured on a 0–10-cm visual analog scale (VAS), with anchors of 0 (not active at all) and 10 (extremely active). Although the meaning of the question was the same, the exact formulation of the question varied across countries. Other PROs assessed were pain (VAS, 0–10 cm) and physical function, measured by the Health Assessment Questionnaire disability index (HAQ DI) (33). The following clinical and demographic parameters were also considered for sample characterization: sex, age at visit, disease duration since diagnosis, gross domestic product per capita of the country, the presence of erosions, and current treatment with biologic disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic DMARDs.

Definitions of remission. The ACR/EULAR Boolean-based definition (5) was adapted to classify patients in 3 main remission states: Boolean-based remission (TJC28, SJC28, CRP level mg/dl, and PtGA, all ≤1), also designated in this study as 4-variable remission; PtGA-near-remission (TJC28, SJC28, CRP level mg/dl, all ≤1, and only PtGA >1) (10); and nonremission (if 2 or more criteria are >1). The proposed binary definition of 3-variable remission (the same criteria as 4-variable remission but excluding PtGA) (10,16) was also tested. Naturally, 3-variable remission is equal to 4-variable remission + 4-variable PtGA-near-remission. The proportions of patients who failed Boolean remission due to a single criterion, other than PtGA, were also calculated (21).

An even stricter 3-variable Boolean-based criterion, defined by the authors as SJC28 = 0, TJC28 = 0, and CRP level (mg/dl) ≤0.5 (strict 3-variable remission) was used in exploratory analyses to assess the percentage of patients scoring PtGA ≤1 under these circumstances. The remission definitions of SDAI (≤3.3) and CDAI (≤2.8) (7,8) were also used to establish their prevalence among patients in the PtGA-near-remission state. For DAS28, remission states were assessed with the DAS28-CRP (34) because it was available in more patients than DAS28-ESR, and because the other definitions of remission also include the CRP level. We used the most recently proposed cutoffs (35).

Statistical analysis. Data were analyzed using SPSS Statistics software, version 20.0. Quantitative data were expressed as mean ± SDs and categorical data as frequencies and percentages. The influence of PtGA in the rates of remission according to the various definitions was assessed in 2 ways: by comparing the remission rates according to 4-variable DAS28-CRP versus 3-variable DAS28-CRP, and by determining the proportion of patients in PtGA-near-remission (Boolean definition). Secondary analyses included determining the distribution of PtGA values from patients fulfilling DAS28-CRP remission, PtGA-near-remission, and strict 3-variable remission, and determining the proportion of patients in PtGA-near-remission who were also in SDAI and CDAI remission states.

Pearson's correlation coefficients between PtGA, and SJC28, TJC28, CRP level, 3-variable DAS28-CRP, pain scores, and function (HAQ DI) were calculated and categorized as high (r ≥ 0.60), moderate (r = 0.40–0.59), and low (r < 0.40) (36). Correlations with 3-variable DAS28-CRP were separately

Table 1. Summary of the clinical and demographic characteristics of the study population (n = 27,768)*

Variable	Observed values	Missing %
Female, no. (%)	21,976 (79.7)	0.7
Age at visit, years	52.6 ± 14.1	1.8
National GDP >20,000 (%)†	16,319 (59.7)	1.5
Disease duration since diagnosis, years‡	4.3 ± 7.3	7.6
Year of diagnosis 2000 or later, no. (%)	21,430 (83.4)	7.6
Rheumatoid factor positive, no. (%)	17,076 (74.7)	17.7
ACPA positive, no. (%)	11,533 (71.5)	58.1
Erosions, no. (%)	7,359 (54.6)	51.4
Treatment with steroids, no. (%)	10,407 (37.5)	0.0
Treatment with csDMARDs, no. (%)	19,556 (70.4)	0.0
Treatment with bDMARDs, no. (%)	6,449 (23.2)	0.0
Treatment with tsDMARDs, no. (%)	2 (<0.1)	0.0
TJC28	9.1 ± 9.0	0.0
SJC28	4.6 ± 5.3	0.0
CRP mg/dl	2.2 ± 3.0	0.0
PtGA (0–10 scale)	4.9 ± 2.6	0.0
3-variable DAS28-CRP	4.2 ± 2.6	0.0
SDAI remission (≤3.3), no. (%)	1,419 (6.4)	20.8
CDAI remission (≤2.8), no. (%)	1,418 (6.4)	20.8
Pain (VAS 0–10 scale)	4.9 ± 2.6	9.3
HAQ DI (0–3 scale)	1.1 ± 0.7	20.0

* Values are the mean ± SD unless indicated otherwise. One visit only per patient (the first visit providing all Boolean criteria). GDP = gross domestic product; ACPA = anti-citrullinated protein antibody; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; bDMARDs = biologic DMARDs; tsDMARDs = target synthetic DMARDs; TJC28 = 28 tender joint count; SJC28 = 28 swollen joint count; CRP = C-reactive protein; PtGA = patient's global assessment; DAS28-CRP = Disease Activity Score with 28-joint counts using CRP level; SDAI = Simplified Disease Activity Index; CDAI = Clinical Disease Activity Index; VAS = visual analog scale; HAQ DI = Health Assessment Questionnaire disability index.
† International dollars.
‡ This definition was chosen instead of time since the date of the onset of symptoms because the latter had significantly more missing data (28.2%; mean ± SD 6.9 ± 8.1 years).

Table 2. Impact of patient's global assessment (PtGA) in the various remission criteria, in the overall sample and by country*

Disease activity status	Overall (n = 27,768)	Netherlands (n = 3,296)	Italy (n = 4,156)	Portugal (n = 4,373)	India (n = 8,936)	Other (n = 7,007)
ACR/EULAR Boolean-based						
4-variable remission†	1,605 (5.8)	202 (6.1)	243 (5.8)	395 (9.0)	5 (0.1)	760 (10.8)
PtGA-near-remission‡	2,776 (10.0)	453 (13.7)	293 (7.1)	784 (17.9)	151 (1.7)	1,095 (15.6)
Nonremission§	23,387 (84.2)	2,641 (80.2)	3,620 (87.1)	3,194 (73.1)	8,780 (98.2)	5,152 (73.6)
Proposed 3-variable remission¶	4,381 (15.8)	655 (19.8)	536 (12.9)	1,179 (26.9)	156 (1.8)	1,855 (26.4)
Near-remission only#						
Due to PtGA	2,776 (79.7)	453 (74.1)	293 (78.3)	784 (82.4)	151 (91.5)	1,095 (79.4)
Due to CRP	271 (7.8)	57 (9.3)	31 (8.3)	82 (8.6)	5 (3.0)	96 (7.0)
Due to TJC28	249 (7.2)	63 (10.3)	32 (8.6)	47 (4.9)	8 (4.8)	99 (7.2)
Due to SJC28	185 (5.3)	38 (6.2)	18 (4.8)	39 (4.1)	1 (0.6)	89 (6.5)
3-variable DAS28-CRP**						
Remission (<2.4)	4,629 (16.7)	601 (18.2)	561 (13.5)	1,269 (29.0)	142 (1.6)	2,056 (29.3)
Low (≥2.4 to ≤2.9)	2,258 (8.1)	434 (13.2)	313 (7.5)	514 (11.8)	210 (2.4)	787 (11.3)
4-variable DAS28-CRP**						
Remission (<2.4)	4,131 (14.9)	551 (16.7)	503 (12.1)	1,130 (25.8)	96 (1.1)	1,851 (26.4)
Low (≥2.4 to ≤2.9)	1,957 (7.0)	395 (12.0)	236 (5.7)	468 (10.7)	150 (1.7)	708 (10.1)
Differences between 3-variable and 4-variable definitions, %						
DAS28-CRP remission/low	1.8/2.9	1.5/2.7	1.4/3.2	3.2/4.3	0.5/1.2	2.9/4.1
ACR/EULAR Boolean remission	10.0	13.7	7.1	17.9	1.7	15.6

* Values are the number (%) unless indicated otherwise. ACR = America College of Rheumatology; EULAR = European League Against Rheumatism; CRP = C-reactive protein; TJC28 = 28 tender joint count; SJC28 = 28 swollen joint count; DAS28-CRP = Disease Activity Score with 28-joint counts using CRP level.
† 4-variable remission = TJC28, SJC28, CRP level mg/dl, and PtGA, all ≤1.
‡ PtGA-near-remission = TJC28, SJC28, and CRP level mg/dl, all ≤1, with PtGA >1.
§ Nonremission = 2 or more of the 4 criteria (TJC28, SJC28, CRP level, or PtGA) >1.
¶ TJC28, SJC28, and CRP level mg/dl all ≤1; PtGA not considered. This proposed remission definition equates to merging 4-variable remission and "PtGA-near-remission" disease states.
# Near-remission = only 1 of the 4 criteria (TJC28, SJC28, CRP level, or PtGA) >1.
** The cutoffs proposed by Fleischmann et al (35) were used.

assessed for patients in remission/low disease activity, because this is the subgroup where the use of PtGA in managing treatment according to current recommendations has the greatest impact. Differences between the most represented countries (n >3,000 patients) in the database were explored. Multivariable linear regression models (using the Enter method, with all variables) with PtGA as a dependent variable were used to analyze the main determinants of the PtGA from 2 primary domains: predominantly inflammatory (SJC28, TJC28, CRP level) and patient-reported impact measures (pain and function).

RESULTS

Patient characteristics. Among the 43,341 patients (264,920 visits) available in the database, only 27,768 patients/visits were included (i.e., the first among 109,556 recorded visits without missing data in the 4 Boolean criteria). Table 1 shows the patient characteristics, representing 32 countries (also see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23866/abstract). Mean ± SD disease duration since diagnosis was 4.3 ± 7.3 years, 83.4% of patients were diagnosed from the year 2000 onward, and 23.2% of the patients were currently receiving bDMARDS. The mean ± SD 3-variable DAS28-CRP was 4.2 ± 2.6 and the mean ± SD PtGA was 4.9 ± 2.6.

Influence of PtGA in remission states. The overall remission rate according to the ACR/EULAR Boolean-based definition was 5.8%. An additional 10.0% of patients failed to achieve remission solely because of PtGA (PtGA-near-remission patients). The rate of PtGA-near-remission across countries was 1.7% in India, 7.1% in Italy, 13.7% in The Netherlands, 15.6% in other countries, and 17.9% in Portugal (Table 2).

Altogether, the remission rate would increase from 5.8% to 15.8% if the Boolean 3-variable remission was used instead of the 4-variable, i.e., if PtGA was excluded from the definition. The maximum difference was observed in Portugal: from 9.0% to 26.9% (Table 2). PtGA was clearly the major obstacle to 4-variable remission, justifying 79.7% of all the cases of near-remission in the overall sample.

The inclusion of PtGA in the DAS28-CRP formula led to a drop of 1.8% in the remission rate in the overall sample (16.7% versus 14.9%) (Table 2), a difference that varied from 0.5% in India to 3.2% in Portugal. If the low disease activity state was considered the target, the decrease in rate imposed by PtGA was 2.9% in the overall sample (24.8% versus 21.9%), reaching a maximum difference of 4.3% in Portugal.

PtGA values among patients in near-remission and strict 3-variable remission. Figure 1 shows the distribution of PtGA in these patients with low or null signs of inflamma-

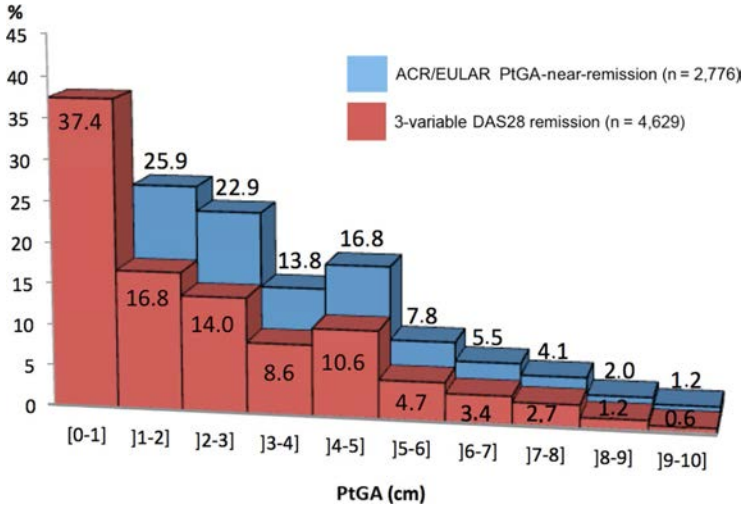

Figure 1. Patient's global assessment (PtGA) distribution in patients with rheumatoid arthritis in remission by the Disease Activity Score with 28-joint counts using the C-reactive protein level (DAS28-CRP) and 3 variables and in PtGA-near-remission. PtGA-near-remission patients are defined as having 28 tender joint counts ≤1, 28 swollen joint counts ≤1, CRP level (mg/dl) ≤1, and PtGA >1 of 10. The blue bars indicate that there are no patients within the 0–1 interval (those patients were classified as being in American College of Rheumatology [ACR]/European League Against Rheumatism [EULAR] Boolean-based remission).

tion, showing that a considerable proportion report a high PtGA: 37.4% of patients in ACR/EULAR Boolean PtGA-near-remission had a PtGA >4 of 10. The mean ± SD PtGA in these patients was 3.9 ± 2.0 for the overall sample, with similar values in the different countries (Table 3). Among patients in PtGA-near-remission, 13.1% and 9.8% were in SDAI and CDAI remission states, respectively (data not shown).

Considering only the patients with SJC28 = 0, TCJ28 = 0, and CRP level mg/dl ≤0.5, defined here as strict 3-variable remission (n = 2,395), only 43.5% had a PtGA ≤1, and 20.0% had a PtGA >4. The mean ± SD PtGA among patients in 3-variable DAS28-CRP remission was 2.5 ± 2.3 cm, while for patients in a low disease activity state, it was 3.7 ± 2.4 cm (Table 3).

PtGA associations with inflammation-related variables and with disease impact measures. In the overall sample, the correlation of PtGA was strong with pain (r_p = 0.75), moderate with function (r_p = 0.52), and 3-variable DAS28-CRP (r_p = 0.51), and weak with the individual components of 3-variable DAS28-CRP (all $P < 0.001$) (Table 4). The correlation between 3-variable DAS28-CRP and PtGA in patients in remission and in low disease activity was 0.25. These correlations varied considerably across countries, with patients from The Netherlands and India presenting the lowest correlations between PtGA and inflammatory and patient-reported measures. There was a clear relationship between DAS28 and PtGA: the mean value of PtGA in patients with high disease activity, as defined by DAS28, was 6.2 as compared to 2.5 for patients in remission (Table 3). In

Table 3. Mean values of patient's global assessment (PtGA) across disease activity states*

Disease activity status	Overall (n = 27,768)	Netherlands (n = 3,296)	Italy (n = 4,156)	Portugal (n = 4,373)	India (n = 8,936)	Other countries (n = 7,007)
ACR/EULAR Boolean-based PtGA near remission						
Remission†	0.4 ± 0.4	0.4 ± 0.4	0.3 ± 0.4	0.4 ± 0.4	0.0 ± 0.0	0.4 ± 0.4
PtGA-near-remission‡	3.9 ± 2.0	3.8 ± 1.9	4.2 ± 2.2	3.9 ± 1.9	3.8 ± 1.6	3.8 ± 2.0
Nonremission§	5.3 ± 2.4	4.1 ± 2.6	6.1 ± 2.5	5.1 ± 2.6	5.5 ± 1.8	5.2 ± 2.7
3-variable DAS28-CRP¶						
Remission (<2.4)	2.5 ± 2.3	2.6 ± 2.2	2.4 ± 2.4	2.7 ± 2.3	3.7 ± 1.6	2.4 ± 2.3
Low (≤2.9)	3.7 ± 2.4	3.2 ± 2.3	4.0 ± 2.6	3.6 ± 2.4	4.2 ± 1.8	3.7 ± 2.5
Moderate (≤4.6)	4.9 ± 2.3	4.0 ± 2.5	4.0 ± 2.5	4.9 ± 2.4	4.9 ± 1.8	4.9 ± 2.4
High (>4.6)	6.2 ± 2.1	4.8 ± 2.6	7.2 ± 2.1	6.5 ± 2.2	5.9 ± 1.7	6.8 ± 2.2

* Values are the mean ± SD in cm. ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; DAS28-CRP = Disease Activity Score with 28-joint counts using C-reactive protein level and 3 variables.
† Remission = 28 tender joint count (TJC28), 28 swollen joint count (SJC28), CRP level mg/dl, and PtGA, all ≤1.
‡ PtGA-near-remission = TJC28, SJC28, CRP level mg/dl, all ≤1, and PtGA >1.
§ Nonremission = TJC28 or SJC28 or CRP level mg/dl >1, irrespective of PtGA value.
¶ The cutoffs proposed by Fleischmann et al (35) were used.

Table 4. Pearson's coefficient correlations between patient's global assessment (PtGA) and inflammatory and disease impact measures by country and by disease activity status*

Country	TJC28	SJC28	CRP (mg/dl)	3-variable DAS28-CRP	Pain (0–10)†	HAQ DI‡
All countries (n = 27,768)	0.43	0.36	0.23	0.51	0.75	0.52
Netherlands (n = 3,296)	0.27	0.17	0.13	0.30	0.57	0.39
Italy (n = 4,156)	0.51†	0.42	0.18	0.58	0.86	0.57
Portugal (n = 4,373)	0.48	0.40	0.21	0.54	0.86	0.57
India (n = 8,936)	0.30	0.20	0.20	0.34	0.65	0.50
Other countries (n = 7,007)	0.52†	0.43	0.24	0.59	0.74	0.56

* Values are the PtGA correlation. $P < 0.001$ in all instances. TJC28 = 28 tender joint count; SJC28 = 28 swollen joint count; CRP = C-reactive protein; DAS28-CRP = Disease Activity Score with 28-joint counts using CRP level and 3 variables; HAQ DI = Health Assessment Questionnaire disability index.
† Percentage of missing data for pain on a visual analog scale was 9.3% (overall), 18.6% (Netherlands), 4.3% (Italy), 21.4% (Portugal), <0.1% (India), and 12.1% (other).
‡ Percentage of missing data for HAQ DI was 19.9% (overall), 49.0% (Netherlands), 13.8% (Italy), 21.6% (Portugal), 6.9% (India), and 25.5% (other).

multivariable analysis, pain ($\beta_{standardized} = 0.591$) and function ($\beta_{standardized} = 0.156$) were the main explanatory factors of PtGA. To a smaller extent, TJC28 ($\beta_{standardized} = 0.111$), CRP level ($\beta_{standardized} = 0.034$), and SJC28 ($\beta_{standardized} = 0.030$) were also statistically significant in the model, which explains 57.3% of PtGA variance ($P < 0.001$) (Table 5).

DISCUSSION

This study assessed the influence of PtGA on the classification of patients' remission status according to 2 definitions, using a large international clinical practice cohort, and tested its associations with factors predominantly associated with inflammatory activity or with the impact of disease. Overall, the ACR/EULAR Boolean-based (4-variable) remission was achieved by 5.8% of the patients, but another 10% failed to meet criteria for this status solely because of PtGA >1. This difference varies across countries, from 1.7% in India to 17.9% in Portugal. Previous studies (10,21–25) have reported PtGA-near-remission rates between 14% (n = 236 European patients) (25) and 38% (n = 309 patients from Coimbra, Portugal) (10). Obviously, dropping a factor from an equation, especially if Boolean, will lead to an increase in the proportion of observations being determined/filtered. However, PtGA stands out from the other factors used to define remission because it is much more subjective than other factors and conveys information that is unrelated to inflammation, it cannot be expected to improve with immunosuppressive therapy in patients who are otherwise in remission, and it is responsible for 10-fold more cases of near-remission in the Boolean-based definition than each of the others factors (10.0% versus 1.0%, 0.9%, and 0.7% for CRP level, TJC28, and SJC28, respectively) (Table 2).

These results demonstrate a remarkable impact of PtGA on the rate of patients achieving treatment target and suggest that 10% of RA patients overall and up to 38% of all RA patients in certain settings (10) may be exposed to an overtreatment risk, if rheumatologists adhere strictly to the current Boolean definition of target (29). This possibility is certainly worrying, unless PtGA is shown to represent disease dimensions that are amenable to improvement by the therapies being considered, typically immunosuppressive agents, but this possibility is not supported by our data.

If we consider only the patients whose treatment is recommended to increase based solely on PtGA (PtGA-near-remission), PtGA shows no relationship with disease activity (Table 5), nor should it be expected to, given that SJC28, TJC28, and CRP level (mg/dl) are all ≤1. The observation that 20% of the 2,395 patients in strict 3-variable remission scored PtGA >4 underlines this interpretation and questions the possibility that high PtGA values in such patients may be a reflection of subclinical inflammation (37,38). Although PtGA has been previously

Table 5. Multivariable linear regression analysis to explain patient's global assessment (n = 20,719)*

Variable	Unstandardized β	β	*P*†	95% CI for β	Adjusted R^2	*P*
Constant	1.232	–	<0.001	1.181–1.284	0.573	<0.001
TJC28	0.030	0.111	<0.001	0.027–0.033	–	–
SJC28	0.014	0.030	<0.001	0.009–0.19	–	–
CRP mg/dl	0.027	0.034	<0.001	0.019–0.035	–	–
Pain	0.058	0.591	<0.001	0.057–0.059	–	–
HAQ DI	0.548	0.156	<0.001	0.510–0.585	–	–

* Using Enter's method and 28 tender joint count (TJC28), 28 swollen joint count (SJC28), C-reactive protein (CRP) level, pain, and Health Assessment Questionnaire disability index (HAQ DI) as independent variables. 95% CI = 95% confidence interval.

attributed high face validity in overall samples of RA patients (18), PtGA's validity becomes obviously questionable in patients with low or absent signs of active inflammation. Confounding factors, namely the different interpretation of nonstandardized questions (20,39), and the impact of unrelated factors, such as comorbidities or psychological distress, become of paramount importance (10,18,40).

Our data also demonstrate, as expected, that PtGA has a positive correlation with disease activity. Considering the overall sample, PtGA was associated with pain and function (HAQ DI) and also, although to a lesser extent, with objective measures of disease activity (SJC28, CRP level). Explaining the discrepancy observed between countries regarding the correlation between PtGA and parameters of disease activity is beyond the scope of this article. A multitude of factors, including patient education on PROs and patient expectations, are probably involved (39,41,42).

Overall, mean values of PtGA were lower in patient's groups with lower indices of disease activity, which is true at the group level (40). However, if we adopt the treat-to-target strategy, classification becomes individual and dichotomized (remission versus nonremission), and correlations are no longer relevant, because even factors with a good correlation may become inadequate for classification. This concept is critical in situations when classification has important treatment implications.

The current study has some strengths and limitations**.** METEOR also incorporates data imported from other registries and the formulation of the PtGA question presented to patients is not exactly the same. Our previous research (19) suggests that PtGA score varies by different formulations of the question. There was a significant amount of missing data (e.g., body mass index, smoking status, erosions) that could introduce some selection bias. A sizeable proportion of the PtGA variance was not explained by our models, in part because other variables that have been shown to impact PtGA, such as fatigue and stiffness, are not available in METEOR. Because health-related quality of life measures are not included in the METEOR, we were unable to assess the correlation between PtGA and quality of life. However, other studies have demonstrated that PtGA correlates better with quality-of-life measures than with these predominantly inflammatory measures (43). There may also exist a selection bias derived from the fact that countries/centers that adopt a more regular metrology, and thus contribute to cooperative databases, are the ones with better adherence to therapeutic guidelines. In our analyses, we have compared results across countries with quite different levels of income and cultural backgrounds. As main strengths of this study, we used a large database, from clinical practice and from rich and poor countries, with a diversity of cultural backgrounds. In addition, we used both simple and powerful statistical analyses, allowing easier interpretation and implementation of the results in clinical practice, while providing strong evidence for practice and further research.

Taken together, the current results and published evidence suggest that PtGA has a general correlation with disease activity level, which makes it an appropriate component of indices used for a semiquantitative evaluation of disease status, in a strategy aimed at making the patient better. This information also demonstrates, however, that PtGA lacks specificity and biologic support around the cutoff points used to define treatment target and make therapeutic decisions, as demonstrated by a correlation of just 0.25 with 3-variable DAS28-CRP in patients in low disease activity and remission states. A target should, by definition, be sharp and meaningful, especially when we are dealing with targeted immunosuppressive agents. The mean value of PtGA for patients otherwise in remission (3.9 cm) and its distribution (37% with a PtGA >4) suggest that this lack of specificity of PtGA cannot be properly resolved by simply increasing its maximum acceptable value to 2 or 3, as previously suggested (27,28).

The evidence supports our proposal for a dual-target strategy to manage RA (10,29): a biologic remission target, aiming at the control of inflammation, defined by the 3-variable remission concept and used to guide immunosuppressive therapy, and a symptom-remission target, defined by a well-validated and discriminative PRO, such as the Rheumatoid Arthritis Impact of Disease score, to guide adjuvant therapy for the control of the disease impact factors (symptom remission). Achieving inflammatory remission should be seen as a strong contribution toward remission of disease impact, but not as a guarantee. Both targets should be considered independent but obligatory and complementary, requiring equal attention from rheumatologists and the care team (12). The full resolution of the impact of disease on patients' lives (the ultimate objective of treatment) will certainly require a multidisciplinary approach involving nurses, physiotherapists, occupational therapists, psychologists, and other health care professionals. This dual target strategy and separation of measures would ensure that remission is more meaningful to patients, while such an approach is likely to reduce the risk of overtreatment with immunosuppressants (10,12,29). A study protocol within the scope of this proposal was recently published by a Danish research group (44), reinforcing its current scientific and clinical relevance.

Nevertheless, with or without PtGA, rheumatologists and health care professionals should always be aware of the limitations of disease activity indices (such as noninclusion of the feet, size and relevance of involved joints to the individual patients, active swollen joints versus cold chronic scarring) and holistically consider patients' symptoms, needs, and individual circumstances (1,2,45).

Further investigation will be required to verify whether the exclusion of PtGA from the definition of remission negatively affects its long-term predictive value of important outcomes such as radiographic damage and physical function. This work is currently underway (46). A detailed examination of the potential association of PtGA with subclinical inflammation in patients otherwise in remission is also warranted.

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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. Mr. Ferreira 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. Ferreira, Ndosi, Duarte, van der Heijde, Machado, da Silva.

Acquisition of data. Ferreira, Carvalho.

Analysis and interpretation of data. Ferreira, Carvalho, Ndosi, Duarte, Chopra, Murphy, van der Heijde, Machado, da Silva.

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Low Persistence Rates in Patients With Rheumatoid Arthritis Treated With Triple Therapy and Adverse Drug Events Associated With Sulfasalazine

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Objective. Combination treatments for patients with rheumatoid arthritis (RA) with an inadequate response to methotrexate (MTX) alone include the addition of a tumor necrosis factor inhibitor (TNFi) or the addition of sulfasalazine (SSZ) and hydroxychloroquine to MTX (triple therapy). We compared persistence and adherence rates between these 2 combination therapies in US veterans and report the reasons for discontinuation of combination treatment in these groups.

Methods. Using Veteran's Affairs clinical and administrative data from 2006 to 2012, veterans with RA escalating treatment from MTX to MTX-TNFi or triple therapy were examined for a 12-month period after combination initiation. Persistence was defined as treatment without a ≥90-day gap in therapy. Adherence was calculated using the proportion of days covered ≥80% at 12 months. Matching weights–adjusted models were applied to more closely mimic randomization in this study. The reasons that patients discontinued their combination regimens were identified by chart abstraction.

Results. Full persistence at 1 year was 45% in the MTX-TNFi patients (n = 2,125) and 18% in the triple therapy patients (n = 171) ($P < 0.001$). Adherence was higher for the MTX-TNFi group (26%) than the triple therapy group (11%) ($P < 0.0001$). The triple therapy group was associated with significantly more treatment discontinuation, which was most often due to adverse drug events from SSZ.

Conclusion. Differences in persistence and adherence between the MTX-TNFi and triple therapy groups appear to be primarily related to adverse drug events that were most often attributed to SSZ.

INTRODUCTION

While methotrexate (MTX) alone is an accepted first-line therapy for the treatment of rheumatoid arthritis (RA) (1,2), many patients require additional treatment. The American College of Rheumatology recommends escalation of therapy with a biologic tumor necrosis factor inhibitor (TNFi) added to MTX, or initiation of triple therapy with conventional synthetic disease-modifying antirheumatic drugs (DMARDs) sulfasalazine (SSZ), hydroxychloroquine (HCQ), and MTX (2–4). Recent randomized, double-blind studies have demonstrated noninferiority between combination MTX-TNFi and triple therapy drug regimens for the treatment of patients with RA (5,6).

With the proven efficacy of these combination therapies, an understanding of the real-world observations outside of clinical trials should be investigated to determine whether similar experiences are seen in clinical practice as in clinical trials. Some clinicians favor adding a TNFi to MTX as initial combination ther-

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SIGNIFICANCE & INNOVATIONS

- Veterans with rheumatoid arthritis who initiated combination therapy with methotrexate (MTX) and a tumor necrosis factor inhibitor (TNFi) showed higher persistence and adherence rates at 1 year compared with veterans who initiated triple therapy.
- Among the triple therapy discontinuation group, sulfasalazine was the drug most frequently discontinued, because it was most frequently associated with adverse drug events.
- Among the MTX-TNFi discontinuation group, a TNFi was more frequently discontinued than MTX.
- More research is warranted to determine how to improve medication persistence and adherence and reduce loss to follow-up.

apy, while others initiate triple therapy (7). Recent studies have shown substantially better cost effectiveness with triple therapy compared to combination therapy with MTX-TNFi (8). A recent study by our group showed that overall persistence and adherence rates were significantly lower in US veterans taking triple therapy as compared with MTX-TNFi therapy (9). In the previous study, however, there were no restrictions placed on how patients started triple or MTX-TNFi therapy; for example, subjects may have sequentially added a DMARD at 3 different instances to qualify for triple therapy. The current study was performed in part to determine whether alternate methods of entry into therapy might have influenced the lower adherence in the triple therapy group. Moreover, the reasons for treatment discontinuation were not identified, which might influence outcomes. The aims of this study were 2-fold: to determine whether real-world persistence and adherence rates were lower for triple therapy in US veterans who added a TNFi or both SSZ and HCQ simultaneously to MTX (to duplicate the regimen used in prior clinical trials), and to investigate the reasons for therapy discontinuation.

MATERIALS AND METHODS

Cohort definition. This was a retrospective cohort study using historical data in databases from the Department of Veterans Affairs (VA), Veterans Health Administration, Corporate Data Warehouse, Pharmacy Benefits Management, and Decision Support Services between January 1, 2006 and December 31, 2012. For a subject to be classified as receiving MTX-TNFi combination therapy initiated on the index date, the subject had to have a prior and active prescription for MTX without a ≥90-day gap in therapy at the time of initiation of any TNFi, as well as at least 1 MTX refill within 90 days of initiating a TNFi to document intent to continue therapy with the combination of MTX-TNFi. Adalimumab, certolizumab, etanercept, golimumab, and infliximab were all included as a TNFi for this analysis. For a subject to be included in the triple therapy group, the subject had to have an active prescription of MTX to which both SSZ and HCQ prescriptions were simultaneously filled by the subject. Similarly, for the MTX-TNFi group, at least 1 MTX refill was required within 90 days following initiation of combination therapy to document intent to continue MTX in the combination.

Patients with RA were included in the analysis if they fulfilled the following inclusion criteria: age ≥18 years at the time combination therapy was initiated, enrollment in the VA for at least 6 months prior to initiation of combination therapy, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for RA during the 182 days prior to or 28 days after the index date, and the potential for 365 days of observation following the initiation of combination therapy after the index date, meaning that subjects could not be indexed <365 days prior to the end of the study period. The index date was defined as the date of escalation of therapy by addition of HCQ and SSZ to MTX for the triple therapy group, or addition of a TNFi to the MTX-TNFi group.

Patients were excluded if 1) there was an ICD-9-CM code for a diagnosis of juvenile idiopathic arthritis (714.3x), psoriasis (696.1x), psoriatic arthritis (696.0x), ankylosing spondylitis (720.0x), Crohn's disease (555.xx), or ulcerative colitis (556.xx) in the 6 months prior to or 28 days after the start of combination therapy; 2) there was treatment with any biologic DMARD or nonbiologic DMARD other than MTX, SSZ, HCQ, or a TNFi during the preindex period; or 3) there were overlapping courses of nonbiologic DMARDs other than index combination drugs from day 1 to day 28 following the index date. Patients who were receiving either of the combinations under study, triple therapy and/or MTX-TNFi, during the 1-year observation period prior to the index date were excluded from the study cohort.

Persistence. Persistence was the primary outcome measure. Persistence for a medication was defined as continuous treatment without a ≥90-day gap in treatment, after the end of each drug's day of supply (e.g., 28 or 84 days for weekly subcutaneous injectable drugs), or typical infusion intervals (e.g., 56 days for infliximab). Adherence and persistence were calculated by extrapolation using prescription fills, and veterans generally get their prescriptions from VA pharmacies (10). The VA typically uses 90-day fills of medications with up to 3 refills allowed, thus allowing subjects to have a single prescription that could be refilled for up to 1 year of medication. Biologic agents are often limited to a 28-day supply of medications but are allowed up to 11 refills, thus allowing a year of medication to be dispensed following a single prescription. Therefore, gaps of ≥90 days between fills were used as surrogate markers for lapses in medication use. Use of a 90-day selection is relatively arbitrary, but this period had been used in previous studies by our coauthors (9). Persistence was calculated for each medication. Three different methods were used to define persistence of the combination therapies. For persistence definition 1, all medications (including MTX) needed to be filled without

a ≥90-day gap in treatment over the 12-month study period to be considered persistent. The addition of other DMARDs during the observation study period was not considered in this primary persistence definition. Persistence to medications was noted based on prescriber direction.

Persistence definition 2 allowed discontinuation of any 1 DMARD (including MTX) in triple therapy or MTX in the MTX-TNFi group, provided no new DMARDs were initiated. Thus, after at least 1 refill for MTX, triple therapy combination regimens were considered persistent if subjects continued using any 2 of the 3 drugs in the triple therapy regimen, and they were considered persistent using the MTX-TNFi combination if they persisted with a TNFi alone without initiating a new DMARD. This alternative persistence outcome was designed to allow subjects to persist on therapy who may have achieved significant improvement of RA using their combination therapy and were undergoing a step-down approach.

Persistence definition 3 was identical to persistence definition 2 with the addition that switching was permitted between drugs within the TNFi class for subjects in the MTX-TNFi combination group, and switching between nonbiologic DMARDs was permitted in subjects in the triple therapy group, if a ≥90-day gap did not occur prior to the switch.

Adherence. Adherence was defined by the proportion of days covered (PDC) at 1 year (11). PDC was calculated for each drug individually and for all the drugs in the combinations over the 12-month study period following the index date. Consistent with prior conventions, regimens were considered to be adherent if PDC was ≥80% (12). When prescriptions overlapped (i.e., the patient refilled the drug early), up to 14 days of overlap was allowed and extended the days' supply of the subsequent prescription.

Chart abstraction to determine reason for drug discontinuation. Discontinuation of combination therapy was defined as discontinuing any of the medications with a ≥90-day gap and/or starting new drug treatments for RA. A subset of both study groups was selected for chart abstraction to determine the factors that influenced drug discontinuation. Subjects discontinuing triple therapy or MTX-TNFi were matched to one another on age (± 5 years), sex, and VA facility stratified by site. There were 115 matched pairs between the 2 combination therapy groups evaluated for the reasons of discontinuation; these were the maximum number of possible pairs from the study population by matching. The specific drugs discontinued and the reasons for discontinuing the combination therapy were determined, with the reason for cessation classified as 1 of the following: lack of efficacy, adverse drug event (ADE; e.g., regardless of real or perceived causality with the medication), or other (step-down therapy, preoperative discontinuation, nonadherence, or potential loss to follow-up). Lack of efficacy was determined by the chart abstracters' clinical judgment, using text review of clinical notes and provider statements in the medical record. If no clear documentation of lack of efficacy was provided in the clinical note, the subject was classified in the "other" category. When included in the note, disease activity scores were used but were not widely available.

Covariates. Potential confounding factors were used as covariates in the analysis. These variables included seropositive status for anti–cyclic citrullinated peptide (anti-CCP) or rheumatoid factor (RF), comorbidity measures, and concurrent medications. RF positivity was defined as >20 IU/ml or >1:40 titer, and anti-CCP positivity was defined as >20 U/ml. Specific medical conditions were identified by ICD-9-CM codes, including congestive heart failure, pneumonia, acute bronchitis, urinary tract infection, skin infection, septicemia, shock, HIV, hepatitis, alcohol-related disorders, and substance use disorders. Comorbidity was also assessed using the composite Rheumatic Disease Comorbidity Index score (13). Aggregate measures of health care utilization in the baseline period included yearly counts of rheumatology visits, urgent care visits, emergency department visits, and inpatient visits. VA drug class codes were used to identify opioid analgesics, nonopioid analgesics, salicylates, antirheumatic drugs, nonsalicylate nonsteroidal antiinflammatory drugs, and prednisone. Proton pump inhibitors were identified using a string search on generic ingredients.

Statistical analysis. Propensity score analysis used matching weights to adjust for baseline patient characteristics and balance covariates between the 2 combination groups (14). Thirty-four pretreatment baseline covariates were identified as possible confounders based on literature review and based on the assumption that these variables could influence treatment decisions and persistence during the 1-year follow-up (Table 1). These covariates were used to generate a propensity score using potential confounders to model treatment choices (i.e., triple therapy versus MTX-TNFi) for each subject using a logistic regression model. The matching weight was designed as a variant of the inverse probability weight (15). The matching weight estimator of the treated effect was calculated to be interpreted as the difference in weighted risks between treatment groups. Relative differences on the ratio scale were also reported. The ability to check the covariate balance between the treatment groups is an important advantage of the propensity score methods over direct regression on the outcome. Lack of balance often suggests that the treatment comparisons may not be feasible on certain subgroups of subjects without extrapolation, or that there may be residual bias due to confounding by the measured covariates. Standardized differences were used to determine differences in covariate balance before and after weighting.

Table 1. Study demographics*

	Unadjusted						Matching weights–adjusted					
Demographics and variables	Triple Rx No./ mean	Triple Rx %/SD	TNFi combo No./mean	TNFi combo %/SD	*P*	SD	Triple Rx No./mean	Triple Rx %/SD	TNFi combo No./mean	TNFi combo %/SD	*P*	SD
Demographics												
Age	60.29	10.17	61.29	10.61	0.236	0.096	60.29	10.17	60.18	3.01	0.802	0.015
Body mass index	29.24	6.51	29.58	6.17	0.498	0.053	29.25	6.51	29.30	1.69	0.840	0.011
Male	152	88.89	1843	86.73	0.421	0.066	151.88	88.88	151.42	89.04	0.962	0.005
Drug class												
Distinct VA drug class	10.54	4.54	9.60	4.89	0.015	0.200	10.54	4.54	10.50	1.48	0.851	0.011
Opioid analgesics	73	42.69	856	40.28	0.537	0.049	72.88	42.65	72.23	42.47	0.974	0.004
Nonopioid analgesics	50	29.24	521	24.52	0.169	0.107	49.96	29.23	48.95	28.79	0.927	0.010
Salicylates, antirheumatic drugs	7	4.09	44	2.07	0.084	0.117	7.00	4.10	6.71	3.94	0.943	0.008
Nonsalicylate NSAIDs, Zantirheumatic drugs	80	46.78	850	40.00	0.082	0.137	79.93	46.77	78.89	46.39	0.944	0.008
PPI use	82	47.95	876	41.22	0.086	0.136	81.88	47.92	80.90	47.57	0.949	0.007
Prednisone use	106	61.99	1117	52.56	0.018	0.191	105.88	61.96	105.73	62.17	0.968	0.004
CCS comorbidity												
Distinct CCS count	10.80	7.21	9.81	5.98	0.040	0.150	10.80	7.20	10.64	1.80	0.584	0.030
Tuberculosis	0	0.00	16	0.75	0.255	0.123	0.00	0.00	0.00	0.00	0.999	0.000
Congestive heart failure; nonhypertensive	12	7.02	39	1.84	<0.0001	0.254	11.96	7.00	11.01	6.47	0.848	0.021
Pneumonia (not caused by tuberculosis or STD)	1	0.58	21	0.99	0.602	0.046	1.00	0.59	0.74	0.44	0.846	0.021
Acute bronchitis	4	2.34	30	1.41	0.334	0.068	4.00	2.34	3.80	2.24	0.948	0.007
Urinary tract infections	2	1.17	35	1.65	0.633	0.041	2.00	1.17	2.13	1.25	0.944	0.008

(continued)

Table 1. *(Cont'd)*

	Unadjusted						Matching weights–adjusted					
Demographics and variables	Triple Rx No./ mean	Triple Rx %/SD	TNFi combo No./mean	TNFi combo %/SD	*P*	SD	Triple Rx No./mean	Triple Rx %/SD	TNFi combo No./mean	TNFi combo %/SD	*P*	SD
Skin and subcutaneous tissue infections	5	2.92	61	2.87	0.968	0.003	5.00	2.93	5.11	3.00	0.967	0.005
Septicemia (except in labor)	0	0.00	1	0.05	0.777	0.031	0.00	0.00	0.00	0.00	1.000	0.000
Shock	0	0.00	1	0.05	0.777	0.031	0.00	0.00	0.00	0.00	1.000	0.000
HIV infection	1	0.58	2	0.09	0.088	0.084	0.93	0.54	0.93	0.54	0.997	0.000
Hepatitis	2	1.17	24	1.13	0.962	0.004	2.00	1.17	2.06	1.21	0.971	0.004
Alcohol-related disorders	15	8.77	69	3.25	0.000	0.234	14.96	8.75	14.21	8.36	0.897	0.014
Substance-related disorders	7	4.09	47	2.21	0.118	0.108	7.00	4.10	6.48	3.81	0.893	0.015
RDCI score	1.84	1.58	1.65	1.50	0.116	0.122	1.84	1.58	1.80	0.44	0.644	0.026
Anti-CCP positive	100	72.46	1212	74.04	0.686	0.036	99.88	72.44	96.62	72.28	0.977	0.004
Anti-CCP test	138	80.70	1637	77.04	0.271	0.090	137.88	80.69	133.67	78.60	0.633	0.052
RF positive	112	70.44	1344	68.82	0.671	0.035	111.96	70.46	111.68	70.87	0.936	0.009
RF test	159	92.98	1953	91.91	0.618	0.041	158.88	92.98	157.57	92.66	0.910	0.012
Smoking ever	118	75.16	1371	70.42	0.209	0.107	117.88	75.14	117.53	75.03	0.982	0.003
Smoking status	157	91.81	1947	91.62	0.931	0.007	156.88	91.81	156.64	92.11	0.918	0.011
Visit type												
ED visit count	0.00	0.00	0.02	0.20	0.332	0.105	0.00	0.00	0.00	0.00	0.996	0.001
Rheumatology visit count	2.94	2.10	2.62	1.86	0.038	0.157	2.93	2.10	2.88	0.56	0.539	0.034
UC visit count	0.01	0.08	0.01	0.11	0.886	0.013	0.01	0.08	0.01	0.03	0.925	0.006
Inpatient visit count	0.14	0.57	0.09	0.37	0.095	0.108	0.14	0.57	0.13	0.13	0.499	0.036

* Rx = prescription; TNFi = tumor necrosis factor inhibitor; VA = Veterans Affairs; NSAIDs = nonsteroidal antiinflammatory drugs; PPI = proton pump inhibitor; CCS = Charleston comorbidity score; STD = sexually transmitted disease; RDCI = Rheumatic Disease Comorbidity Index; anti-CCP = anti–cyclic citrullinated peptide; RF = rheumatoid factor; ED = emergency department; UC = urgent care.

The formula for standardized difference was computed using weighted adjusted means and variances. In typical applications of pair-matching methods, the standardized differences in a good match are the magnitude of a few percentage points. A level of 10% has been suggested as the threshold for determining balance (16). Standardized differences using the matching weights methods can easily reach below 1%. Therefore, the matching weights method may lead to substantially better covariate balance than the matching pair method. Matching weight–adjusted Kapan-Meier plots were created to illustrate time to discontinuation among treatment groups. Microsoft SQL server and SAS software, version 9.4, with Enterprise Guide, version 6.1, were used to prepare data and conduct statistical analyses. The research was approved by the Institutional Review Board of the University of Utah and reviewed and approved by the Salt Lake City VA research review committee.

RESULTS

Patient characteristics. The MTX-TNFi therapy arm included 2,125 subjects, and the triple therapy arm included 171 subjects. Before matching weights were applied, the triple therapy group appeared to be less healthy and have more comorbidities on average because they had significantly more unique VA drug classes, a higher prevalence of prednisone use, a congestive heart failure history, alcohol-related disorders, and a greater number of rheumatology visits. After applying matching weights, all variables were balanced between groups (Table 1).

Persistence. For persistence definition 1, the MTX-TNFi arm demonstrated 43.2% persistence, while the triple therapy arm demonstrated 17.6% persistence (Table 2 and Figure 1A). For persistence definition 2, which allowed for possible step-down of medicines within each combination arm, persistence on the MTX-TNFi arm was 50.3%, compared with 32.8% for the triple therapy arm (Table 2 and Figure 1B). Finally, for persistence definition 3, encompassing definition 2 but also allowing for other medications to be started, 57.06% were persistent in the MTX-TNFi arm while 33.9% were persistent in the triple therapy arm (Table 2 and Figure 1C). The differences in persistence rates between the 2 combination groups reached statistical significance for all definitions. Of note, there is a drop-off noted at days 30 and 90 of the survival curves, indicating a lapse in prescription refills after the initial 30- or 90-day supply. A subgroup analysis of subjects who were persistent using medication 100 days after the index date, excluding the initial cases of not refilling, continued to demonstrate significant differences in persistence between the groups, mirroring the results found on the raw data analysis, to suggest that the difference between the groups was not limited only to the initial treatment period (data not shown).

Adherence. Adherence to the different combination regimens is shown in Table 3. In the MTX-TNFi arm, combination adherence was 25.3%. Adherence to MTX was 44.3%, whereas the TNFi adherence was 46.0% over the 12-month period. For the triple therapy arm, adherence was calculated to be 10.5% for the combination, 48.6% for MTX, 18.7% for SSZ, and 32.8% for HCQ, indicating that SSZ was the most commonly discontinued component of the triple regimen (Table 3). The differences in adherence rates between the 2 combination groups were statistically significant for all definitions.

Chart abstraction to determine reason for drug discontinuation. The drugs discontinued (Table 4) and reasons for discontinuation were lack of efficacy, ADEs (gastrointestinal [GI] toxicity, rash, infection), step-down of therapy by the provider, discontinuation prior to surgery, and loss to follow-up (Table 5). The single drug most commonly discontinued in the MTX-TNFi group was a TNFi (53.9%), and SSZ (20.9%) in the triple therapy group. The absolute rates for dis-

Table 2. Persistence and adherence for combinations*

	Crude analysis				Matching weights–adjusted			
Outcomes	MTX-TNFi (n = 2,125)	Triple Rx (n = 171)	RR (95% CI)	*P*	MTX-TNFi (n = 170.0)	Triple Rx (n = 170.9)	RR (95% CI)	*P*
Persistence definition 1	960 (45.18)	30 (17.54)	2.58 (1.85–3.58)	<0.0001	73 (42.94)	30 (17.56)	2.46 (1.70–3.55)	<0.0001
Persistence definition 2	1,115 (52.47)	56 (32.75)	1.60 (1.29–1.99)	<0.0001	86 (50.59)	56 (32.77)	1.54 (1.182–1.994)	0.0022
Persistence definition 3	1,235 (58.12)	58 (33.92)	1.71 (1.39–2.12)	<0.0001	97 (57.06)	58 (33.94)	1.68 (1.32–2.15)	<0.0001
Adherence outcome	547 (25.74)	18 (10.53)	2.45 (0.57–3.81)	<0.0001	43 (25.30)	18 (10.53)	2.40 (1.45–3.99)	<0.0001

* Values are the number (%) unless indicated otherwise. Crude and matching weights–adjusted model for persistence using combination drug therapies, using persistence definitions 1, 2, and 3. Adherence was defined by the proportion of days covered (PDC) for each drug individually and for all the drugs in the combinations over the 12-month study period following the index date. Subjects were considered to be adherent if PDC was ≥80%. MTX = methotrexate; TNFi = tumor necrosis factor inhibitor; Rx = prescription; RR = rate ratio.

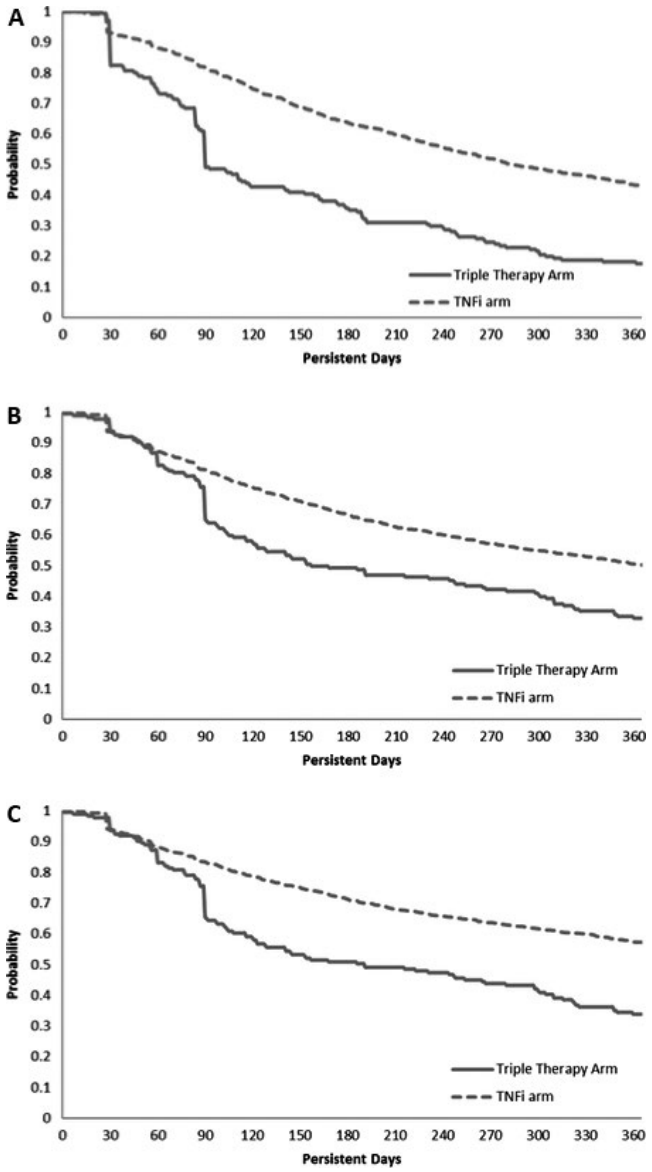

Figure 1. Persistence using methotrexate (MTX)–tumor necrosis factor inhibitor (TNFi) versus triple therapy. Persistence for each study group was defined as continuous treatment without a ≥90-day gap in treatment for the 12-month study period. Adjusted persistence was calculated for each medication. MTX-TNFi persistence is depicted by the dashed line, while triple therapy persistence is depicted by the solid line. **A**, For persistence definition 1, all medications in the combination had to be continued over the 12-month period. **B**, Persistence definition 2 allowed discontinuation of any 1 disease-modifying antirheumatic drug (DMARD) in triple therapy or MTX in the MTX-TNFi group, provided no new DMARDs were initiated. **C**, Persistence definition 3 was identical to persistence definition 2, with the addition that switching was permitted between drugs within the TNFi class for subjects in the MTX-TNFi combination group and switching between nonbiologic DMARDs in subjects in the triple therapy group.

continuation by cause were estimated by extrapolating data over the entire cohort for the 2 combination treatment groups. Comparing discontinuation of triple therapy to discontinuation of MTX-TNFi, the triple therapy group was associated with more discontinuations due to ADEs by both absolute and relative comparisons. Discontinuation due to lack of efficacy and other reasons for discontinuation were similar between the 2 groups. MTX had the lowest discontinuation frequency in either group, with SSZ being the most common drug discontinued in the triple therapy group. Most SSZ discontinuations were reported as ADEs, most often due to concerns of gastrointestinal toxicity. Specific dosing regimens at the time of discontinuation were not specifically studied. Of note, there was a significantly large number of subjects who were lost to follow-up (34.8% in the triple therapy group and 32.2% in the MTX-TNFi group); enrollment in the study only required a 12-month potential for follow-up but did not prevent actual loss to follow-up from occurring. Subjects classified as lost to follow-up did not have records of any VA contact after this designation, which needed to occur before the 1-year anniversary of the index date. Loss to follow-up included the observation that no RA and non-RA prescriptions were being filled, and no follow-up visits were documented, as the subjects had left the VA system.

DISCUSSION

This observational cohort study in US veterans attempted to replicate randomized clinical trials (RCTs) study design by requiring initiation of therapy consistent with several RA trials of inadequate responders to MTX monotherapy and found that real-world persistence and adherence rates were higher in patients with RA receiving MTX-TNFi therapy compared with triple therapy. Additionally, the differences in persistence appear to be primarily related to a difference in ADEs between

Table 3. Adherence of patients to specific agents in combination therapy, with crude and matching weights–adjusted model*

Treatment arm	Crude analysis†	Matching weights–adjusted‡
MTX-TNFi		
Both	547/25.7 (23.9–27.6)	43.0/25.3 (23.4–27.2)
TNFi	1,008/47.4 (45.3–49.6)	78.2/46.0 (43.9–48.1)
MTX	952/44.8 (42.7–46.9)	75.4/44.3 (42.2–46.4)
Triple therapy		
All	18/10.5 (5.9–15.2)	18.0/10.5 (5.9–15.2)
SSZ	32/18.7 (12.8–24.6)	32.0/18.7 (12.8–24.6)
MTX	83/48.5 (41.0–56.1)	83.0/48.6 (41.0–56.1)
HCQ	56/32.8 (25.6–39.8)	56.0/32.8 (25.6–40.0)

* Values are the number/percentage (95% confidence interval). Adherence was defined by the proportion of days covered (PDC) for each drug individually and for all the drugs in the combinations over the 12-month study period following the index date. Subjects were adherent if PDC was ≥80%. MTX = methotrexate; TNFi = tumor necrosis factor inhibitor; SSZ = sulfasalazine; HCQ = hydroxychloroquine.
† MTX-TNFi (n = 2,125), triple therapy (n = 171).
‡ MTX-TNFi (n = 170.0), triple therapy (n = 170.9).

Table 4. Number of patients discontinuing specific drugs alone or in combination at termination of combination therapy (n = 115 matched pairs)*

	Triple Rx	MTX-TNFi
Single drug discontinued		
TNFi	NA	62 (53.9)
MTX	10 (8.7)	22 (19.1)
SSZ	24 (20.9)	NA
HCQ	9 (7.8)	NA
Combinations discontinued simultaneously		
SSZ + HCQ	43 (37.4)	NA
MTX+ HCQ	2 (1.7)	NA
All drugs of the combination	27 (23.5)	31 (27.0)
Total discontinuation	115 (100)	115 (100)

* Values are the number (%). Rx = prescription; MTX = methotrexate; TNFi = tumor necrosis factor inhibitor; NA = not applicable; SSZ = sulfasalazine; HCQ = hydroxychloroquine.

the 2 groups. The greatest number of ADEs was attributed to SSZ, which was also the drug most frequently discontinued. These results were similar when applying multiple definitions for persistence and adjusting for covariates. Additionally, the high rate of loss to follow-up may help explain why adherence and persistence rates were overall lower in our study than in typical RCTs.

These findings are in contrast with findings of similar persistence outcomes between the 2 combination therapies in recent RCTs. However, our findings are consistent with a prior study by Bonafede et al (17), in which persistence rates were 29.4% for MTX-TNFi and 23.2% for triple therapy at 1 year, and adherence rates were 27.9% for MTX-TNFi versus 18.2% for triple therapy. Other studies have shown relatively low adherence to RA treatment in real-world clinical practice, including a recent publication by our group, using a larger cohort of US veterans (9). Lower persistence and adherence rates represent a greater extent of unrealized treatment benefit and poorer clinical outcomes in RA. Clinical trial goals typically ensure tightly controlled medication usage, leading to high medication persistence and adherence in all treatment arms. This real-world observational study demonstrated that there are challenges to addressing medication persistence and adherence rates, which may undoubtedly affect treatment outcomes. DMARD therapy reduces disease activity in RA and slows radiographic progression of disease (18). Conversely, nonadherence to treatment is associated with increased disease flares and disability (19,20). A critical review of the current literature found adherence to be low in 9 studies exclusively addressing adherence to RA DMARD therapy, ranging from 30% to 80% (21). Adherence to medication regimens can be influenced by a number of factors, including socioeconomic factors, health care system factors, the patient's clinical condition, the prescribed regimen, and the patient-provider relationship (22). Simple, once-daily regimens (23), including those with low pill burden, without a food requirement, and few side effects or toxicities, have been associated with higher levels of adherence (24,25). Efforts at improving medication adherence rates may in turn result in lower disease activity.

A major strength of this study is that it included a large number of subjects at multiple sites across the US in a uniform health care system that allows data capture through the integrative electronic medical record from the national Veterans Health Administration database. Additionally, findings from this study may allow clinicians to understand that there are likely multiple variables involved in medication persistence in real world practice.

Our study has several limitations. This was an observational study and subject to biases for this type of research. Our study population was primarily older, male US veterans, with higher comorbidities that may be different from other RA populations, which may limit the generalizability of the study. We calculated persistence and adherence rates based on prescription fills as a surrogate marker. We recognize that subjects may have filled a prescription but had never taken a dose of the medication. While veterans may have received medications from health care providers outside of the VA system, recent work has documented the fact that most US veterans with RA receive all of their therapy within the VA (10). Additionally, patient factors may influence nonadherence, including pain scores, treatment history, self-administration of injections, negative beliefs about treatment, and a lack of perceived medical and social support (26). We did not evaluate these factors in our study, and they are a potential area of research in future studies involving drug therapy persistence.

The assumption of our initial analysis was that all patients were followed until the end of the study period. After completion of the database analysis, we conducted chart review on the 115 patients from each treatment group and found that approximately

Table 5. Reasons for discontinuation of combination therapy (n = 115 matched pairs)*

Reasons	Triple Rx	MTX-TNFi
Lack of efficacy	18 (15.7)	25 (21.7)
Adverse drug event	50 (43.5)	41 (35.7)
GI toxicity/symptoms	21 (18.3)	2 (1.7)
Rash	5 (4.3)	4 (3.5)
Infection	6 (5.2)	13 (11.3)
Other adverse drug event	18 (15.7)	22 (19.1)
Other	47 (40.9)	49 (42.6)
Step-down of therapy	7 (6.1)	4 (3.5)
Discontinued prior to surgery	0 (0.0)	8 (7.0)
Lost to follow-up/unknown	40 (34.8)	37 (32.2)
Total discontinuation	115 (100)	115 (100)

* Values are the number (%). Rx = prescription; MTX = methotrexate; TNFi = tumor necrosis factor inhibitor; GI = gastrointestinal.

32–34% of patients were lost to follow-up. Given that there was a similar rate of loss to follow-up between groups, our impression is that the relative effect is valid, but the absolute risk of nonpersistence may be artificially low. Another potential explanation for artificially lower adherence and persistence rates is that our study focused only on prescription fills. For this reason, whether the subject or the provider discontinued the medication is uncertain, but both possibilities were labeled as persistence and adherence failures. Additionally, labeling of ADEs is subject to interpretation and bias from both provider and subject. Occasionally, SSZ and HCQ were added and discontinued simultaneously due to reported ADEs, but often the relevant agent was not identified, and the entire combination regimen was discontinued without further efforts to continue any single agent. GI toxicity is relatively common with SSZ, yet there are well-accepted techniques for mitigating this problem (e.g., use of initial low doses followed by gradual escalation, enteric coated preparations), and we did not assess whether these techniques were implemented. Moreover, our study did not assess the role of provider preferences regarding therapy discontinuation. Providers may be inherently more biased toward a biologic therapy or triple therapy, and this preference may influence their threshold on discontinuing therapy prematurely or labeling a nuisance ADE as sufficient to justify a change in therapy.

Last, given that this study was limited to the analysis of administrative data, we did not have access to clinical outcomes, including disease activity markers, joint counts, or patient-reported outcomes. In an observational open-label follow-up of the Rheumatoid Arthritis: Comparison of Active Therapies trial, no major differences were reported in all disease activity outcomes, including disease activity scores and erythrocyte sedimentation rate values, between subjects taking triple therapy versus MTX-TNFi (27). Interestingly, the study demonstrated higher durability and persistence rates in subjects using triple therapy rather than MTX-TNFi, which contrasts with the findings of our study and may reflect the fact that in real-world settings, subjects are more likely to pay for the cheaper cost associated with triple therapy instead of MTX-TNFi. In clinical practice, patients with lower disease activity may benefit from stepwise rather than simultaneous escalation of HCQ/SSZ to MTX. However, given that we did not have access to disease activity measures, we were unable to test this hypothesis.

In summary, this observational cohort study demonstrated that in US veterans with RA, persistence and adherence rates remained relatively low when escalating from MTX to combination MTX-TNFi and triple therapy, findings that mirror a larger recent study published by our group involving a larger cohort of US veterans (9). However, the current study also helped elucidate via chart abstraction the reasons why patients discontinue their combination medications for their RA. Findings from our study indicate that ADEs play a significant role in influencing drug discontinuation, and further efforts should focus on ways to mitigate ADEs when initiating or escalating drug regimens for RA. An additional finding was that a significant number of subjects who discontinued their combination therapy for RA were lost to follow-up from the VA system, and research should continue to focus on ascertaining methods to improve real-world treatment retention rates. More research is also warranted to determine whether patient factors that influence medication adherence independently affect the likelihood of achieving clinical remission, regardless of which therapy is chosen for the treatment of their RA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Cannon 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. Cannon, Sauer.
Acquisition of data. Erhardt, Teng.
Analysis and interpretation of data. Mikuls, Curtis.

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Detection of Flares by Decrease in Physical Activity, Collected Using Wearable Activity Trackers in Rheumatoid Arthritis or Axial Spondyloarthritis: An Application of Machine Learning Analyses in Rheumatology

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Objective. Flares in rheumatoid arthritis (RA) and axial spondyloarthritis (SpA) may influence physical activity. The aim of this study was to assess longitudinally the association between patient-reported flares and activity-tracker–provided steps per minute, using machine learning.

Methods. This prospective observational study (ActConnect) included patients with definite RA or axial SpA. For a 3-month time period, physical activity was assessed continuously by number of steps/minute, using a consumer grade activity tracker, and flares were self-assessed weekly. Machine-learning techniques were applied to the data set. After intrapatient normalization of the physical activity data, multiclass Bayesian methods were used to calculate sensitivities, specificities, and predictive values of the machine-generated models of physical activity in order to predict patient-reported flares.

Results. Overall, 155 patients (1,339 weekly flare assessments and 224,952 hours of physical activity assessments) were analyzed. The mean ± SD age for patients with RA (n = 82) was 48.9 ± 12.6 years and was 41.2 ± 10.3 years for those with axial SpA (n = 73). The mean ± SD disease duration was 10.5 ± 8.8 years for patients with RA and 10.8 ± 9.1 years for those with axial SpA. Fourteen patients with RA (17.1%) and 41 patients with axial SpA (56.2%) were male. Disease was well-controlled (Disease Activity Score in 28 joints mean ± SD 2.2 ± 1.2; Bath Ankylosing Spondylitis Disease Activity Index score mean ± SD 3.1 ± 2.0), but flares were frequent (22.7% of all weekly assessments). The model generated by machine learning performed well against patient-reported flares (mean sensitivity 96% [95% confidence interval (95% CI) 94–97%], mean specificity 97% [95% CI 96–97%], mean positive predictive value 91% [95% CI 88–96%], and negative predictive value 99% [95% CI 98–100%]). Sensitivity analyses were confirmatory.

Conclusion. Although these pilot findings will have to be confirmed, the correct detection of flares by machine-learning processing of activity tracker data provides a framework for future studies of remote-control monitoring of disease activity, with great precision and minimal patient burden.

INTRODUCTION

The evolution of rheumatoid arthritis (RA) and axial spondyloarthritis (SpA) is marked by alternated periods of flares and stable disease activity (1–7). Flares are important for patients because they contribute to the unpredictability of the disease (8,9). Furthermore, due to the link between inflammation and structural degradation, flares are important in order to assess

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SIGNIFICANCE & INNOVATIONS

- Patient-reported flares, as measured by activity trackers, were associated with less physical activity in patients with rheumatoid arthritis (RA) and axial spondyloarthritis (SpA), confirming the objective consequences of patient-reported flares.
- Using machine-learning processing, changes in physical activity patterns were found to be associated with patient-reported flares based on physical activity data, with a sensitivity of 96% and a specificity of 97%.
- Given the relatively small sample size and the lack of a separate validation population, these findings should be further confirmed.
- Connecting activity trackers with machine-learning processing may be an opportunity for continuous indication of disease activity in RA and axial SpA.

for disease management (10–12). There is growing interest in both RA and axial SpA to characterize the reality behind the concept of patient-reported flares (2,4,13–16). Flares appear to have objective consequences on daily life and in particular on physical activity (17,18). Physical activity, including daily walking as well as aerobic exercise, may be objectively and longitudinally assessed using connected activity trackers. These devices allow interactive feedback of physical activity and the visualization of activity patterns, according to duration, intensity, and frequency of physical activity (19).

The ActConnect study was a 3-month longitudinal study of patients with either RA or axial SpA, where patient-reported flares were assessed weekly and physical activity was collected continuously using a connected activity tracker (20,21). The data were analyzed using standard statistics, and we found that flares were related to a moderate decrease in physical activity. During weeks with flares, there was a relative decrease in physical activity of 12–21% (i.e., an absolute decrease of 836–1,462 steps/day) (21). This study thus objectively confirmed the functional impact of patient-reported flares; however, at the group level and on amalgamated data, the link between flares and physical activity was weak and it was not possible to determine modifications in physical activity patterns, which could adequately reflect patient-reported flares (21).

Machine learning allows multiple analyses of large data sets and make the best use of the available data, with minimal data amalgamation (22). Although machine-learning methods have not been used frequently in rheumatology to date (23), their usefulness in other medical fields has been clearly shown (24–29). The specificity of such analyses is that the data is fed into a machine-learning operations tool, which will build, by itself, classification models that are generated most often using an "averaging" of numerous naive Bayesian classifications. The objective of this reanalysis of the ActConnect data set was to assess longitudinally the association between patient-reported flares and activity-tracker–provided continuous flows of steps per minute, using machine learning.

PATIENTS AND METHODS

Study design and patients. As previously reported, the ActConnect study was a prospective, multicenter, pragmatic, longitudinal observational study in France in 2016 (20,21). Briefly, patients had definite clinician-confirmed RA or axial SpA and owned a smartphone or tablet that was compatible with the connected activity tracker and had internet access. There were no inclusion criteria related to disease activity or to physical activity. Ethical approval was obtained from the institutional review board (CPP Ile de France VI) and the human research ethics committee (CCTIRS, number 16.057bis).

Data collection. *General and patient-reported data*. Patient demographics and disease characteristics were collected at baseline, including ongoing pharmacologic treatment. Where available, in RA patients, the status for rheumatoid factor (RF) and for anti–cyclic citrullinated peptide (anti-CCP), the presence of radiographic erosions and the Disease Activity Score 28 (DAS28) at inclusion were recorded (30). In patients with axial SpA, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI, range 0–10) (31,32), HLA–B27 status, history of peripheral and extraarticular symptoms, and the presence of sacroiliitis (according to medical files) on radiograph and/or magnetic resonance imaging (MRI) were recorded. Physical function was assessed by the modified Health Assessment Questionnaire (33). Comorbidities were collected using the Functional Comorbidity Index, which ranges from 0 to 18 (0 = no comorbidity, however the minimal score was 1 in the present study, because of the rheumatic disease) (34).

Flares were assessed from the patient perspective with the question that has been used in previous studies, "has your disease flared up since the last assessment?" (2). The categorical responses were no flare, flare lasting 1–3 days (short flare), or flare lasting >3 days (persistent flare). Flares were completed online from home each week during the 3-month period, following a text message reminder (21).

Physical activity data. Each participant received an activity tracker (the Withings Activité Pop watch) (35) and was instructed to wear it every day for 3 months. The Withings tracker records the number of steps per minute. Data were collected for the 90 consecutive days from the first Monday following activation of the device. No instruction about physical activity was given to the participants, however patients could visualize their physical activity on their smartphones (21).

Statistical analysis. Patients were analyzed if they had at least 1 complete time point. This time point included having available physical activity data over the 7 days preceding a flare assessment.

Data preparation. Weeks that contained >12 consecutive hours of missing or blank data were removed from the data set (leading to 10,559 days of a potential total 13,950 days that could be analyzed). The remaining short-duration missing activity data (mostly due to nonwear periods and at night) were not imputed (and were not analyzed in the algorithm). For each patient, the mean and variance of number of steps for each aggregation interval with no flare were bootstrapped. The data for each patient were then normalized using these values, leading to a distribution of steps during a given aggregation interval with no flare with a mean of 0 and a variance of 1. Data preparation was performed on R software, version 3.6.1 (36). The normalization was performed several times, since data were normalized for each aggregation interval.

Physical activity data aggregation. The ActConnect study collected physical activity information (steps) at the minute level for 3 months, leading to 13.5 million information points. Although very limited data aggregation is necessary for machine-learning software using Bayesian analyses, several levels of aggregation (24, 12, 4, and 1 hour) were tested, resulting in 4 distinct models.

Longitudinal relationship between physical activity and disease activity. The goal of the analysis was to classify each week as flare/no flare, based on the weekly physical activity data. The models were built using only the normalized steps and the patient-reported flare. Steps were analyzed both for deviation with respect to the reference week and for the importance of the time intervals with deviations. No other covariate was used. Of note, the models were developed at the population level not at the patient level (but patient data were individually normalized). For all of the analyses, multiclass selective naïve Bayesian methods were performed using Khiops software (Orange Labs) (37–39). Naive Bayes classifiers are among the standard classification methods used in machine learning and are based on a direct application of Bayes theorem (26,40–42). Models corresponding to the 4 distinct aggregation intervals were built for 10 training/validation sets, and analyses were initially performed for the 3 levels of flare (no flare, flare ≤ 3 days, flare > 3 days), but this did not perform well (see Supplementary Figures 1 and 2, available on the *Arthritis Care &* Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23768/abstract). Thus, the binary variable (flare/no flare) was used. Then, the performance of the models was evaluated using patient-reported flares (assessed weekly) as gold standard and sensitivity and specificity, as well as positive and negative predictive values were assessed. Furthermore, in order to assess agreement, Cohen's kappa was calculated (43).

Training and validation sets. In order to evaluate the performance of a classifier (and of any machine-learning model in general), it is designed using a set of data (the training set), and its performance is evaluated using the classification of a distinct set of data (the validation set). To select a model (in the present study, the aggregation interval) and to take into account its mean performance and the variation of the performance (i.e., the bias-variance tradeoff (40), 10 different training/validation sets were built. The generation of the training/validation set was set at the weekly observation level. On each of the 10 sets, the analyses were then performed for each aggregation interval. Each training/validation set was constructed using a random stratified 70% of the total weekly data set (i.e., 936 weeks) as the training set, and the 30% remaining data as the validation set (403 weeks). Each training/validation set used all of the available data (and the sets were not at all mutually exclusive). Thus, the data sets overlapped and on average, a given week was counted in 3 different validation sets. Data were stratified on flare/no flare. Performances were calculated for each set and on the pooled validation sets. Of note, in the pooled analysis, the data for each week were used several times because the training/validation sets overlapped; thus, these results should be considered as indicative only.

Illustration of results. The variations of the main statistical characteristics of the classifications in relation with the aggregation interval were reported for 2 training/validation examples. In order to illustrate changes for a single patient, a patient correctly classified as flare/no flare was chosen based on having age, number of flares, and overall physical activity close to the population mean. For this patient, mean physical

Table 1. Characteristics of 82 RA and 73 axial SpA patients*

	RA (n = 82)	Axial SpA (n = 73)
Men	14 (17.1)	41 (56.2)
Age, mean ± SD years	48.9 ± 12.6	41.2 ± 10.3
BMI, mean ± SD kg/m²	24.7 ± 4.5	24.6 ± 4.6
Disease duration, mean ± SD years	10.5 ± 8.8	10.8 ± 9.1
Work status, employed	61 (74.4)	61 (83.6)
Manual work	3 (4.9)	2 (3.3)
Intellectual work	58 (95.1)	62 (96.7)
Education >high school	69 (84.1)	66 (90.4)
Functional Comorbidity Index score (range 1–18), mean ± SD	1.6 ± 0.9	1.4 ± 0.9
Modified HAQ score (range 0–3), mean ± SD	0.23 ± 0.39	0.30 ± 0.33
Ongoing treatment		
NSAIDs	17 (20.7)	44 (60.3)
Glucocorticoids	19 (23.2)	1 (1.4)
Conventional synthetic DMARDs	76 (92.7)	17 (23.3)
Methotrexate	66 (86.8)	13 (76.5)
Biologic therapy	37 (45.1)	44 (60.3)
Anti-TNF	23 (62.2)	44 (100)
No change in arthritis drugs in the 3 months prior to inclusion	59 (72.0)	47 (64.4)

* Values are the number (%) of patients unless indicated otherwise. Percentages are calculated on all complete data. RA = rheumatoid arthritis; SpA = spondyloarthritis, BMI = body mass index; HAQ = Health Assessment Questionnaire (27); NSAIDs = nonsteroidal anti-inflammatory drugs; DMARDs = disease-modifying antirheumatic drugs; TNF = tumor necrosis factor.

Table 2. Association between physical activity and self-reported flares*

Validation set	Kappa (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
1	0.88 (0.83–0.94)	0.96 (0.91–0.99)	0.96 (0.94–0.98)	0.87 (0.81–0.94)	0.99 (0.98–1.0)
2	0.89 (0.84–0.94)	0.98 (0.95–1.00)	0.95 (0.93–0.98)	0.87 (0.80–0.93)	0.99 (0.98–1.0)
3	0.91 (0.86–0.96)	0.95 (0.90–0.99)	0.97 (0.95–0.99)	0.91 (0.86–0.98)	0.98 (0.97–1.0)
4	0.88 (0.82–0.93)	0.93 (0.88–0.98)	0.96 (0.94–0.98)	0.88 (0.82–0.95)	0.98 (0.97–1.0)
5	0.92 (0.87–0.96)	0.98 (0.95–1.00)	0.97 (0.95–0.99)	0.90 (0.85–0.96)	0.99 (0.98–1.0)
6	0.88 (0.82–0.94)	0.90 (0.84–0.96)	0.97 (0.96–0.99)	0.91 (0.86–0.97)	0.97 (0.96–0.99)
7	0.92 (0.88–0.96)	0.97 (0.93–1.00)	0.97 (0.96–0.99)	0.92 (0.87–0.98)	0.99 (0.98–1.0)
8	0.90 (0.85–0.95)	0.96 (0.91–0.99)	0.97 (0.95–0.99)	0.89 (0.84–0.96)	0.99 (0.97–1.0)
9	0.92 (0.88–0.97)	0.96 (0.90–0.99)	0.98 (0.96–0.99)	0.93 (0.87–0.98)	0.99 (0.98–1.0)
10	0.89 (0.85–0.95)	0.99 (0.96–1.00)	0.95 (0.93–0.98)	0.89 (0.88–0.91)	0.99 (0.98–0.99)
Pooled results	0.90 (0.89–0.92)	0.96 (0.94–0.97)	0.97 (0.96–0.97)	0.89 (0.88–0.91)	0.99 (0.98–1.00)

* Values are the association of Kappa statistics, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the model against self-reported flares as gold standard, for the 10 validation sets (403 weekly data) and for the aggregation of 1 hour. 95% CI = 95% confidence interval.

activity for weeks without flare and for weeks with flare was graphically presented.

In the results of the modeling phase, Khiops provides an evaluation of the importance (the weight) of each explanatory variable in the model. Using these weights, a time line map of "significant" moments of activity during the week was created. This time line shows the weight of the moments of the days used by the algorithm to perform the score calculation for the classification. With the aggregation being hourly, these weights characterize the importance of each hour of each day of the week in the resulting flare classification.

Sensitivity analyses. All analyses, from the data preparation to the model building, were performed twice on Khiops, independently by 2 statisticians. The analyses were also performed again using another machine-learning method (random forests classifiers) (44) on R software (for the code, see the Supplementary Appendix, available on the *Arthritis Care &* Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23768/abstract).

RESULTS

Patients. Of the 170 patients included in the study, 155 (82 with RA and 73 with axial SpA) were analyzed. This corresponds to 1,339 weekly flare assessments and 224,952 hours physical activity assessment time frames. For physical activity provided at the minute, the data set contained close to 13.5 million activity points.

Of the 155 patients, the mean ± SD age for those with RA (n = 82) was 48.9 ± 12.6 years, the mean ± SD disease duration was 10.5 ± 8.8 years, and 14 (17.1%) were male. For patients with axial SpA (n = 73), the mean ± SD age was 41.2 ± 10.3 years, the mean ± SD disease duration was 10.8 ± 9.1 years, and 41 (56.2%) were male (Table 1). Disease was well-controlled (mean ± SD DAS28 score 2.2 ± 1.2; mean ± SD BASDAI score 3.1 ± 2.0). Forty-eight of the 82 patients with RA (58.5%) had radiographic erosions, and 63 of 79 (79.7%) had positive RF and/or anti-CCP. Among patients with axial SpA, 44 of 73 (60.3%) had experienced extraarticular symptoms, 42 of 70 (60.0%) had past or present peripheral symptoms, 50 of 65 (76.9%) carried HLA–B27, and 54 of 64 (84.4%) had radiographic and/or sacroiliitis on MRI. Overall, 81 of 155 patients (52.3%) were receiving biologics and 106 of 155 (68.4%) were stable in terms of treatment throughout the 3 months prior to inclusion (Table 1).

Among the 155 patients, 112 (72.2%) reported having at least 1 flare during the 3-month follow-up period. Patients reported having experienced a flare on an average of 22.7% of the questionnaires. For all of the assessments, the mean ± SD steps per day was 6,838 ± 4,033 steps, with a median of 6,265 (interquartile range 3,843–9,144; range 0–38,212) steps per day.

Detection of flares. The Khiops program detected correctly both flares and absence of flare (mean sensitivity 95.7% [95% confidence interval (95% CI) 94.4–97.0], mean specificity 96.7% [95% CI 96.0–97.3]), with high predictive values as well (Tables 2 and 3).

Performance increased as the aggregation interval decreased; the best performance in terms of proportion of correctly/incorrectly classified instances was evidenced for 1-hour intervals (Table 2). The increase in the agreement

Table 3. Detection of patient-reported flares by physical activity: pooled results*

	No patient-reported flare	Patient-reported flare
No flare	3,006 (74.6)	40 (1.0)
Flare	104 (2.6)	880 (21.8)

* Values are the number (%) of patient-reported flares during 4,030 weeks. Presence or absence of flare according to Khiops. Results presented are the sum over the 10 training/validation sets of the confusion matrices with 1-hour aggregation (4,030 weeks containing 3,110 weeks patient-reported as no-flare and 920 reported as flare). Each week's data is used several times since the training/validation sets overlapped; thus, these results should be considered indicative only.

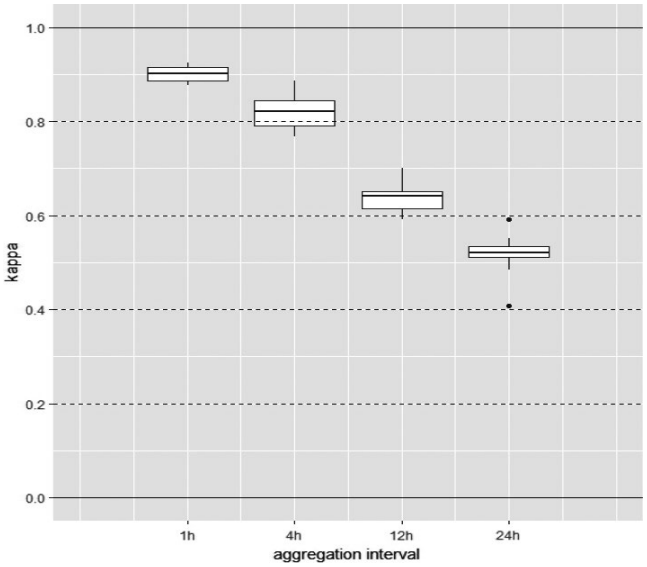

Figure 1. Data are shown as box plots. Box plots represent the distributions of the kappa statistics (2-levels classification) observed on the different validation sets. Agreement between patient-reported flares and predicted flares for different time-aggregation intervals is shown. Scale for kappa values: very bad = <0, weak = 0–0.2, decent = 0.2–0.4, moderate = 0.4–0.6, substantial = 0.6–0.8, almost perfect = 0.8–1, perfect = 1.

between flares and predicted flares was also reflected in the substantial increase of the Kappa coefficient when the size of the aggregation intervals decreased (Figure 1). The variations of the main statistical characteristics of the classifications in relation with the aggregation interval are reported for 2 training/validation examples in Supplementary Table 3 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23768/abstract).

Illustration of results. Figure 2 shows mean physical activity throughout weeks with flares versus those without flares, for a random patient with RA. There were considerable fluctuations overall and variations in patterns. The model generated by the machine established "significant" moments of activity during the week that were more strongly related to flares (Figure 3). It appeared weekday mornings were not highly "significant" while the end of the afternoons as well as Saturday afternoons appeared strongly associated with flare detection. When in flare, these might be moments when patients can rest more. In other words, when physical activity is different (from previous weeks) at a "significant" time point (e.g., Saturday afternoons), this is a flare state change indicator for the machine. Reversely, a physical activity change in a "nonsignificant" time point in the week, would be less contributive to flare state detection.

Sensitivity analyses. The second round of analyses and the analyses using another statistical technique on R software, were confirmatory with >95% sensitivities and specificities (see Supplementary Table 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23768/abstract).

DISCUSSION

The present study demonstrated that patient-reported flares were strongly linked to physical activity and that machine-learning processing of patient-level physical activity can be used to detect flares with great accuracy. Furthermore, this study also demonstrated the usefulness of machine learning applied to large rheumatology data sets.

This study has strengths and weaknesses. First, the sample size in the present study was only moderate, and the relatively low number of flares may lead to power issues. However, the data set for physical activity time points was very large. Furthermore, patients had either RA or axial SpA and, as the analyses were pooled, this study did not allow interpretation of possible differences between these 2 diseases. Second, this was a French, Paris-based study, thus extrapolation to other cultures and social habits merits discussion given the role of cultural background in perception and expression of patient-reported outcomes (45). The strong link found between modifications in physical activity and patient-reported flares should not be directly interpreted as demonstrating causality. Confounding factors may have intervened. Indeed, factors other than flares that may impact physical activity (e.g., illness, mood, weather) were not collected, and it is currently uncertain how machine-learning methods that are solely based on physical activity can distinguish between activity variation caused by disease flare and by other causes (although the model performances were remarkable in the present study). A strength of the present study is that the analyses were run several times on several subsets of the data; however, the subsets were selected for frequency of flares, which could introduce a bias if the obtained models were used on another data set because the pro-

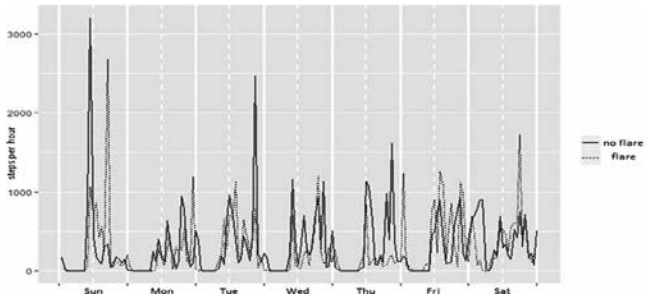

Figure 2. Example of activity for weeks with versus weeks without flare, for a randomly chosen patient for all weeks of activity (mean values are for weeks with or without flares). The x-axis represents hours in 1 week (starting Sunday at 1:00 AM), and the y-axis represents physical activity in steps per hour. Graphs show the mean steps per hour in weeks with flare (dotted line), and the mean steps per hour in weeks without flare (solid line).

Figure 3. Importance (weight) of the various time intervals throughout a week to predict flares. The moments of the week (and the day) are weighted by the algorithm to perform the classification (i.e., 1 instance of training/validation sets). The x-axis represents the days of the week, split in 1-hour intervals (dotted line divides AM and PM for each day). The darker the color, the more important the time interval in the classification.

portions of week with flares may be different. Night movements and the associated impact of flares on sleep could not be analyzed in the present study. Another point refers to the definition of flares, which were classified as "short" or "long," but these definitions have not been validated. Finally, the obtained classifications are not easy to interpret since the machine chooses its criteria to build models without human guidance.

Flares significantly impacted physical activity. The results of our study confirm that patient-reported flares have an observable functional impact. The reality of the concept of flares has been much discussed (1–7,16). In the present study, changes in physical activity patterns allowed for accurate detection of patient-reported flares, particularly short flares rather than longer (>3 day) flares. This is most likely because shorter flares were much more frequent, although their clinical relevance is not well-established. The classification model generated by the machine allowed accurate detection of both periods of flare and periods of absence of flare. Interestingly, although flares were reported weekly (thus with moderate granularity), shorter intervals of aggregation for the physical activity data led to better prediction of flares rather than longer intervals. The reasoning for this includes that flares may be more represented by the "way" the patients move during the day (implementing their own coping strategy) than the total number of steps during the day. Indeed, the model generated by the machine established "significant" moments of activity during the week, which were markers of flares. These were patient-dependent, but we observed that they were often (but not only) the "less stressful" moments, where patients can slow down or postpone their physical activity (e.g., in the evenings or on Saturdays). In contrast, weekday mornings seemed less "significant" to detect flares. This indicates flares of moderate severity may not lead to huge changes in physical activity such as being bedridden, but rather to the patient self-pacing his/her efforts (6,16). We hypothesize that patients may force themselves to deal with everyday activities and work, even when in flare, and to slow down mainly when being in flare is not too disruptive to their lives. This happens particularly in cases of moderate flares that do not necessitate medical intervention, as was the case in the present study. It would be interesting to explore the long-term consequences of such moderate flares (12).

The present reanalysis was centered around machine learning. In this study, flares were collected from the patient regularly, once a week, and cross-tabulated with objective measurements of physical activity using a connected activity tracker. The data set was first analyzed using traditional statistical methods for longitudinal data sets, and a significant but moderate decrease in physical activity was noted concomitantly to patient-reported flares. Furthermore, it was not possible to determine specific cutoffs of decrease in activity that would allow to predict a flare (for example, a decrease of 20% of steps or of 500 steps per day) (21). Interestingly, in the present reanalysis, when applying different, innovative statistics with machine learning, it was possible to find strong associations with excellent predictive capacities between steps performed and patient-reported flares. This may be in part due to the capacity of the machine to compare the patient to himself.

Machine-learning statistics are complex procedures. Typically, the machine will use a data set to develop a model, then a validation phase is necessary (46). In the present study, this 2-phase approach was applied; but the lack of a separate validation group is a weakness. Indeed, the findings of the present study should be seen as "pilot findings," and it will be important to reproduce these findings in another cohort. Several techniques have been proposed for machine learning. The random forests method performs well on data sets of reasonable size (44). However, it is a lengthy process and is hard to industrialize with very large data sets. The other main method, which was applied in the present study, relies on Bayesian statistics. Both methods appear to perform similarly (47,48). Although Bayesian modeling performed extremely well here, as in all machine-learning processes, some mystery remains, since the exact decision mechanism of the machine when predicting flares is internal and implicit rather than explicit, making the interpretation difficult. Khiops is based on sophisticated naive Bayes method (using both features selection and models averaging) and was initially developed as an easy-to-use and efficient marketing tool (37–39). Khiops is used in many domains where classification or clustering is the subject and where massive data need to be analyzed. This study is a pilot for the use of Khiops program on health care data.

Connected devices and Internet of things bring a continuous flow of data that cannot be handled with traditional statistical tools without important complexity reduction and data aggregation. Through the use of machine learning in the present study, data could be analyzed with minimal data aggregation. However, the comparison of models for different time aggregations was necessary. The fact that smaller time frames performed better probably reflects the fact that, for flare characterization, the way patients are moving during the day is more indicative than their total activity throughout 1 day.

Data preparation was an essential (and time-consuming) step in the present analyses. Preliminary analyses confirmed that patterns of physical activity of 2 distinct patients may be quite different. A given physical activity for a patient during a week with flare may be similar to the physical activity of another patient during a week with no flare (data not shown). The normalization of steps led to all patients becoming comparable during weeks without flare and, from there, classification models were possible. It is probable that such normalization would allow analyses in different datasets with different characteristics, but this remains to be proven by further studies. Notably, measurement error (variability) in the device was not taken into account, since trends over time were studied here.

Despite making preliminary choices to limit periods of taking the device off or of nonwear, the selection of a device that does not require plugging in to a power source for months or removing to wash, nonwear periods were detected. This means that we lost some information due to nonwear. Furthermore, the use of overlapping subsets of patients and the lack of an independent testing set is an important issue which means that overfitting is a possibility. Future studies are needed. Overall, machine-learning technologies are still a growing field and require high-level technology but also relevant human expertise. These constraints need to be taken into account when planning future studies.

The correct detection of flares by the activity tracker and adapted statistics is of great interest. Indeed, activity trackers have great accuracy and lead to minimal patient burden compared to online questionnaires or in-person visits. These results open perspectives to integrate connected devices in the future of monitoring of patients with chronic arthritis, in clinical research as well as in clinical practice. It is possible to imagine mixed-methods monitoring, with continuous data collection via activity trackers and physical assessments in person in case of frequent flares, for example. Of course, the cost of the wearable devices needs to be taken into account. In a context of treating to a target, such continuous assessments (passively for the patient) may be of capital importance as the health care organization could benefit from more targeted outpatient visits (i.e., in case of flares). Finally, machine-learning methods may contribute to a more precise quantification of existing links or to the identification of new links in rheumatologic data sets.

In conclusion, this pilot application of machine learning to physical activity assessment will open the way to future studies. The design of operational monitoring systems based on machine-learning models would, however, require careful validation on much larger data sets and the present analyses should be considered as a proof of concept of such an approach.

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. Gossec 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. Gossec, Jacquemin, Fautrel, Servy.

Acquisition of data. Gossec, Jacquemin, Molto, Sellam, Foltz, Gandjbakhch, Hudry, Mitrovic, Fautrel.

Analysis and interpretation of data. Gossec, Guyard, Leroy, Lafargue, Seiler, Jacquemin, Servy.

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Mobile Phone Text Messages and Effect on Treatment Adherence in Patients Taking Methotrexate for Rheumatoid Arthritis: A Randomized Pilot Study

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Objective. To assess the impact of weekly text messages on adherence in patients taking methotrexate (MTX) for rheumatoid arthritis (RA).

Methods. This prospective, randomized pilot, single-site study included patients with RA stabilized using MTX alone or combined with biologics. Participants were randomized to 3 interventions: a standard consultation (controls), a 15-minute pharmacist-led counseling session, or the receipt of text message reminders. The change over time in the Compliance Questionnaire Rheumatology (CQR-19) score between baseline and 6 months was defined as the primary outcome for adherence. Multivariable analyses and final adherence (as a composite outcome of the CQR-19 score, the Girerd score, and the medication possession ratio) were probed in sensitivity tests. Rheumatologic scales, inflammation, and patient satisfaction were also analyzed.

Results. A total of 96 patients (mean ± SD Disease Activity Score in 28 joints 2.42 ± 1.03) were monitored. The change over time in the CQR-19 score was significantly higher in the text message group (mean ± SD 3.32 ± 5.66; $P = 0.02$) than in the control group (mean ± SD 0.22 ± 6.56) and the pharmacist-led counseling group (mean ± SD –0.14 ± 7.56). Multivariable logistic regression showed that text messages remained associated with an increase in the CQR-19 score, independently of the baseline CQR-19 score (odds ratio 3.63 [95% confidence interval 1.26–10.49]; $P = 0.017$). In the text message group, the increase in the CQR-19 score was correlated with the Health Assessment Questionnaire score ($r = –0.405$, $P = 0.021$), and patient satisfaction was significantly higher ($P < 0.01$) than in the control group.

Conclusion. Our results showed evidence of a positive impact of text messages on adherence to MTX treatment for RA. The clinical benefit and the ideal target patient remain to be determined.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common form of chronic, inflammatory rheumatologic disease. Although the introduction of biologics has revolutionized the management of RA, the first-line treatment for this disease is still methotrexate (MTX) (1). Adherence (the level of consistency between the patient's behavior toward treatment and the medical prescription) is known to influence the efficacy of MTX in RA (2,3).

A recent meta-analysis showed that nonadherence in RA is responsible for a mean increase of 0.48 in the Disease Activity Score in 28 joints (DAS28), and a mean increase of 1.29 in the number of painful joints (4). In addition to the loss of opportunity for the patient to improve, poor adherence has a health economic impact on society via a combination of direct costs (related to waste) and indirect costs (related to poor disease control) (5). The higher the clinical impact (as evaluated by the Health Assessment Questionnaire [HAQ] score), the greater the impact on the patient's professional activity. Estimates are that 23–45% of patients with RA will face work disability within 10 years of diagnosis (6).

In 2003, the World Health Organization estimated that only 50% of patients with a chronic disease were adherent (5). In RA,

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- Approximately 40% of patients taking methotrexate for rheumatoid arthritis had suboptimal adherence to methotrexate, when evaluated with a combination of metrics.
- Text messages reminding patients to take methotrexate were well accepted and significantly increased patients' adherence (as evaluated by the Compliance Questionnaire Rheumatology), independently of potential covariates, including baseline adherence and clinical, sociodemographic, and therapeutic characteristics.
- A single pharmacist-led counseling session was not enough to note a difference in adherence to methotrexate.
- Patients with poor adherence had worse clinical scores (e.g., Disease Activity Score in 28 joints); larger cohorts are required to clinically validate the impact of text message reminders.

the estimated percentage of patients with good adherence to MTX ranges from 59% to 100%, depending on the evaluation method used (7). In a pooled analysis of 13,358 patients in published MTX adherence studies, this percentage was 75.6% (7–9). Studies based on electronic medication event monitoring systems gave similar results (10). MTX may be associated with a risk of poor treatment adherence in view of the drug's side effects and the occasional lack of symptoms (and thus a lack of perceived need to treat) in patients with chronic RA. In line with previous studies of patients with RA (11), the most common reasons for nonadherence to MTX are unintentional forgetfulness (poor pill-taking routines, memory lapses, etc.) (33%), the lack of a perceived need for treatment (24%), and worries about adverse effects (24%) (12). In addition to nonadherence, the 1-year nonpersistence rate for MTX is high (50%) (13).

The strong association between poor adherence in patients with RA and worsening clinical scores suggests that early interventions to improve adherence to MTX may slow joint erosion and reduce the subsequent need for more expensive immunosuppressive drugs (2,14). Various post-prescription methods have been suggested to improve adherence. For example, pharmaceutical programs provide the patient with additional education on his or her disease and treatment, including the advantages of a regular, continuous drug treatment in chronic disease (15,16). The use of iterative text message (TM) reminders about taking drugs (sent to the patient's mobile phone by short message service) is a recently initiated method for improving the management of chronic disease (17). This approach has given positive results in the treatment of HIV (18), hypertension (19), and hypercholesterolemia (20). Compared with standard care, the receipt of TM reminders has produced a 10% absolute increase in the proportion of patients with good adherence in these studies (17–20). A recent meta-analysis of 2,742 patients with chronic pathologies confirmed that the iterative use of TM reminders doubled the odds ratio (OR) for adherence and resulted in an absolute increase of 17.8% in the adherence rate (21). We therefore hypothesized that mobile phone TM reminders might be an effective method of helping patients remember to take their weekly dose of MTX.

Thus, we studied the impact on MTX adherence of TM reminders following a standard medical consultation, which was supplemented with a pharmacist-led counseling session for some patients. We also measured the main clinical and laboratory parameters for RA and the patient's satisfaction with his or her participation in the study.

PATIENTS AND METHODS

Study design. This was a 6-month, pilot, interventional, single-center, open, prospective, randomized, controlled study in which patients were divided into 3 parallel groups (Figure 1): standard care alone (the control group), standard care associated with specific pharmacist counseling (PC) about MTX in RA (the PC group), and standard care plus a weekly TM reminder (the TM group). The study protocol was approved by the local independent ethics committee (Comité de Protection des Personnes Nord-Ouest II, Amiens, France; reference: 2016/40) and the French National Agency for Medicines and Health Product Safety (reference 2016062900051).

The main inclusion criteria were age >18 years, consultation in our rheumatology department for RA, treatment with MTX (alone or combined), a drug regimen that had not been modified for at least 3 months, provision of informed consent, possession of a mobile phone, sufficient proficiency in French, and social security coverage. The main exclusion criteria were loss of personal responsibility for administering treatments (e.g., hospitalization or home care), changes in drug dose, and medical discontinuation of MTX treatment during the study.

Study protocol. The baseline visit consisted of a consultation with a rheumatologist. Each patient's clinical and sociodemographic characteristics were recorded, including age, sex, education level, occupation, marital status, medical history, time since diagnosis of RA, total number of prescribed medications, and details of the MTX prescription (duration of treatment, day of administration, dose level, pharmaceutical formulation, and whether or not MTX was combined with a biologic). Clinical scores for RA and adherence scores were also evaluated.

During the 4-month inclusion period, the patients were randomized to receive group-specific care (computer-generated block size of 50 for each arm). In the control group, patients were given standard advice by their rheumatologist during the baseline consultation and by their usual pharmacist when MTX was dispensed. After the initial consultation, patients in the PC group additionally received a 15-minute counseling session led

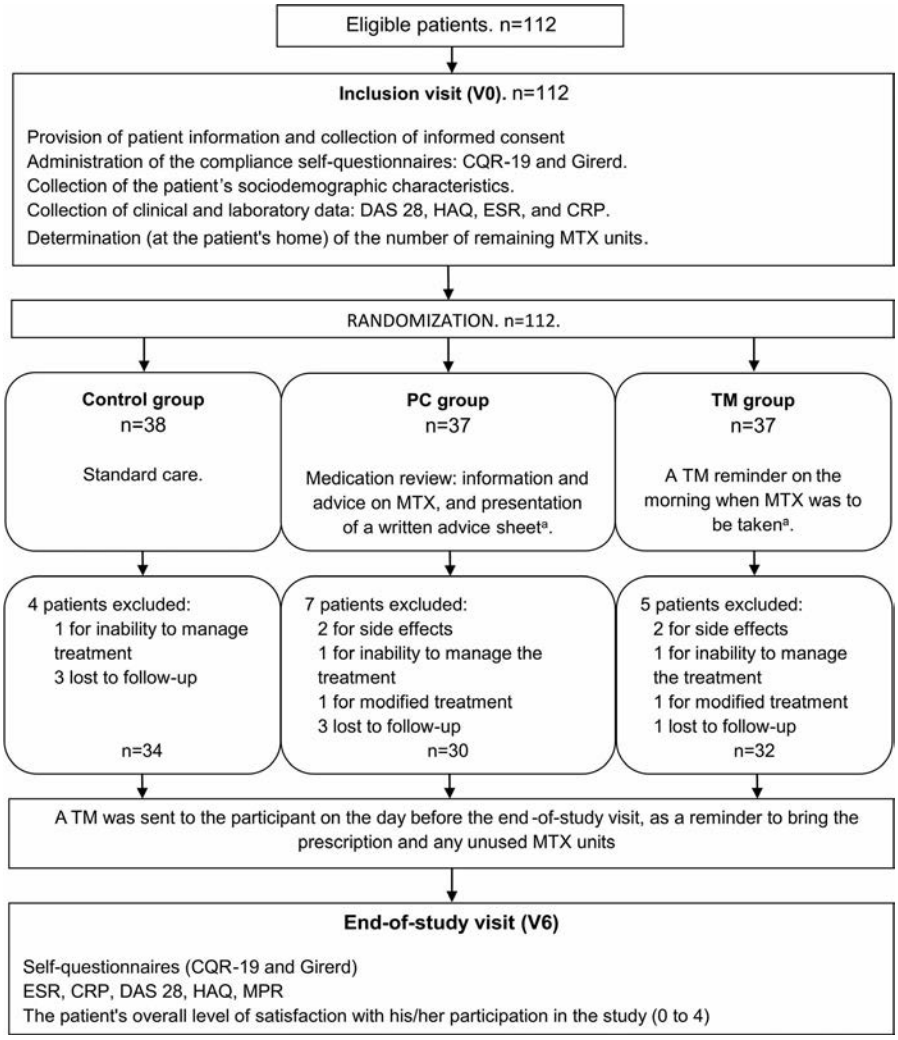

Figure 1. Flow chart of the study. The study included all 112 eligible patients, randomized into 3 groups (ratio of 1:1:1): standard care (the control group), a 15-minute pharmacist-led counseling session (pharmacist counseling [PC] group), or weekly text reminders (text message [TM] group). A total of 16 patients met the exclusion criteria, with no significant differences between the groups (P = 0.56, Fisher's exact test). a = text message and the advice sheet are shown in Supplementary Appendix 1, available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23750/abstract. CQR-19 = Compliance Questionnaire Rheumatology; DAS 28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; MTX = methotrexate; MPR = medication possession ratio.

by a hospital pharmacist (see Supplementary Appendix 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23750/abstract). The session focused on the administration of MTX, its adverse effects and the need for treatment adherence to gain the full benefit of MTX in the treatment of RA. A standardized advice sheet was given to the patient during this session (see Supplementary Appendix 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23750/abstract). In the TM group, patients had a standard consultation but were additionally sent a weekly, standardized TM on the morning when MTX was to be taken (see Supplementary Appendix 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23750/abstract). After mean ± SD 6 ± 1 months of follow-up during a second consultation, clinical parameters and adherence were reevaluated. Each patient also rated their satisfaction with therapeutic management regarding MTX on a 4-point Likert scale.

Measurement of clinical scores and laboratory parameters. Clinical RA scores (DAS28 [22] and HAQ [23]) and laboratory parameters (erythrocyte sedimentation rate [ESR] and serum C-reactive protein [CRP] level) were measured to evaluate disease activity. Automated assays were used: the ESR was assessed optically (VES-MATIC Cube 30, Diesse), and serum CRP level was assessed using an immunoturbidimetric technique (ADVIA, Siemens Healthcare Diagnostics).

The primary criterion for adherence. The study's primary outcome was the change over time in the Compliance Questionnaire Rheumatology (CQR-19) score, a self-questionnaire comprising a subjective measure of adherence (score from 0 to 100). We selected the CQR-19 a priori because it was developed specifically for rheumatology and shows high specificity (95%) and sensitivity (62%) (24). This choice was also justified by the numerical nature of the score (offering greater statistical power than dichotomous qualitative variables) and the ability to measure the change over time in the score. The CQR-19 was slightly modified to focus solely on MTX adherence. The detailed questionnaire is shown in Supplementary Appendix 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23750/abstract.

Secondary criteria for adherence. To complement the psychometric evaluation of adherence (the CQR-19), we used a second self-questionnaire to calculate the change over time in the Girerd score (validated in hypertension and used in general practice in the French health care system) (25), and an objective measure of final adherence by determining the medication possession ratio (MPR), based on the number of MTX prescription renewals and the number of MTX units in the patient's possession at each visit (26). The Girerd questionnaire was modified to focus on MTX (see Supplementary Appendix 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23750/abstract), and the MPR was calculated only for MTX. Since a combination of measurements is recommended to assess the different facets of therapeutic adherence (27), a composite adherence measure (CQR-19 score >80, Girerd score ≤1, and MPR score >80) was probed in a sensitivity analysis.

Statistical analysis. We selected a minimum sample size of 30 patients per group. With an alpha risk of 0.025 and a power of 90%, this sample size allowed a post hoc Mann-Whitney test to detect the ability of PC or TM to induce a greater increase in the CQR-19 score than the control method, with an OR of 3. Demographic, laboratory, and clinical variables were given as the mean ± SD. Qualitative variables were given as the number (frequency). Analysis of variance, Kruskal-Wallis, Mann-Whitney, or Wilcoxon's tests were applied for quantitative variables, whereas the chi-square test or Fisher's exact test were applied for qualitative variables.

Pearson's correlation coefficients were calculated for the different measures of adherence and for the change over time in the CQR-19 score versus patient characteristics. In a sensitivity analysis, the variables that were significantly correlated were included in a multivariable logistic regression model, to check the independence of their association with an increase in adherence (as evaluated by the CQR-19 score).

All statistical analyses were carried out on a per protocol basis using SPSS software, version 13.0, and GraphPad Prism software, version 5.0. The threshold for statistical significance was set at P less than 0.05 (except in the post-test comparing each method with the control, when it was set to P less than 0.025 in order to apply Bonferroni's correction).

RESULTS

Characteristics of the study population. A total of 112 patients with RA were included in the study. Patients were randomized into each group as follows: control (n = 38), PC (n = 37), and TM (n = 37) (Figure 1). Sixteen patients met the exclusion criteria because measuring their adherence at the end of the study was impossible. Seven stopped their rheumatologist consultation, 3 were no longer responsible for managing their treatment, and 6 had their treatment changed by their physician due to lack of effectiveness or the occurrence of adverse events (Figure 1). Therefore, adherence was monitored in a total of 96 patients (78.1% women). The age was mean ± SD 57.9 ± 11.4, and the time since diagnosis was mean ± SD 12 ± 11 years. On average, the participants had been taking MTX for mean ± SD 10 ± 9 years, and 57% were also taking biologics. The most frequent comorbidities were hypertension (32.3%), dyslipidemia (22.9%), osteoporosis (12.5%), and thyroid disease (11.5%) (Table 1). After exclusion, the patients were divided into 3 groups as: control (n = 34), PC (n = 30), and TM (n = 32). At baseline, the 3 groups of patients were similar in terms of all the criteria studied, except for a higher frequency of MTX administration on the weekend and a lower HAQ score in the PC group (Table 1). The same comparison of 3 groups prior to the exclusion of 16 patients gave the same results with regard to demographic, laboratory, and clinical data.

Baseline adherence. The mean ± SD CQR-19 scores were 81.9 ± 8.9, and the median was 82.5 (range 61.4–100). The Girerd scores were mean ± SD 0.75 ± 0.89, and the median was 1 (range 0–4). When considering the combination of a CQR-19 score >80 and a Girerd score ≤1 as a predictor of sufficient adherence, 57 patients (59%) showed good adherence at baseline. Thirty-one patients (32%) and 8 patients (9%) had suboptimal adherence according to 1 of the 2 measures or both measures, respectively (Table 1). The 3 study subgroups did not differ significantly with regard to adherence at baseline (Table 1). The baseline CQR-19 and Girerd scores from excluded patients (mean ± SD 79.5 ± 14.7 and 0.81 ± 1.3, respectively) were not significantly different from those of nonexcluded patients (P = 0.37 and P = 0.81, respectively). Nonadherent patients had a significantly lower HAQ score, significantly higher DAS28, ESR, and CRP level, a longer duration of RA, and a greater frequency of treatment with biologics (see Supplementary Appendix 5, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23750/abstract).

Table 1. Characteristics of the study population*

Characteristics	Total (n = 96)	Control (n = 34)	PC (n = 30)	TM (n = 32)	*P*
Patient characteristics					
Age, years	57.9 ± 11.4	58.2 ± 8.8	56.3 ± 10.6	59.1 ± 14.4	0.62
Women, no. (%)	75 (78.1)	27 (79.4)	22 (73.3)	26 (81.3)	0.73
Degree or higher, no. (%)	29 (30.2)	9 (26.5)	12 (40.0)	8 (25.0)	0.37
Profession, no. (%)					
Working	39 (40.6)	14 (41.2)	13 (43.3)	12 (37.5)	0.49
Retired	41 (42.7)	12 (35.3)	12 (40.0)	17 (53.1)	0.49
Other nonworking	16 (16.7)	8 (23.5)	5 (16.7)	3 (9.4)	0.49
Family status: not single	73 (76)	28 (82.4)	24 (80)	21 (65.6)	0.23
Comorbidities					
Hypertension, no. (%)	31 (32.3)	14 (41.2)	9 (30.0)	8 (25)	0.35
Dyslipidemia, no. (%)	22 (22.9)	11 (32.4)	7 (23.3)	4 (12.5)	0.16
Osteoporosis, no. (%)	12 (12.5)	4 (11.8)	3 (10)	5 (15.6)	0.86
Thyroid disease, no. (%)	11 (11.5)	3 (8.8)	4 (13.3)	4 (12.5)	0.85
Depression, no. (%)	9 (9.4)	4 (11.8)	3 (10.0)	2 (6.3)	0.76
No. prescribed drugs	6.4 ± 3.2	6 ± 2.9	5.7 ± 2.9	7.3 ± 3.7	0.12
Duration of RA, years	12.0 ± 10.8	9.5 ± 9.8	12.6 ± 11.3	14 ± 11.1	0.23
MTX administration					
MTX treatment duration, years	10.1 ± 8.9	7.8 ± 7.8	11.2 ± 10.6	11.4 ± 8.0	0.18
Dose of MTX, mg	14.4 ± 4.2	15.7 ± 4.2	13.5 ± 4.0	14.0 ± 4.2	0.09
Weekend administration, no. (%)	25 (26.0)	9 (26.5)	12 (40.0)†	4 (12.5)	0.05‡
Parenteral administration, no. (%)	12 (12.5)	5 (14.7)	1 (3.3)	6 (18.8)	0.15
Generic drug, no. (%)	57 (59.4)	21 (61.8)	19 (63.3)	17 (53.1)	0.67
Combined with a biologic, no. (%)	55 (57.3)	20 (58.8)	16 (53.3)	19 (59.4)	0.87
RA activity					
HAQ score	0.73 ± 0.68	0.81 ± 0.62	0.46 ± 0.68†	0.90 ± 0.70	0.03‡
DAS28	2.42 ± 1.03	2.45 ± 1.12	2.41 ± 1.00	2.39 ± 0.98	0.97
ESR, mm	12 ± 10	11 ± 9	13 ± 10	13 ± 11	0.47
CRP, mg/ml	5.1 ± 6.7	5.4 ± 8.1	4.8 ± 5.1	5.1 ± 6.6	0.94
Adherence with MTX at baseline					
Initial Girerd score	0.75 ± 0.89	0.71 ± 0.97	0.87 ± 0.97	0.69 ± 0.74	0.69
Initial CQR-19 score	81.9 ± 8.9	83.0 ± 7.8	80.5 ± 9.3	82.0 ± 9.7	0.55
Good adherence (both scores), no. (%)	57 (59.3)	21 (61.8)	18 (60.0)	18 (56.3)	0.62
Fair adherence (one score), no. (%)	31 (32.3)	12 (35.3)	8 (26.7)	11 (34.4)	0.62
Insufficient adherence (both scores), no. (%)	8 (8.3)	1 (2.9)	4 (13.3)	3 (9.4)	0.62

* Values are the mean ± SD unless indicated otherwise. *P* values correspond to the results of an analysis of variance, and a chi-square test was performed by default. When the number of events was too low, Fisher's exact test was performed. Only the most frequent comorbidities (≥10% in at least 1 group) are shown. PC = pharmacist counseling; TM = text message; RA = rheumatoid arthritis; MTX = methotrexate; HAQ = Health Assessment Questionnaire; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; CQR-19 = Compliance Questionnaire Rheumatology.
† $P < 0.05$ versus the TM group.
‡ Statistically significant.

Impact of interventions on the primary measures of adherence to MTX. The main study end point was the intergroup difference in the change over time in the CQR-19 score (the final score minus the initial one). A significant difference was observed between the control and TM groups (mean ± SD −0.14 ± 7.56 and 3.32 ± 5.66, respectively; $P = 0.019$). In contrast, the change over time in the CQR-19 scores did not differ significantly for the control versus PC groups (mean ± SD −0.22 ± 6.56) (Figure 2). Of note, the CQR-19 scores increased significantly from zero in the TM group only (Figure 2). A sensitivity analysis (based on multivariable logistic regression) was performed to determine whether baseline adherence influenced the TM-associated improvement in the CQR-19 score. In this model, the receipt of TMs was associated with an increase in the CQR-19 score independently of the baseline CQR-19 score and the dose level of MTX (OR 3.63 [95% CI 1.26–10.49]; $P = 0.017$) (Table 2).

Impact of interventions on secondary measures of adherence to MTX. Other measures (i.e., the Girerd score and the MPR) were probed in sensitivity tests. At the end of the study, the proportion of adherent patients (defined by the composite outcome) was 56% in the control group, 53% in the PC group, and 78% in the TM group. The difference between the TM group

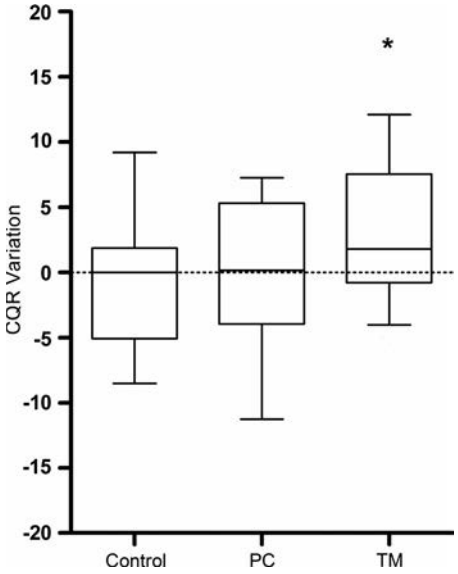

Figure 2. Change over time in the Compliance Questionnaire Rheumatology (CQR-19) scores. The box plots indicate the median value, framed by the interquartile range, the 10th percentile, and the 90th percentile change in the CQR-19 score. There was a significant intergroup difference in a Kruskal-Wallis test ($P = 0.048$). Compared with zero, the P values for the change in the CQR-19 score were 0.69, 0.92, and 0.004 for the control, pharmacist counseling (PC), and text message (TM) groups, respectively. * = $P < 0.025$ versus the control group.

and the 2 other groups was significant (Figure 3). Nevertheless, the intergroup differences were not statistically significant for the change over time in the Girerd score alone (mean ± SD –0.29 ± 0.84, –0.34 ± 0.85, and –0.38 ± 0.61 in the control, PC, and TM groups, respectively) or the final MPR alone (89 ± 13%, 86 ± 20%, and 90 ± 11% in the control, PC, and TM groups, respectively). MPR values were significantly correlated with CQR-19 scores in all subgroups, whereas they correlated with Girerd scores in the PC group only (see Supplementary Appendix 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23750/abstract).

Impact of interventions on changes over time in laboratory and clinical criteria. In the TM group, the mean HAQ score fell, but this change was not statistically significant ($P = 0.11$). The changes in the DAS28 and the HAQ scores did not differ significantly from zero in any of the 3 study groups. The same was true for the laboratory parameters ESR and CRP level (Figure 4). In the TM group, the decrease in the HAQ scores was correlated with change over time in the CQR-19 scores (r = –0.405, $P = 0.021$). The final DAS28 was below 2.6 (the usual cutoff for remission) in 56%, 57%, and 62.5% of the patients in the control, PC, and TM groups, respectively ($P = 0.84$).

Patient satisfaction. The mean level of patient satisfaction was 2.07, which corresponds to approximately 75% of patients being satisfied or very satisfied with their therapeutic management. The mean ± SD levels of satisfaction were significantly higher ($P < 0.01$) in the PC group (2.23 ± 0.85) and the TM group (2.28 ± 0.85) than in the control group (1.73 ± 0.62).

DISCUSSION

RA is a chronic, progressive inflammatory disease that often leads to disability. Its treatment is now well codified; MTX is the first-line drug and is usually maintained when biologics become necessary (1). Various studies suggest that adherence may be suboptimal in 25% of patients taking MTX (7–10). In the current study, the proportion of nonadherent patients was slightly higher (close to 40%), since the use of a combination of scores is known to avoid the overestimation of adherence (27). Recently TMs were used in RA to reduce the daily sitting time (28), but no study has focused on the impact of TMs on treatment adherence in patients with RA.

To the best of our knowledge, the current study (designed as a pilot proof-of-concept study, with a per protocol analysis) is the first to show that in RA, adherence to MTX is improved by sending weekly TM reminders to take the drug. The primary criterion for adherence (change over time in the CQR-19 score)

Table 2. Factors associated with an increase in the CQR-19 score in univariate and multivariable analyses*

Characteristics	Univariate correlation		Multivariable regression	
	r	*P*	OR (95% CI)	*P*
Dose of MTX, mg	0.228	0.026	1.33 (0.99–1.77)†	0.057
Initial CQR-19 score	–0.505‡	<0.001‡	0.89 (0.84–0.95)§	<0.001‡
TM reminders	0.24‡	0.017‡	3.63 (1.26–10.49) ‡	0.017‡

* Univariate correlations between an increase over time in the Compliance Questionnaire Rheumatology (CQR-19) score and the various factors are shown as Pearson's correlation coefficient r. Variables not shown all had $P > 0.10$. The association between an increase over time in the CQR-19 score and the variables was analyzed by multivariable logistic regression, which included variables significantly associated with good adherence in the univariate correlation analysis. OR = odds ratio; 95% CI = 95% confidence interval; MTX = methotrexate; TM = text message.
† Per increment of 2.5 mg/week.
‡ Statistically significant.
§ Per increment of 1. Statistically significant.

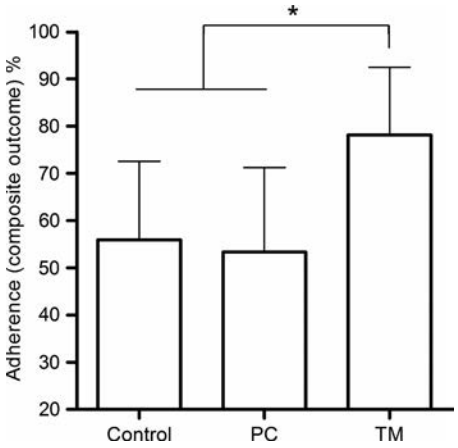

Figure 3. Percentage of patients with good adherence, as evaluated by the composite score. At the end-of-study visits, the proportion of patients with good adherence (defined by the combination of a Compliance Questionnaire Rheumatology score >80, a Girerd score ≤1, and a medication possession ratio >80%) is shown, together with the estimated SD. The overall chi-square *P* values were 0.080. * *P* = 0.025 for text message (TM) versus control plus pharmacist counseling (PC).

was significantly higher in the TM group. The proportion of patients considered to have good adherence at the end of the study was higher in the TM group (78%) than among non-TM patients (55%). This absolute difference (23%) corresponds to the improvement in adherence usually found when TM reminders are sent to the patients in the context of chronic drug treatment (21). A sensitivity analysis showed that the improvement in adherence was independent of patient characteristics, including the baseline CQR-19 score.

The choice of the CQR-19 score as the primary outcome for adherence was corroborated by our observation that these scores were correlated with the MPR (more than the Girerd scores). Moreover, the change over time in the CQR-19 score was negatively correlated with the change in HAQ score, whereas the Girerd score was not correlated. Surprisingly, the Girerd score improved in all groups. The low statistical power (related to the small number of questions and the absence of a Likert scale) and the questionnaire's psychometric properties might explain the difference with the CQR-19 outcome. Indeed, all 6 questions in the Girerd questionnaire focus on MTX intake (versus only 4 of 19 in the CQR-19), with answers potentially more influenced by inclusion in an interventional study of adherence (29). Notably, the MPR does not take account of the quality of MTX intake (whether the drug was taken on the right day and at the right time of day) or logistical aspects (e.g., whether the drug had been lost). So the MPR might have been biased by "pharmacy hopping" and counting of units by the patient. The absence of a significant impact of TM reminders on the MPR alone is therefore probably due to a loss of statistical power (due to measurement bias) and the inability to calculate intragroup variations with a prospective 2-visit design. These considerations justified an analysis of the change over time in the CQR-19 score and the use of a composite score to define adherence (27).

In accordance with the epidemiology of RA, the study population was predominantly female. The mean age was approximately 58 years, and the time since diagnosis was close to 12 years. All patients were treated with MTX (for 10 years on average) at a mean dose of 15 mg. Nearly 60% of the patients were also taking a biologic. Most patients had controlled RA, with a mean DAS28 below 2.4 and a mean HAQ score of 0.73. Thus, the study population was representative of patients with clinically and biologically stable RA due to long-term treatment with MTX (usually combined with a biologic). Our results showed that adherence to MTX treatment in this population can possibly be improved through the use of iterative TM reminders. However, these population characteristics make it difficult to extrapolate the efficacy of TM in patients with high disease activities or very poor adherence to treatment.

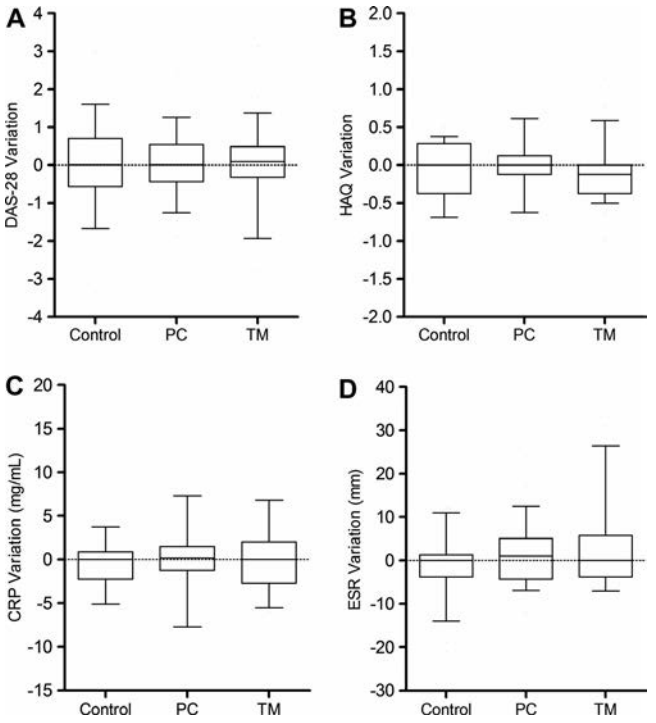

Figure 4. Change over time in clinical and laboratory parameters, showing interindividual differences. **A**, Disease Activity Score in 28 joints (DAS-28). **B**, Health Assessment Questionnaire (HAQ) score. **C**, C-reactive protein (CRP) level. **D**, Erythrocyte sedimentation rate (ESR). The box plots indicate the median values, framed by the interquartile range, the 10th percentile, and the 90th percentile. *P* values by the Kruskal-Wallis test were 0.99, 0.30, 0.53, and 0.57 for the DAS-28, the HAQ score, the CRP level, and the ESR, respectively. No significant intergroup differences in the variation were observed. None of the variations differed significantly from zero. PC = pharmacist counseling. TM = text message.

According to studies of adherence with MTX treatment, age, family status (divorce), psychological disorders, ethnic origin, disease activity, MTX dosage, and potential toxicity are associated with poor adherence, although discordant results have been reported for most of these factors (7,13). We found that nonadherent patients had a higher level of disease activity at baseline (with a higher DAS28 and a lower HAQ score). Accordingly, these patients were more likely to be taking biologics and had been experiencing RA for longer. Given the cross-sectional nature of our evaluation of adherence at baseline, a causal relationship is difficult to prove. However, one could make the case that poor adherence might be responsible for higher levels of disease activity (2–4).

Several studies have shown that pharmacist interventions have a positive effect on adherence in disease areas such as type II diabetes mellitus (30,31), hypercholesterolemia (32), and hypertension in the elderly (33). Nevertheless, the single medication review in the current study was not associated with statistically significant improvement in the CQR-19 score and the MPR. Thus, a single, pharmacist-led counseling session (even when accompanied by written information) does not appear to be appropriate for patients who have a good level of knowledge about their disease and its treatment. A recent study conducted at the Brigham and Women's Hospital Arthritis Center showed that non–health professional navigators providing monthly contacts were also not able to significantly improve the adherence of patients with RA to disease modifying antirheumatic drugs (34). Likewise, giving the rheumatologist written information about patients' nonadherence did not improve adherence in RA (35). Taken together, these data show that patient education has limitations, even when education improves the level of knowledge about the disease and its treatment. Optimization of this approach could perhaps be integrated into a patient education program including health professionals (36,37) or a continuous pharmaceutical care program (16).

For the specific purpose of improving adherence, electronic reminders could be an easier and less expensive technique to implement, but need to take into account privacy laws. Cellphone TM technology is generally not considered to protect personal health information sufficiently. Secure messaging could be deployed but would be limited to smartphone owners. Alternatively, cell phone owners could receive intake reminders that do not mention MTX, or patients could give their specific consent if allowed by local/national privacy laws.

Unfortunately, our results did not provide evidence of slower disease progression in any group (as measured by the DAS28 and mainly by laboratory parameters like the ESR and CRP level). The lack of significance was probably related to the sample size and the duration of the study, or the weak impact of a 3-point increase in the CQR-19 score (i.e., a mean improvement in 2 items). However, we observed a correlation between the change in the CQR-19 score and the change in HAQ score in the TM group, suggesting a modest clinical impact. In view of the well-documented link between adherence and the effectiveness of MTX, the anticipated clinical impact would lead to a decrease in the DAS28 (2–4) and, potentially, in cardiovascular mortality (38). Last, overall patient satisfaction was high, and even higher in patients with an additional intervention (the PC and TM groups). This higher level of satisfaction was generally observed when the patient received TM reminders (21) or had a medication review (39).

The limitations of the current study are related to the size of the present cohort (divided into 3 groups), the relatively high variability within the groups (shown by a lower initial HAQ score in the PC group), the subjective self-reporting of the CQR-19, the absence of electronic measurements of drug intake, and the lack of an MPR measurement before inclusion. The current study's strengths include its design (being both randomized and interventional), the use of several different measures of adherence, and the multivariable analysis of many confounding factors.

In conclusion, the receipt of TM reminders slightly but significantly increased treatment adherence in patients with RA taking MTX. The relatively low cost of this intervention (which, for example, is included in the free application recently developed by the French Rheumatology Society) might justify its use in the care of patients receiving long-term treatment with MTX. The results of this pilot study need to be confirmed by further studies in new users of MTX and in the highest risk patients (with both poor adherence and high activity of RA).

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Mary 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. Mary, Boursier, Brazier, Goëb.

Acquisition of data. Mary, Boursier, Desailly Henry, Grados, Séjourné, Salomon, Fardellone, Goëb.

Analysis and interpretation of data. Mary, Boursier, Brazier, Goëb.

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Association of Varus Knee Thrust During Walking With Worsening Western Ontario and McMaster Universities Osteoarthritis Index Knee Pain: A Prospective Cohort Study

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Objective. To investigate the 2-year association of varus knee thrust observed during walking to the odds of worsening Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) knee pain in older adults with or at risk of osteoarthritis (OA).

Methods. Video recordings of self-paced walking trials of Multicenter Osteoarthritis Study participants were assessed for the presence of varus thrust at baseline. Knee pain was assessed using the WOMAC questionnaire at baseline and at 2 years. Logistic regression was used to estimate the odds of worsening knee pain (defined as either any increase in WOMAC score or as clinically important worsening), adjusting for age, sex, race, body mass index, clinic site, gait speed, and static knee alignment. Analyses were repeated, stratified by baseline radiographic OA status and among the subset of knees without baseline WOMAC pain.

Results. A total of 1,623 participants contributed 3,204 knees. Varus thrust was observed in 31.5% of knees. Knees with varus thrust had 1.44 times (95% confidence interval [95% CI] 1.19–1.73) the odds of any worsening and 1.37 times (95% CI 1.11–1.69) the odds of clinically important worsening WOMAC pain compared to knees without thrust. Knees with thrust without baseline WOMAC pain had 2.01 times (95% CI 1.47–2.74) the odds of incident total pain.

Conclusion. Results indicate that varus thrust is a risk factor for worsening and incident knee pain. Targeting varus thrust through noninvasive therapies could prevent development or worsening of knee pain in older adults with or at risk for knee OA.

INTRODUCTION

The prevalence of knee pain in older adults has been estimated at 25% (1) and may be increasing (2). Knee pain is also a predictor of future knee joint replacement in individuals with osteoarthritis (OA) (3). In addition to pharmacologic therapies (which may have associated toxicities or contraindications that patients are not willing to tolerate) and walking aids, biomechanic interventions are recommended for the nonsurgical management of knee pain as a symptom of OA; however, evidence of the efficacy of biomechanical interventions varies (4). Identifying modifiable biomechanical risk factors for knee pain related to OA is of interest.

Varus knee thrust is a visible manifestation of excessive varus frontal-plane tibiofemoral movement during the weight-acceptance phase of gait with a return to neutral or less varus alignment in the late-stance phase (5). The relation of varus thrust to structural damage at the knee has been well-documented. Varus thrust has been previously linked to increased odds of medial radiographic OA disease progression (6,7), increased odds of worsening medial tibiofemoral cartilage damage and incident and worsening bone marrow lesions (8), and prevalent

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SIGNIFICANCE & INNOVATIONS

- Findings demonstrate a longitudinal relationship between varus knee thrust observed during walking and knee pain; this relationship has previously only been described cross-sectionally.
- The longitudinal relationship between knee thrust and Western Ontario and McMaster Universities Osteoarthritis Index pain justifies the use of biomechanic interventions to mitigate thrust in the prevention of new and worsening pain.

patellofemoral OA (9). Importantly, knee thrust can be identified visually in a clinical setting, and evidence suggests that thrust may be modified using inexpensive and noninvasive therapies (10).

As knee symptoms are more indicative of clinical intervention than structural changes, separate inquiry into the relation of varus knee thrust to knee symptoms (i.e., pain) is warranted. Previous studies have shown a cross-sectional association between varus knee thrust and knee pain (11–13). Longitudinal data are lacking to confirm the directionality of the relationship between thrust and pain and to describe the effect of thrust on both the onset of new pain and worsening of existing pain. Using data from the Multicenter Osteoarthritis Study (MOST), our objective was to evaluate the relation of varus thrust observed during walking to the 2-year incidence and worsening of knee pain. We hypothesized that knees exhibiting a varus thrust have increased odds of 2-year incident and worsening knee pain as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale, as well as odds of clinically important knee pain compared to knees without thrust, due to increased mechanical stress during gait.

PATIENTS AND METHODS

Sample. MOST is a prospective, observational cohort study of knee OA in older Americans who have OA or are at an increased risk of developing OA. Factors considered to contribute to an increased risk of knee OA include being overweight, having knee symptoms without radiographic OA, and having a prior knee injury or previous knee surgery. Participants were recruited from 2 communities: Birmingham, Alabama, and Iowa City, Iowa. The MOST protocol was approved by the institutional review boards at the University of Iowa; University of Alabama, Birmingham; University of California, San Francisco; and Boston University. Details of the MOST sample are described elsewhere (14). Briefly, participants were excluded if, at baseline, they had bilateral knee replacements, were unable to provide informed consent, planned to move out of the area prior to follow-up, were unlikely to survive to follow-up, or had been diagnosed with rheumatoid or other inflammatory arthritis (14).

MOST participants in the 60-month gait examination had to be able to walk independently over short indoor distances without the use of a walking aid or orthotic knee brace. Participants with recent (<6 weeks) lower-extremity injury resulting in restricted weight-bearing for >1 week, recent hospitalization for a cardiovascular or respiratory disorder, lower-extremity amputation proximal to the toes, or difficulty walking because of a neurologic condition were excluded.

Gait data were collected from eligible participants who completed the MOST 60-month clinic visit. Participants were dressed in short pants and their customary shoes and were instructed to walk across a 4.9-meter pressure-sensitive gait carpet, during repeated trials at a self-selected normal pace. Start and finish lines for the gait trials were positioned 1.5 meters (5 feet) before and after the gait carpet. A high-speed (60 Hz) video camera positioned 0.9 meters (3 feet) from the end of the finish line recorded each participant's gait pattern. The camera was mounted to the wall at a level to approximate adult hip height; the camera position was standardized at both clinic sites. GAITRite resident software (http://www.gaitrite.com) was used to compute gait speed.

Assessment of varus knee thrust. A single observer (AEW), trained in gait analysis by an experienced physical therapist and gait scientist (KDG) and blinded to knee disease and pain status, assessed thrust from high-speed videos of participants in the MOST 60-month gait examination during 2 self-paced forward walking trials. Skin markers were placed over the centers of the patellae and tibial tuberosities to facilitate visualization of the knee. Knees were excluded from the thrust assessment if a clear view of either marker was obscured by clothing. Videos were viewed in real speed. Thrust was defined as the dynamic worsening or abrupt onset of varus alignment during the weight-acceptance phase of gait, with a return to more neutral alignment during the lift-off and swing phases (5). Thrust presence was graded on a Likert-type scale as definitely present, probably present, probably absent, or definitely absent. Further, for knees with thrust definitely present or probably present, the proportion of steps exhibiting definite or probable thrust was noted as thrust during all steps, during at least half of the steps (but not all), or during fewer than half of the steps. Because varus thrust is likely to be defined as simply present or absent when evaluated in the clinic, a simplified dichotomous variable was defined for this analysis, wherein thrust was considered present when it was graded definitely present during any steps (≥1) or probably present during all steps. A randomly selected subsample of 150 knees (with balanced representation of the 2 clinic sites) underwent blinded reassessment 1 month later (to reduce the possibility of remembering an individual), revealing substantial intrarater reliability for the dichotomous variable of varus thrust (simple $\kappa = 0.73$).

Assessment of knee pain. Pain in each knee was evaluated using the WOMAC Likert 3.1 pain scale at 60 and 84 months. The WOMAC is a valid and reliable self-report measure of pain and physical function for individuals with knee OA (15). The pain questionnaire consists of 5 questions related to pain over the past 30 days during weight-bearing (walking, using stairs, standing upright) and non–weight-bearing activities (in bed, sitting or lying), scored according to the severity of pain: 0 (none), 1 (mild), 2 (moderate), 3 (severe), or 4 (extreme). These individual WOMAC scores (range 0–4) are summed to obtain the total WOMAC score (maximum score 20). Among knees with submaximal WOMAC scores at 60 months, worsening pain at 84 months was defined as any increase in WOMAC score. Clinically important worsening was defined as a ≥20% increase in total WOMAC score for knees with nonzero total WOMAC scores at baseline, and an increase of ≥2 in total WOMAC score for knees with a total WOMAC score of 0 at baseline. These criteria for clinically important worsening are based on definitions reported by Angst et al (16) and Tubach et al (17).

Assessment of covariates. Covariates for this study were selected to account for demographic or anatomic factors previously shown to differ between those with and those without thrust (5,8) or to account for potential sources of variability in the data collection process (14). Age, sex, and race were self-reported by MOST participants. The clinic site was either Birmingham, Alabama, or Iowa City, Iowa. Weight and height were assessed using standard measures, and body mass index (BMI) was calculated as kg/m^2. Gait speed was computed during the gait examination, as previously described. Mechanical hip-knee-ankle (HKA) alignment was assessed from full-view, fully extended weight-bearing anterior-posterior radiographs of the lower extremity. The HKA angle was defined as the angle formed by the intersection of a line from the center of the head of the femur to the center of the tibial spines and a second line from the center of the talus to the center of the tibial spines.

Statistical analysis. In our primary analyses, we assessed the relation of varus thrust observed as present or absent during walking to worsening total WOMAC pain and clinically important worsening total WOMAC pain. Following the work of Lo et al (11), we assessed the odds of worsening pain across the 5 individual WOMAC activity questions in the presence of varus thrust. We used logistic regression with generalized estimating equations to account for correlation between 2 extremities from a participant, adjusting for age, sex, race, BMI, clinic site, gait speed, and static HKA alignment. We repeated the main analysis of total and clinically important worsening WOMAC pain stratified by baseline radiographic OA status (Kellgren/Lawrence [K/L] grade <2 versus K/L grade ≥2). We also assessed the relation of varus thrust to incident WOMAC knee pain; to do so, we repeated the main analysis on the subset of knees with WOMAC scores of 0 at 60 months (study baseline). Results are reported as odds ratios (ORs) and 95% confidence intervals (95% CIs). Statistical analyses were performed using SAS software, version 9.3.

RESULTS

Of 2,768 participants at the MOST 60-month clinic visit, 2,049 met eligibility criteria for completion of the gait examination. Of these, 1,623 participants contributing 3,204 knees had readable videos for thrust assessment and completed WOMAC pain questionnaires at the 60- and 84-month clinic visits (Figure 1). Demographic characteristics of the study sample are shown in Table 1. Varus thrust, when dichotomized as defined above, was observed in 31.5% of knees (1,010 of 3,204). Definite varus thrust was identified in 545 knees: 380 knees had definite varus thrust on all steps, 119 had definite varus thrust on 50%–99% of steps, and 46 had definite varus thrust on less than half of steps. Probable varus thrust was identified in 619 knees, with 465 meeting the criteria (probable presence on all steps) for the dichotomous thrust variable. Of those individuals with thrust in at least 1 knee, 49% had unilateral varus thrust and 51% had bilateral varus thrust.

For the purposes of the current study, "baseline" refers to the MOST 60-month clinic visit and "2 years" refers to the MOST 84-month visit. At baseline, the mean total WOMAC pain score was 2.40 for all knees; the mean total WOMAC pain scores for knees with and without thrust were 2.57 and 2.32, respectively. At baseline, 41% of knees had radiographic knee OA (indicated by K/L grade ≥2); the prevalence of radiographic knee OA in knees with and without thrust was 48.4% and

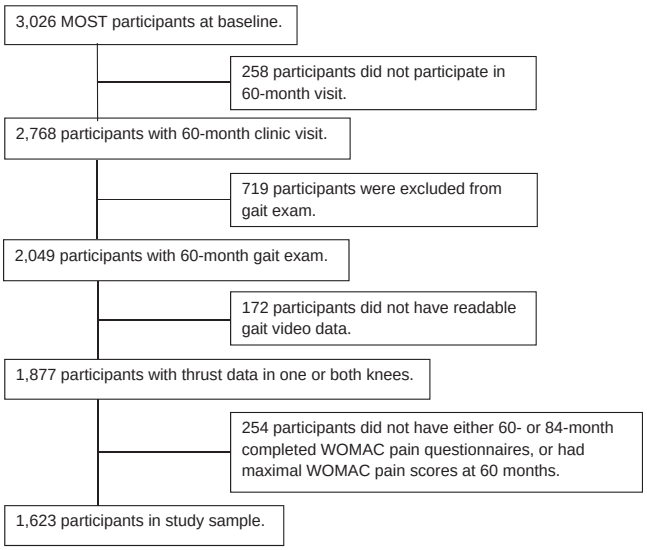

Figure 1. Study participant selection flow chart. MOST = Multicenter Osteoarthritis Study; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Table 1. Characteristics of the study sample*

Characteristic	Value
Person-level characteristics (n = 1,623 participants)	
Age, mean ± SD years	67.3 ± 7.6
Women	59.9
White	88.7
Body mass index, mean ± SD kg/m^2	30.4 ± 5.9
Alabama clinic site	41.1
Knee-level characteristics (n = 3,204 knees)	
Varus thrust present	31.5
Baseline total WOMAC score, mean ± SD	2.40 ± 2.97
Radiographic tibiofemoral OA (K/L grade ≥2)	41.0
K/L grade 2	17.4
K/L grade 3	19.0
K/L grade 4	4.6
Baseline static HKA alignment, mean ± SD degrees	178.3 ± 3.7

* Values are the percentage, unless indicated otherwise. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; OA = osteoarthritis; K/L = Kellgren/Lawrence; HKA = hip-knee-ankle.

37.5%, respectively. The mean ± SD HKA angle of knees with thrust was 176.7 ± 3.97° while the mean ± SD HKA angle of knees without thrust was 179.0 ± 3.36°.

After adjusting for covariates, knees with a varus thrust had 1.44 times (95% CI 1.19–1.73) the odds of any worsening total WOMAC pain and 1.37 times (95% CI 1.11–1.69) the odds of clinically important worsening total WOMAC pain compared to knees without thrust (Table 2). These results were not altered by further adjustment for baseline WOMAC pain score.

A sensitivity analysis using a stricter definition of varus thrust (definite thrust on at least 50% of steps) yielded similar results for total worsening WOMAC pain (OR 1.34 [95% CI 1.06–1.70]) but attenuated the statistical significance of the association with clinically important worsening WOMAC pain (OR 1.24 [95% CI 0.95–1.63]). We performed a second sensitivity analysis to take into account the frequency of steps with thrust among those categorized as definite thrusters. This analysis showed that as the frequency of steps with thrust increased (from none, to less than half, to greater than half, to all steps), the odds of worsening WOMAC scale pain increased (OR 1.13 [95% CI 1.04–1.23]). The same analysis with probable thrusters yielded a positive, but not statistically significant, association.

Table 2. Odds of worsening WOMAC pain in the presence of varus thrust*

WOMAC pain score	No./total†	Adjusted OR (95% CI)‡	*P*
Any worsening			
Varus thrust present	355/1,010	1.44 (1.19–1.73)§	0.0002§
Varus thrust absent	625/2,194	1.00 (Ref.)	–
Clinically important worsening¶			
Varus thrust present	278/1,010	1.37 (1.11–1.69)§	0.004§
Varus thrust absent	500/2,194	1.00 (Ref.)	–

* WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; OR = odds ratio; 95% CI = 95% confidence interval; Ref. = reference.
† Number of knees with worsening pain/total knees.
‡ Adjusted for age, sex, race, body mass index, clinic site, gait speed, and static hip-knee-ankle alignment.
§ Significant.
¶ Clinically important worsening is an increase of ≥2 in WOMAC score for knees with a baseline score of 0 or an increase of ≥20% for knees with WOMAC scores >0 (16,17).

Examination of the 5 individual WOMAC components showed that knees with varus thrust had statistically significant increased odds of any worsening WOMAC pain across all individual weight-bearing activity questions (walking OR 1.27 [95% CI 1.01–1.58], standing OR 1.32 [95% CI 1.05–1.68], using stairs OR 1.44 [95% CI 1.17–1.78]) as well as during sitting or lying (OR 1.33 [95% CI 1.05–1.70]). The association of varus thrust to WOMAC pain at night in bed was not statistically significant (OR 1.26 [95% CI 0.99–1.61]).

After stratifying by baseline radiographic OA status and adjusting for covariates, we only found a statistically significant positive association (OR 1.38 [95% CI 1.05–1.83]) between thrust and worsening total WOMAC pain in knees without baseline radiographic OA (Table 3). In the subset of 1,239 knees that had a WOMAC pain score of 0 at baseline, compared to knees without varus thrust, knees with varus thrust had 2.01 (95% CI 1.47–2.74) times the odds of incident total WOMAC pain at 2 years (Table 3). This statistically significant positive association persisted regardless of baseline radiographic OA status and when using a stricter definition of incidence: an increase of ≥2 in the WOMAC pain score (data not shown).

DISCUSSION

This study investigated the role of varus thrust in the worsening of WOMAC knee pain after 2 years. Varus knee thrust observed during walking was associated with increased odds of worsening, clinically important worsening, and incident total WOMAC pain after adjusting for age, sex, race, BMI, clinic site, gait speed, and static knee alignment.

Lo et al (11) first described an association between visually assessed varus thrust and WOMAC knee pain in a cross-sectional analysis of 82 participants with symptomatic knee OA. Their study showed increased odds of WOMAC knee pain during weight-bearing activities only. Iijima et al (12) found a statistically significant association between varus thrust and knee pain during gait, regardless of varus alignment status, in a cross-sectional study of 266 Japanese patients with medial radiographic knee OA. Fukutani et al (13) found a statistically significant cross-sectional association between varus thrust and pain and stiffness at the knee in a sample of 284 Japanese patients with medial tibiofemoral OA. Our work builds upon these previous studies by demonstrating a longitudinal association between varus thrust and knee pain in a large cohort of 1,623 participants with and without radiographic knee OA.

Table 3. Relation of thrust to WOMAC knee pain in subsets of knees without and with baseline radiographic osteoarthritis (ROA) and without pain at baseline*

Total WOMAC knee pain	No./total†	Adjusted OR (95% CI)‡	*P*
Odds of worsening			
Knees without baseline ROA (K/L <2)			
Varus thrust present	135/447	1.38 (1.05–1.83)§	0.02§
Varus thrust absent	290/1,171	1.00 (Ref.)	–
Knees with baseline ROA (K/L ≥2)			
Varus thrust present	171/420	1.31 (0.99–1.75)	0.06
Varus thrust absent	227/703	1.00 (Ref.)	–
Odds of clinically important worsening¶			
Knees without baseline ROA (K/L <2)			
Varus thrust present	97/447	1.09 (0.81–1.48)	0.57
Varus thrust absent	232/1,171	1.00 (Ref.)	–
Knees with baseline ROA (K/L ≥2)			
Varus thrust present	137/420	1.26 (0.94–1.69)	0.12
Varus thrust absent	189/703	1.00 (Ref.)	–
Odds of incident pain			
Knees with baseline WOMAC scores of 0			
Varus thrust present	122/362	2.01 (1.47–2.74) §	<0.0001§
Varus thrust absent	217/877	1.00 (Ref.)	–

* WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; OR = odds ratio; 95% CI = 95% confidence interval; K/L = Kellgren/Lawrence; Ref. = reference.
† Number of knees with outcome/total knees.
‡ Adjusted for age, sex, race, body mass index, clinic site, gait speed, and static hip-knee-ankle alignment.
§ Significant.
¶ Clinically important worsening is an increase of ≥2 in WOMAC score for knees with a baseline score of 0 or an increase of ≥20% for knees with WOMAC scores >0 (16,17).

It has been suggested that the summed WOMAC score may not be an appropriate assessment of pain (11,18); therefore, we examined the 5 individual WOMAC questions separately and found increased odds of worsening knee pain across all weight-bearing activities, as well as during sitting or lying. Our results differ somewhat from the findings of Lo et al (11), who found statistically significant increases in prevalence odds of WOMAC pain in the presence of thrust during weight-bearing activities only. Our larger sample size possibly afforded us greater power to detect statistically significant associations. Another possible explanation is that the effects of thrust on pain during non–weight-bearing WOMAC activities may only be observable in a longitudinal study of worsening, and not a cross-sectional study of prevalence (i.e., after a 2-year period, thrust causes sufficient damage to the knee to elicit pain during both weight-bearing and non–weight-bearing activities).

Previous work has shown an association between varus thrust and incident and worsening medial bone marrow lesions (8). Bone marrow lesions, thought to be related to bone trauma, are strongly associated with the presence of pain in knee OA (19,20). The association of varus thrust with worsening knee pain may be due in part to the development or enlargement of bone marrow lesions.

Knee pain intensity is a predictor of total knee joint replacement in OA (3). Mitigating knee pain through inexpensive and noninvasive therapies that modify knee thrust and associated joint loads is therefore of interest, especially for those wishing to delay total knee replacement. These therapies include specialized orthotics, gait retraining, exercise regimes, and bracing. Lateral-wedged insoles were shown to reduce the amplitude of acceleration associated with varus thrust as well as pain in individuals with early-stage medial knee OA (21); however, a separate study did not find any reduction in varus angles or knee loads associated with thrust with the use of lateral wedges or custom orthotics (10). In a single-subject case study, Hunt et al (10) showed that modifying gait through increased toe-out and trunk lean decreased the magnitude of the varus thrust angle as well as the peak knee adduction moment, although the magnitude of pain was only reduced slightly with trunk lean (importantly, these were immediate effects and the long-term effects of these interventions were not reported). Bennell et al (22) found that a neuromuscular exercise regime focusing on trunk and lower extremity position and movement quality improved pain and physical function in those with thrust, although thrust during the course of the exercise intervention was not assessed. Pollo et al (23) observed a trend toward a reduction in external knee varus moments associated with varus thrust as a result of valgus knee bracing. The long-term effects of these interventions are unknown, and further research into the specific causes of knee thrust is required to create effective interventions.

This study has several limitations related to the assessment of the exposure (varus thrust) and the primary outcome (pain). In our study, thrust was assessed visually from high-speed videos in a clinical setting. This method allows the

observer to visualize the varus position of the knee, but quantitative measures associated with thrust, such as varus angle and angular velocity (24,25), cannot be accurately estimated. These quantitative measures may be necessary for testing clinical interventions (10); however, our method for assessing thrust (and subsequent pain risk) is likely similar to what might be employed in a clinic setting where quantitative methods are unavailable. A second limitation is that thrust was only assessed by 1 observer. Iijima et al (12) reported good inter-rater reliability ($\kappa = 0.73$) for visual assessment of thrust, using a similar protocol to ours. The use of 1 observer minimized the introduction of variability from multiple observers. A clear consensus on the best practice for operationally defining thrust has yet to be reached, as definitions of thrust and methods for assessing thrust vary across the literature (5–13). The studies cited here categorize thrust as a binary variable (present or absent), although some authors (e.g., 9,11,12,24) graded thrust on an ordinal scale before ultimately dichotomizing the thrust variable. We chose a robust dichotomous definition of varus thrust that includes knees with probable thrust as well as knees that do not exhibit a thrust on all steps during a gait trial. With this definition, the prevalence of varus thrust was consistent with previous reports of similar populations (5,9), and sensitivity analyses using a stricter definition of varus thrust did not change the direction of our findings. To our knowledge, ours is the only study that considers the proportion of steps exhibiting thrust during a gait trial in categorizing thrust as present or absent. An additional sensitivity analysis of this higher-order data indicated that the odds of WOMAC pain increased as thrust became more consistent.

Assessing pain longitudinally also brings limitations. Our definition of worsening pain is a net increase in WOMAC score during 2 years; however, as pain levels can increase and decrease over time, this definition leaves us unaware of more nuanced changes in participants' pain levels that may have occurred within the follow-up period. Questions on the WOMAC instrument refer to participants' pain experience over a period of 30 days; thus, we remain confident that participants' pain responses refer to consistent levels of pain at baseline and 2 years. Further, small increases in total WOMAC pain score (e.g., an increase of 1) as well as changes in individual component score may represent measurement error and random fluctuation; likewise, in individuals with low total WOMAC scores, a 20% increase in pain may not actually be clinically important. We found similar results whether we defined clinically important pain as a 20% increase in total WOMAC score or an increase of ≥2.

In summary, our results indicate that varus thrust is a risk factor for incident and worsening WOMAC knee pain. Targeting varus thrust through noninvasive therapies could reduce the risk of knee pain in older adults with or at risk for knee OA.

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. Wink 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. Wink, Gross, Sharma, Felson.
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AMERICAN COLLEGE of RHEUMATOLOGY
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BRIEF REPORT

Sex-Specific Influence of Quadriceps Weakness on Worsening Patellofemoral and Tibiofemoral Cartilage Damage: A Prospective Cohort Study

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Objective. Reports on quadriceps weakness as a risk factor for incident and progressive knee osteoarthritis are conflicting, potentially due to differing effects of muscle strength on patellofemoral and tibiofemoral compartments. This study aimed to examine the sex-specific relation of quadriceps strength to worsening patellofemoral and tibiofemoral cartilage damage over 84 months.

Methods. The Multicenter Osteoarthritis Study is a cohort study of individuals with or at risk for knee osteoarthritis. Maximal quadriceps strength was assessed at baseline. Cartilage damage was semiquantitatively assessed by magnetic resonance imaging at baseline and 84-month follow-up using the Whole-Organ Magnetic Resonance Imaging Score (WORMS). Worsening patellofemoral and tibiofemoral cartilage damage was defined as any WORMS score increase in each subregion within medial and lateral compartments separately. Logistic regression with generalized estimating equations was used to assess the sex-specific relation of quadriceps strength to worsening cartilage damage.

Results. A total of 1,018 participants (mean ± SD age 61 ± 8 years, and mean ± SD body mass index 29.3 ± 4.5 kg/m^2; 64% female) were included. Quadriceps weakness increased the risk of worsening lateral patellofemoral cartilage damage in women (risk ratio for lowest versus highest quartile of strength 1.50 [95% confidence interval 1.03–2.20]; $P = 0.007$ for linear trend) but not in men. There was generally no association between quadriceps weakness and worsening cartilage damage in the medial or lateral tibiofemoral compartment for either women or men.

Conclusion. Low quadriceps strength increased the risk of worsening cartilage damage in the lateral patellofemoral joint of women, suggesting that optimizing quadriceps strength may help prevent worsening of structural damage in the patellofemoral joint in women.

INTRODUCTION

Quadriceps muscle weakness is a common feature of individuals with knee osteoarthritis (OA) and is an important target for managing symptoms and functional decline. Reports on quadriceps weakness as a risk factor for the development of knee OA have, however, shown conflicting results (1). Indeed, recent data from more than 40,000 Swedish men revealed that higher quadriceps strength during adolescence was associated with increased knee OA risk by middle age (2). Similarly, after knee OA is present,

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*Correction added on 26 September 2019, after first online publication: A sentence was omitted in the footnotes and has been restored in this version of the article.

SIGNIFICANCE & INNOVATIONS

- Low quadriceps strength increased the risk of worsening cartilage damage in the lateral patellofemoral joint but not the tibiofemoral joint of women and not men.
- Optimizing quadriceps strength may help prevent worsening of structural damage in the patellofemoral joint in women.
- Sex differences in the association of thigh muscle strength and patellofemoral osteoarthritis worsening deserve further investigation.

the influence of quadriceps weakness on further joint deterioration is poorly understood (3).

The conflicting results in relation to both knee OA incidence and progression may reflect differing effects of quadriceps weakness on different knee joint compartments as well as a difference in these effects between men and women. Despite knee OA being primarily viewed as a disorder of the tibiofemoral joint, the patellofemoral joint is often the most affected compartment from a structural perspective (4). Analyses of quadriceps weakness and the risk of OA outcomes have almost exclusively focused on the tibiofemoral joint, without consideration of coexistent (or isolated) patellofemoral pathology.

In a recent systematic review evaluating the risk of quadriceps weakness on OA outcomes, only 3 studies reported on patellofemoral structural pathology (3). In these studies, low quadriceps strength was found to increase the risk of patellofemoral and tibiofemoral joint space narrowing in women, but not men, in 1 cohort (5), and not in either men or women in another cohort (6); and to increase the risk of lateral but not medial patellofemoral cartilage lesion worsening (not stratified by sex, and no relationship observed in the tibiofemoral joint) (7). Whether quadriceps weakness increases the risk of medial or lateral patellofemoral structural pathology in men and women, despite sex differences in muscle strength, and whether the influence of quadriceps weakness differs between the patellofemoral and tibiofemoral joints is unclear. Importantly, detection of early preradiographic structural changes, such as cartilage deterioration, may permit early intervention, such as compartment-specific load management (e.g., exercise therapy, knee brace), which may be more effective prior to the development of advanced disease.

Greater understanding of whether quadriceps weakness is a risk factor for patellofemoral and tibiofemoral worsening cartilage damage in men and women is clinically important, because muscle strength is a potentially modifiable risk factor. Identifying distinct relationships between strength and worsening cartilage damage may therefore affect current nonpharmacologic treatment approaches of knee OA. The aim of the current study was to evaluate whether quadriceps weakness increases the risk of worsening cartilage damage assessed by magnetic resonance imaging (MRI) at both the patellofemoral and tibiofemoral joints of the knee in men and women.

SUBJECTS AND METHODS

Study design. The Multicenter Osteoarthritis Study (MOST) is a National Institutes of Health–funded prospective cohort study of 3,026 participants, ages 50–79 years at baseline, with or at risk of radiographic knee OA. Participants were recruited from Iowa City, Iowa and Birmingham, Alabama. Details of participant recruitment and inclusion/exclusion criteria have been published previously (5). The study was approved by the local institutional review board at each site, and all participants gave informed consent. For the current study, we included participants with quadriceps strength assessed at baseline and knee MRI assessed at baseline and 84 months.

Quadriceps strength assessment. Maximal quadriceps strength was assessed at baseline using a Cybex 350 computerized dynamometer at 60°/second (HUMAC software, version 4.3.2 and Cybex 300 for Windows 98, Avocent) (5). These measurements were performed by certified examiners using a standardized protocol with the same verbal encouragement to assure consistency between the 2 test sites, with test–retest reliability (intraclass correlation coefficient) of 0.94 (95% confidence interval [95% CI] 0.82–0.99). After 3 warm-up trials at 50% effort, 4 repetitions at maximal effort were obtained and the peak concentric torque normalized to body mass (Nm/kg) was recorded.

MRI acquisition. Knee MRI examinations were performed using a 1.0T extremity system (OrthOne, ONI Medical Systems) with a phased-array knee coil at the baseline and 84-month visits. The MOST imaging protocol consisted of the following sequences: 1) fat-suppressed fast spin-echo proton density–weighted sequences in 2 planes, sagittal (repetition time [TR]/echo time [TE] 4,800 msec/35 msec, 3-mm slice thickness, 0-mm interslice gap, 32 slices, 288 × 192 matrix, 140 mm^2 field-of-view, echo train length 8) and axial (TR/TE 4,680 msec/13 msec, 3-mm slice thickness, 0-mm interslice gap, 20 slices, 288 × 192 matrix, 140 mm^2 field-of-view, echo train length 8); and 2) a short tau inversion recovery sequence in the coronal plane (TR/TE 6,650 msec/15 msec, inversion time 100 msec, 3-mm slice thickness, 0-mm interslice gap, 28 slices, 256 × 192 matrix, 140 mm^2 field-of-view, echo train length 8).

Cartilage damage assessment. Cartilage damage was assessed in 1 randomly selected knee per participant by 2 experienced musculoskeletal radiologists (AG, FR) using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) (8). The WORMS divides the knee into 14 subregions in the patellofemoral and tibiofemoral joints to score cartilage damage from 0 (normal cartilage) to 6 (diffuse full-thickness dam-

age). The central and posterior femoral subregions and all tibial subregions (anterior, central, and posterior) were used to assess cartilage damage in the medial and lateral tibiofemoral compartments (i.e., 5 subregions each), respectively. Medial and lateral patellofemoral cartilage damage was assessed in the medial and lateral femoral trochlea and patellar facets, respectively (i.e., 2 subregions each). Interreader weighted kappa values for WORMS ranged from 0.62 to 0.78.

Worsening of cartilage damage in each subregion was defined as any increase in WORMS ≥1 grade from baseline to 84 months in the specific subregion, including within-grade changes to increase sensitivity to change (8). Because grade 1 does not represent a morphologic abnormality (i.e., cartilage signal change only), a change from grade 0 to 1 was not considered as worsening cartilage damage. Subregions with a maximal WORMS of 6 at baseline were excluded to avoid ceiling effects.

Statistical analysis. All analyses were stratified by sex due to differences in both muscle strength and OA worsening in men and women (5). Participants were grouped into sex-specific quartiles of baseline quadriceps strength, with the strongest quartile as the referent. Potential relationships between baseline quadriceps weakness and cartilage damage worsening were evaluated using logistic regression models with generalized estimating equations, adjusted for age, body mass index (BMI), clinic site, knee injury/surgery history, and frontal plane knee alignment, to account for correlations between subregions from the same knee. Risk ratios (RRs) >1 represent greater risk for cartilage damage worsening in the presence of quadriceps weakness. Analyses were completed using SAS software, version 9.4. *P* values less than 0.05 were considered statistically significant.

RESULTS

A total of 1,018 participants (one knee per participant) who had baseline quadriceps strength assessed as well as longitudinal cartilage assessment on MRI from baseline to 84 months were included (Figure 1). Participants were 655 women, mean ± SD age 61 ± 8 years, mean ± SD BMI 29.0 ± 4.8 kg/m^2, and 363 men, mean ± SD age 60 ± 8 years, mean ± SD BMI 29.8 ± 4.0 kg/m^2. In all, 158 women (24%) and 71 men (20%) had established radiographic knee OA (Kellgren/Lawrence score ≥2). The medial patellofemoral compartment was the most affected compartment with cartilage damage (partial- and full-thickness) at both baseline and follow-up in men and women (see Supplementary Tables 1 and 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23773/abstract).

Cartilage damage worsening in women. The number of female knees with lateral and medial patellofemoral and tibiofemoral cartilage damage worsening in each quartile of quadriceps strength is shown in Table 1. Women in the lowest quartile of quadriceps strength were at an increased risk of worsening lateral (RR 1.50 [95% CI 1.03–2.20]), but not medial (RR 0.90 [95% CI 0.62–1.32]), patellofemoral cartilage damage, with a significant overall linear trend across all quartiles (*P* = 0.007). There was no significantly increased risk of medial or lateral tibiofemoral cartilage damage worsening for women with quadriceps weakness (Table 1).

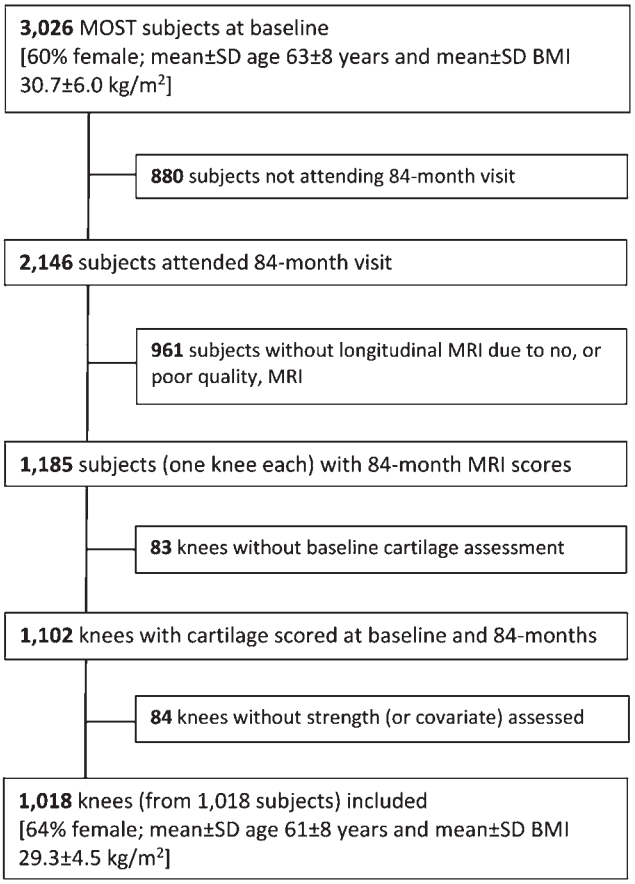

Figure 1. Flow chart of participant inclusion. MOST = Multicenter Osteoarthritis Study; BMI = body mass index; MRI = magnetic resonance imaging.

Cartilage damage worsening in men. During the 84-month follow-up period, the number of male knees with lateral and medial patellofemoral and tibiofemoral cartilage damage worsening in each quartile of quadriceps strength is shown in Table 2. Men with quadriceps weakness did not display an increased risk of medial or lateral patellofemoral cartilage damage worsening (Table 2). In contrast, men in the second highest quartile of quadriceps strength were at significantly increased risk of medial tibiofemoral cartilage damage worsening (RR 1.72 [95% CI 1.07–2.78]). Similarly, men in the lowest quartile of quadriceps strength had an elevated risk of medial tibiofemoral cartilage damage worsening, but this risk did not reach statistical significance (RR 1.61 [95% CI 0.96–2.71]), and the overall linear trend across the 4 quartiles was not statistically significant (*P* = 0.3).

Table 1. Among 655 women: relation of quadriceps strength quartiles to worsening cartilage damage in patellofemoral and tibiofemoral subregions*

Quartile: strength (range)†	Patellofemoral lateral		Patellofemoral medial		Tibiofemoral lateral		Tibiofemoral medial	
	Frequency of outcome‡	Adjusted RR (95% CI)§	Frequency of outcome‡	Adjusted RR (95% CI)§	Frequency of outcome‡	Adjusted RR (95% CI)§	Frequency of outcome‡	Adjusted RR (95% CI)§
4 (0.07–0.73), weak	63/285 (22.1)	1.50 (1.03–2.20)	53/309 (17.2)	0.90 (0.62–1.32)	123/809 (15.2)	1.09 (0.74–1.59)	127/794 (16.0)	1.04 (0.72–1.51)
3 (0.74–0.96)	57/300 (19.0)	1.25 (0.85–1.83)	65/312 (20.8)	1.07 (0.76–1.52)	100/829 (12.1)	0.86 (0.58–1.27)	153/828 (18.5)	1.25 (0.89–1.75)
2 (0.97–1.21)	47/319 (14.7)	0.91 (0.61–1.38)	59/316 (18.7)	0.94 (0.66–1.35)	104/817 (12.7)	0.91 (0.63–1.33)	112/818 (13.7)	0.94 (0.65–1.36)
1 (1.22–1.90), strong	46/305 (15.1)	1.00 (Ref.)	61/307 (19.9)	1.00 (Ref.)	100/806 (12.4)	1.00 (Ref.)	116/800 (14.5)	1.00 (Ref.)
P value for trend	–	0.007	–	0.6	–	0.9	–	0.5

* Values are the number/total (%) unless indicated otherwise. RR = risk ratio; 95% CI = 95% confidence interval; Ref. = reference.
† Nm/kg.
‡ Denominators may vary based on unreadable subregions, maximal scores at baseline, or missing covariates.
§ Adjusted for age, body mass index, clinic site, knee injury/surgery history, and frontal plane knee alignment.

There was also no significant relationship observed between quadriceps weakness and lateral cartilage damage worsening (Table 2).

DISCUSSION

Our study revealed that women with quadriceps weakness had a significantly elevated risk of worsening lateral patellofemoral cartilage damage during 84 months, whereas no relationship was observed in the tibiofemoral joint. In men, quadriceps weakness was generally not associated with the risk of worsening patellofemoral or tibiofemoral cartilage damage. These results underpin the importance of optimizing quadriceps strength for patellofemoral joint health, particularly in women.

This is the first large-scale prospective study evaluating the sex-specific relationship between quadriceps weakness and MRI-assessed structural deterioration in both the patellofemoral and tibiofemoral compartments. Analyses of OA risk factors in general have focused on the tibiofemoral compartment, despite emerging evidence of OA in the patellofemoral compartment being more prevalent and burdensome than tibiofemoral OA (4). The results of the current study, suggesting that in women, quadriceps weakness impacts the patellofemoral joint more than the tibiofemoral joint, are partly in concordance with earlier longitudinal MOST study results for joint space narrowing during 30 months (5). In that study, women, but not men, in the middle quadriceps strength tertile (but not the lowest tertile) had an elevated risk of radiographic patellofemoral joint space narrowing (5). By using a preradiographic location-specific measure (i.e., medial and lateral cartilage separately) over a much longer follow-up (84 months), we were able to identify more cases of disease worsening in the current study and detect a strong linear trend in the lateral patellofemoral joint. Our findings differed from previous findings in the same cohort that quadriceps weakness increased the risk of worsening tibiofemoral disease using a radiographic joint space narrowing outcome (5). Our current study assessed articular cartilage defects only, which are distinct from radiographic joint space narrowing, a composite measure of both cartilage and meniscus loss.

Using imaging assessment of medial and lateral compartmental cartilage defects enabled us to identify the distinct effect of quadriceps weakness on patellofemoral and tibiofemoral joints. The increased risk of worsening cartilage damage in the presence of quadriceps weakness that we found only in the lateral patellofemoral compartment of women extends preliminary data from 265 adults with established radiographic OA (men and women combined), showing that quadriceps weakness impacts only lateral patellofemoral (and not tibiofemoral) cartilage (7). Our study adds important data supporting the idea that the quadriceps influence patellofemoral and tibiofemoral joint articular cartilage degeneration differently. The quadriceps muscles function as general shock absorbers, protecting articular joint surfaces during loading. While excessive mechanical stress on knee cartilage due to muscle weakness has been suggested to contribute to degenerative processes (9), the menisci assist in dissipating load within the tibiofemoral joint. In contrast, the patellofemoral joint relies on optimal quadriceps function, particularly of the vastus medialis, to maintain alignment and joint stability and to restrict the tendency of the patella to track and sublux laterally (10). Our positive findings in the patellofemoral joint of women and not men may reflect the inherent greater passive joint laxity in women, who as a result rely more

Table 2. Among 363 men: relation of quadriceps strength quartiles to worsening of MRI-detected cartilage damage in patellofemoral and tibiofemoral subregions*

Quartile: strength (range)†	Patellofemoral lateral		Patellofemoral medial		Tibiofemoral lateral		Tibiofemoral medial	
	Frequency of outcome‡	Adjusted RR (95% CI)§	Frequency of outcome‡	Adjusted RR (95% CI)§	Frequency of outcome‡	Adjusted RR (95% CI)§	Frequency of outcome‡	Adjusted RR (95% CI)§
4 (0.14–1.05), weak	21/167 (12.6)	0.74 (0.38–1.45)	23/172 (13.4)	0.60 (0.34–1.07)	46/449 (10.2)	1.48 (0.67–3.30)	91/444 (20.5)	1.61 (0.96–2.71)
3 (1.06–1.41)	33/178 (18.5)	1.13 (0.67–1.92)	24/180 (13.3)	0.67 (0.38–1.20)	33/464 (7.1)	1.03 (0.54–2.00)	74/463 (16.0)	1.37 (0.83–2.27)
2 (1.42–1.71)	15/175 (8.6)	0.54 (0.29–1.02)	24/175 (13.7)	0.71 (0.40–1.23)	34/447 (7.6)	1.20 (0.64–2.22)	89/449 (19.8)	1.72 (1.07–2.78)
1 (1.72–2.67), strong	27/174 (15.5)	1.00 (Ref.)	28/172 (16.3)	1.00 (Ref.)	31/450 (6.9)	1.00 (Ref.)	45/449 (10.0)	1.00 (Ref.)
P value for trend	–	0.7	–	0.1	–	0.3	–	0.3

* Values are the number/total (%) unless indicated otherwise. MRI = magnetic resonance imaging; RR = risk ratio; 95% CI = 95% confidence interval; Ref. = reference.
† Nm/kg.
‡ Denominators may vary based on unreadable subregions, maximal scores at baseline, or missing covariates.
§ Adjusted for age, body mass index, clinic site, knee injury/surgery history, and frontal plane knee alignment.

on optimal muscular stability for patellofemoral function. While we acknowledge that hip muscle weakness (i.e., hip abductors) and associated hip kinematics (i.e., increased peak hip adduction and internal rotation) that were not assessed in the MOST cohort may impact patellofemoral joint dysfunction, strengthening the quadriceps may aid in decreasing the risk of worsening patellofemoral cartilage damage more than tibiofemoral cartilage, particularly in women.

The limited number of clinical trials evaluating the effect of quadriceps muscle strengthening on radiographic knee OA fail to show a significant effect on disease progression (11,12), which supports our general lack of findings in the tibiofemoral joint. However, small clinical trials of quadriceps strengthening using MRI-based cartilage outcomes have shown promise to slow progression in the earliest stages of disease (13,14). In particular, a lower-extremity strengthening program, specifically in women, exerted favorable effects on patellar cartilage quality (i.e., T2 relaxation times) (13). These results, together with our findings, highlight the importance for women with muscle weakness (i.e., <0.73 Nm/kg) to optimize quadriceps strength to minimize the risk of worsening patellofemoral cartilage, which can be a potent source of knee pain, contributing to a 6-fold increased risk of knee joint replacement (15).

Men in the second highest quartile of quadriceps strength displayed a significantly higher risk of worsening medial tibiofemoral cartilage damage, yet men with the greatest muscle weakness did not, resulting in a nonsignificant overall linear trend. Fewer men than women were included in our sample; however, this difference did not appear to influence the lack of an association between quadriceps weakness and the risk of worsening cartilage damage. Indeed, in the patellofemoral joint of men, quadriceps weakness tended to be protective of worsening cartilage defects, although this did not reach statistical significance. This apparently contradictory finding in men compared to women has also been observed in relation to knee replacement risk (3) and incident radiographic knee OA (2). Although previous findings have suggested that this contradictory relationship may be due to the moderating effect of knee malalignment (6), we adjusted all analyses for frontal plane alignment.

One of the limitations of evaluating location-specific cartilage deterioration (i.e., medial and lateral patellofemoral and tibiofemoral regions) is the more modest number of worsening cartilage defect outcomes per subregion compared to a whole knee or compartmental analysis. By analyzing all individual cartilage areas that contributed to each subregion (e.g., medial patella and medial trochlea contributing to the medial patellofemoral compartment) to increase statistical power, and using generalized estimating equations to account for correlations between subregions of the same knee, we were able to identify important associations between quadriceps weakness and worsening lateral patellofemoral cartilage damage. Importantly, this joint compartment had approximately half as many worsening cartilage defects as the tibiofemoral compartments, suggesting that we were adequately powered to detect a potential difference. Second, the presence of pain at baseline may have influenced maximal strength performance; however, a sensitivity analysis excluding those who reported that pain prevented them from achieving maximal strength (n = 51) did not result in any important differences. Third, although we adjusted for baseline BMI and knee alignment, these can change during a 7-year follow-up period. Assessing the interaction between BMI or alignment and muscle strength over time was outside the scope of the current evaluation.

In conclusion, low quadriceps strength was associated with an increased risk of worsening cartilage damage in the lateral patellofemoral joint of women. Low quadriceps strength did not increase the risk of worsening cartilage damage in the patellofemoral joint in men, nor in the tibiofemoral joint in either men or women. Sex differences in the association of thigh muscle strength and patellofemoral OA worsening deserve further investigation.

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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. Culvenor 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. Culvenor, Segal, Stefanik.
Acquisition of data. Guermazi, Roemer.
Analysis and interpretation of data. Culvenor, Segal, Guermazi, Roemer, Felson, Nevitt, Lewis, Stefanik.

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BRIEF REPORT

Childhood Maltreatment as a Risk Factor for Arthritis: Findings From a Population-Based Survey of Canadian Adults

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Objective. To establish whether there is a relationship between the frequency and severity of different types of childhood maltreatment and adulthood arthritis.

Methods. Analysis of the 2012 Canadian Community Health Survey–Mental Health included 21,889 respondents ages ≥18 years. Severity and frequency of childhood physical abuse (CPA), and childhood sexual abuse (CSA), and the frequency of childhood exposure to intimate partner violence (CEIPV) were assessed by asking about "things that may have happened to you before you were 16 in your school, in your neighborhood, or in your family." Respondents were also asked about chronic conditions diagnosed by a health professional, including arthritis. Covariates were sociodemographic characteristics, health risk variables (e.g., obesity), mental disorders, and a count of other chronic conditions. Multivariate logistic regression analysis was used to examine associations between childhood maltreatment and arthritis.

Results. A total of 17.5% of respondents reported arthritis. A higher prevalence of arthritis was observed for those who had experienced severe and/or frequent childhood maltreatment (32% for CPA and 27% for both CSA and CEIPV). These relationships persisted after controlling for sociodemographic variables. After controlling for all covariates, arthritis remained independently associated with severe and/or frequent CPA (dose-response relationship) and frequent CEIPV.

Conclusion. We found that the greater the frequency and severity of childhood maltreatment, the greater the magnitude of association with arthritis. This might reflect the role of the enduring immune and metabolic abnormalities and chronic inflammation associated with childhood maltreatment in the etiopathogensis of osteoarthritis (OA) or be an indicator of the role of joint injury in causing OA.

INTRODUCTION

Population-based studies have found significant associations between childhood physical abuse (CPA) and adulthood arthritis (1–3), and with osteoarthritis (OA) specifically (4). In some studies, childhood sexual abuse (CSA) (3,5) and childhood exposure to intimate partner violence (CEIPV) (1,2) have also been shown to increase the risk of arthritis in adults. Given recent insights that childhood maltreatment has the potential to lead to persistent biologic changes in inflammatory cytokines and the neuroendocrine and neurotransmitter systems, as well as in the brain (6–8), the association of childhood maltreatment with arthritis in adulthood may help further our understanding of the pathobiologic mechanisms in OA.

The present study builds on findings of an earlier study by Afifi et al, which demonstrated an association between childhood maltreatment and arthritis among Canadians ages ≥18 years. Much of this association was accounted for by lifestyle, mental disorders, and other physical chronic conditions (1). However, the authors dichotomized maltreatment into a yes/no variable and did not take into account the frequency and severity of the maltreatment. Given that childhood maltreatment can vary in severity, less severe exposure may have masked relationships between extent of maltreatment and adulthood arthritis. Therefore, the objective of this study was to establish whether there is a relationship between the frequency and severity of different types of childhood maltreatment and

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- Severe and/or frequent childhood physical abuse and frequent childhood exposure to intimate partner violence increased the risk of adulthood arthritis, even after controlling for a range of covariates.
- A potential mechanism for the increased risk of arthritis is that severe childhood abuse is known to result in enduring immune and metabolic abnormalities that are increasingly being recognized as potentially playing a role in the pathogenesis of arthritis, particularly osteoarthritis (OA).
- The strong association between arthritis and frequent and/or severe childhood physical abuse could also be an indicator of the role that joint injury plays in the development of OA.

adulthood arthritis. We hypothesize that if, as noted above, childhood maltreatment results in persistent biologic changes, then the greater the frequency and severity of maltreatment, the larger the magnitude of association between childhood maltreatment and arthritis in adulthood.

MATERIALS AND METHODS

Data source and study sample. The 2012 Canadian Community Health Survey–Mental Health (CCHS-MH), a cross-sectional survey, was conducted by Statistics Canada using a multistage, stratified, clustered sampling design targeting household residents ages ≥15 years who were living in the 10 Canadian provinces (9). Excluded from the survey's coverage were persons who were living on reserves and other Crown lands, full-time mem-

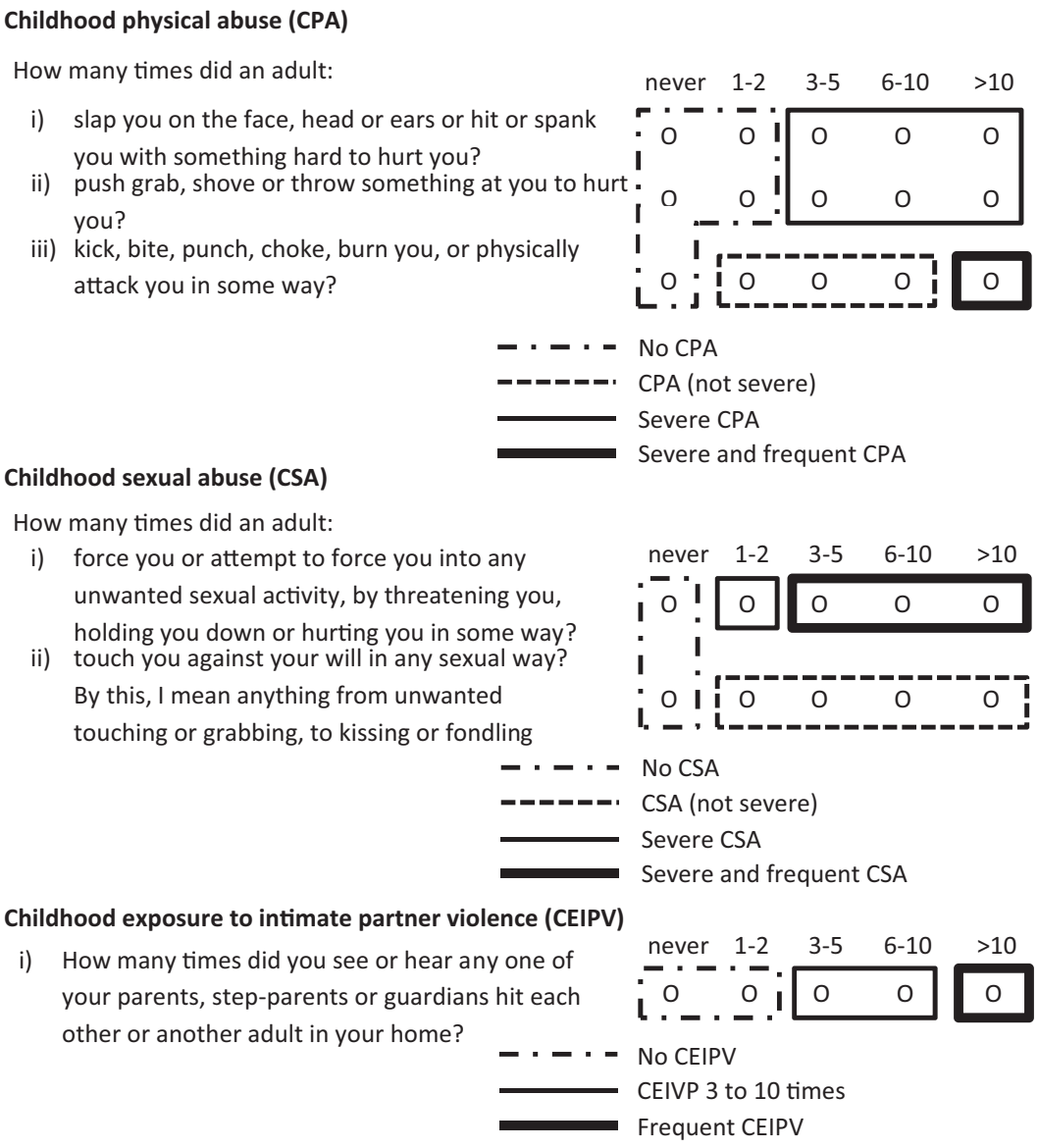

Figure 1. Childhood maltreatment questions and severity definitions.

bers of the Canadian Forces, and the institutionalized population (representing about 3% of the target population). The overall survey response rate was 68.9%, of whom 94% (n = 23,709) agreed to share their information with specific government departments including the Public Health Agency of Canada (9). The present study is based on a subset of 21,889 share-file respondents ages ≥18 years with data for arthritis, childhood maltreatment and other relevant variables. Data for the CCHS-MH were collected on a voluntary basis by Statistics Canada under the provisions of the Statistics Act. This article is based on data from the existing share file and thus the project did not undergo ethics review.

Measures. *Childhood maltreatment variables*. CPA, CSA, and CEIPV were assessed by asking respondents about "things that may have happened to you before you were 16 in your school, in your neighborhood, or in your family." As shown in Figure 1, three CPA questions asked how many times the respondent experienced specific acts from an adult. As in previous studies, respondents' CPA experiences were coded into 1 of 4 mutually exclusive categories, including no CPA, CPA (not severe), severe CPA, and severe and frequent CPA (10).

CSA was similarly coded the 4 following ways: no CSA, CSA (not severe), severe CSA, and severe and frequent CSA. CEIPV was coded into 3 groups, including no CEIPV, CEIPV 3–10 times, and CEIPV >10 times.

Arthritis. Respondents were asked about any current "long-term health conditions that have lasted or are expected to last 6 months or more and that have been diagnosed by a health professional." A checklist of conditions followed, 1 of which was "arthritis, excluding fibromyalgia" (9).

Covariates. The sociodemographic characteristics included as covariates in the multivariate logistic regression models were current age (used as a continuous variable), sex, marital status (married, widowed, divorced/separated, single/never married), highest level of education attained by the respondent (less than secondary graduation, secondary graduation, some postsecondary, postsecondary graduation), household income (quintiles based on household income adjusted by Statistics Canada's low-income cutoffs specific to the number of individuals in the household, the size of the community, and the survey year), immigrant status (<20 years in Canada, ≥20 years in Canada, Canadian born), ethnicity (white, African American, Southeast/East Asian, off-reserve Aboriginal, other), and place of residence (urban, rural).

Health risk variables were obesity, smoking status, and physical activity. Obesity was assessed using body mass index (BMI) adjusted for biases in self-reported height and weight (10). World Health Organization recommended categories were created based on corrected BMI (kg/m^2) ranging from underweight (<18.5 kg/m^2) to obese class III (≥40.0 kg/m^2) (10). Smoking status was divided into 3 categories, including daily smoker, former daily smoker, or never a daily smoker. Based on the Canadian physical activity guidelines, respondents were classified as being physically active if they reported ≥150 minutes of moderate or vigorous physical activity in the past 7 days (9).

Mental disorders, including lifetime history of mood disorders (depression and bipolar disorder) and generalized anxiety disorder, were assessed using a Canadian adaptation of the World Health Organization Composite International Diagnostic Interview criteria. This is a standardized instrument for the assessment of mental disorders and conditions according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (9,11).

Other physical chronic conditions were assessed in a similar manner to arthritis. The conditions included in the checklist were asthma, back problems (excluding arthritis), high blood pressure, migraine, chronic obstructive pulmonary disease, diabetes mellitus, epilepsy, heart disease, cancer, stroke, and bowel disorders. Respondents were classified as having 0, 1, 2, or ≥3 of these other chronic conditions.

Statistical analysis. Descriptive analyses were used to document the frequency of arthritis for each type of childhood maltreatment category. A series of multivariate logistic regression

Table 1. Prevalence of childhood maltreatment and adulthood arthritis by childhood maltreatment category*

	A	B
Childhood maltreatment variables	General population reporting childhood maltreatment	General population reporting adulthood arthritis†
CPA		
Severe and frequent	2.6 (2.1–3.0)	31.7 (23.4–40.0)‡
Severe	7.1 (6.6–7.6)	20.9 (18.0–23.9)‡
CPA (not severe)	16.4 (15.5–17.3)	16.7 (15.0–18.5)
No CPA (reference)	73.9 (72.9–74.9)	16.8 (16.0–17.6)
CSA		
Severe and frequent	2.6 (2.3–3.0)	27.0 (21.6–32.5)‡
Severe	3.2 (2.9–3.6)	26.5 (22.3–30.6)‡
CSA (not severe)	4.4 (4.0–4.8)	24.5 (21.0–28.1)‡
No CSA (reference)	89.8 (89.1–90.4)	16.5 (15.8–17.2)
Frequency of CEIPV		
>10 times	4.3 (3.8–4.8)	27.2 (21.3–33.0)‡
3–10 times	3.6 (3.2–4.0)	20.6 (16.6–24.6)
No CEIPV (reference)	92.1 (91.5–92.8)	16.9 (16.2–17.6)

* Values are the percent (95% confidence interval [95% CI]) of respondents (household population ages ≥18 years in Canada, in 2012). Source: Statistics Canada, Canadian Community Health Survey–Mental Health, 2012 (9). CPA = childhood physical abuse; CSA= childhood sexual abuse; CEIPV = childhood exposure to intimate partner violence.

† The percent (95% CI) of the population that reported adulthood arthritis overall was 17.5 (16.8–18.1).

‡ Significantly higher than reference group ($P < 0.05$).

models were used to examine associations between each type of childhood maltreatment and arthritis. Starting from an unadjusted model (model 1), model 2 adjusted for age, model 3 adjusted for age, sex, and other sociodemographic characteristics, model 4 further adjusted for health risk variables and mental disorders, and model 5 adjusted for co-occurring physical chronic conditions. Dummy variables were created to adjust for missing values for the health risk variables, mental disorders, and the number of other physical chronic conditions.

Analyses were conducted using SAS Enterprise Guide, version 5.1. All estimates are based on weighted data. Weights were created at Statistics Canada so that the data would be representative of the Canadian population living in the 10 provinces in 2012 and were adjusted to compensate for non-response to the CCHS-MH. Variance estimates and 95% confidence intervals (95% CIs) were calculated using the bootstrap technique, to account for the complex survey design of the 2012 CCHS-MH (9).

RESULTS

The overall characteristics of the population have been published elsewhere (1). Arthritis was reported by 17.5% (95% CI 16.8–18.1) of Canadians ages ≥18 years. Table 1, shows the percent of the total population that reported childhood maltreatment. Severe and frequent CPA was reported by 2.6% of the population, likewise severe and frequent CSA was reported by 2.6% and frequent CEIPV by 4.3%. Table 1 also shows the percent of the population reporting arthritis by childhood maltreatment category. The results indicate a dose-response relationship between childhood maltreatment and adulthood arthritis; those who experienced severe and/or frequent childhood maltreatment were the most likely to report adulthood arthritis. For example, among those reporting no history of CPA, the prevalence of adulthood arthritis was 16.8%. Among those reporting severe and frequent CPA, the prevalence rose to 31.7%. Similar higher prevalences were found for severe and frequent CSA (27.0%) and frequent CEIPV (27.2%).

Compared with the unadjusted odds for CPA, odds ratio (OR 2.3 [95% CI 1.5–3.3]) (Table 2, model 1), controlling for age (model 2), somewhat strengthened the association between severe and/or frequent CPA and arthritis, OR 3.3 (95% CI 2.0–5.4). The addition of sex and other sociodemographic variables somewhat attenuated the association OR 3.0 (95% CI 1.9–4.8) (model 3). Additionally, controlling for health risk variables (obesity, smoking, physical activity) and mental disorders further reduced the magnitude of the association, OR 2.5 (95% CI 1.5–4.2) (model 4). Nevertheless, arthritis was independently and significantly associated with severe and frequent CPA, severe CPA and either level of CEIPV. After further adjustment for co-occurring physical chronic conditions (model 5), arthritis remained independently associated with

Table 2. Association of different types of childhood maltreatment with adulthood arthritis*

Childhood maltreatment variables	Unadjusted (model 1)	Age (model 2)	Age, sex, and other sociodemographic characteristics (model 3)†	Health risk and mental disorders (model 4)‡	Chronic physical condition count (model 5)§
CPA					
Severe and frequent	2.3 (1.5–3.4)¶	3.3 (2.0–5.4)#	3.0 (1.9–4.8)#	2.5 (1.5–4.2)#	2.0 (1.2–3.5)¶
Severe	1.3 (1.1–1.6)¶	1.6 (1.2–1.9)#	1.7 (1.4–2.1)#	1.5 (1.2–1.9)#	1.4 (1.1–1.7)#
CPA (not severe)	1.0 (0.9–1.1)	1.1 (1.0–1.3)	1.2 (1.0–1.4)¶	1.1 (1.0– .3)	1.1 (0.9–1.3)
CSA					
Severe and frequent	1.9 (1.4–2.5)#	2.2 (1.7– 3.0)#	1.7 (1.2–2.3)#	1.3 (1.0–1.8)	1.1 (0.8–1.5)
Severe	1.8 (1.5–2.3)#	1.8 (1.4– 2.4)#	1.5 (1.2–2.0)#	1.3 (1.0–1.6)	1.2 (0.9–1.5)
CSA (not severe)	1.6 (1.3–2.0)#	1.5 (1.2–1.8)#	1.2 (1.0–1.6)	1.1 (0.9–1.4)	1.1 (0.9–1.4)
No CSA (ref.)	–	–	–	–	–
Frequency of CEIPV					
>10 times	1.8 (1.3–2.5)#	2.5 (1.7–3.6)#	2.1 (1.4–2.9)#	1.8 (1.2–2.7)#	1.6 (1.1–2.4)¶
3–10 times	1.3 (1.0–1.6)	1.6 (1.2–2.1)#	1.5 (1.1–1.9)#	1.4 (1.0–1.8)¶	1.2 (0.9–1.6)
No CEIPV (ref.)	–	–	–	–	–

* Values are the odds ratio (95% confidence interval) adjusted for childhood maltreatment variables of respondents (household population ages ≥18 years in Canada, in 2012) Source: Statistics Canada, Canadian Community Health Survey–Mental Health, 2012 (9). CPA = childhood physical abuse; CSA = childhood sexual abuse; ref. = reference; CEIPV = childhood exposure to intimate partner violence.

† Sociodemographic characteristics (i.e., age, sex, marital status, education, household income, immigrant status, ethnicity, and place of residence).

‡ Sociodemographic characteristics, health risk variables (i.e., obesity, smoking status, and physical activity level), and mental disorders (i.e., mood disorders and generalized anxiety disorder).

§ Sociodemographic characteristics, health risk variables, mental disorders, and other chronic physical condition (i.e., asthma, back problems excluding arthritis, high blood pressure, migraine, chronic obstructive pulmonary disease, diabetes mellitus, epilepsy, heart disease, cancer, stroke, and bowel disorders).

¶ $P < 0.05$.

# $P < 0.01$.

frequent CEIPV (>10 times), severe CPA, and most strongly with severe and frequent CPA, OR 2.0 (95% CI 1.2–3.5).

DISCUSSION

Our study shows that the greater the frequency and severity of childhood maltreatment, the greater the magnitude of association with arthritis. Comparison with other studies is difficult because of variations in the scope of the childhood maltreatment questions, and range of covariates considered. Most previous studies regarding the relationship between childhood maltreatment and arthritis have not considered the effect of the frequency and severity of the different types of maltreatment. A study by Von Korff et al demonstrated that the number of childhood adversities increased the risk of arthritis, however this included a broader range of variables including parental loss and economic adversity (3). After adjusting for covariates, Afifi et al did not find a relationship with arthritis and individual types of maltreatment (1). The inclusion in their study of less severe forms of child maltreatment may have led to a masking of the relationship between arthritis and maltreatment.

While the term "arthritis" includes a variety of different diseases and conditions, overwhelmingly the most common type is OA, and as a result, reports of arthritis at the population level are frequently taken to represent OA (3). While OA has traditionally been thought of as a noninflammatory degenerative disease of the cartilage, there is increasing awareness that OA is associated with low-grade inflammation. Hypotheses in recent studies relate OA to metabolic syndrome, and it has been suggested that immune, metabolic or inflammatory properties may play a role in the pathogenesis of OA (12–14). Childhood maltreatment has been shown to result in enduring immune and metabolic abnormalities and is associated with a chronic inflammatory state (7,8). Putting this together with the suggestions that immune or metabolic processes may also play a role in the pathogenesis of OA (12–14), more research is needed to determine how the frequency/severity of childhood maltreatment may affect the biologic processes that are associated with the pathogenesis of arthritis, particularly OA.

The magnitude of the association of childhood maltreatment and arthritis was reduced particularly when a count of co-occurring other physical chronic conditions was adjusted for in our regression model. Rather than dismissing this as confounding, an alternative explanation could relate to the pervasive role, for example, of inflammatory markers across a range of conditions (7). This includes the potential role of shared inflammatory mediators in conditions such as hypertension and diabetes mellitus, both of which have also been found to be associated with childhood maltreatment (1,2). Further research is needed to explore the nature of the complex relationship between childhood maltreatment, arthritis, and other chronic mental and physical health conditions.

The strong association between arthritis and frequent and/or severe CPA after controlling for covariates could also well be an indicator of the additional role of injury to the joints in causing arthritis. Trauma, including fracture and ligamentous injury, is a well-established risk factor for arthritis (15). Frequent CEIPV was also related to arthritis. The literature shows that children exposed to intimate partner violence also have an increased risk of being exposed to CPA and CSA themselves (16).

Major strengths of this study include the use of a large representative survey of Canadian adults, which was administered by trained personnel using a structured format. Also, the childhood maltreatment items included in the survey made it possible to consider the severity and frequency of 3 types of childhood maltreatment. The questions were behaviorally-specific, and thus are likely to have higher validity and reliability than broad and subjectively defined items (17). A limitation of our study is the cross-sectional nature of the data. While the structure of the survey questions indicates that the childhood maltreatment precedes the onset of arthritis, the temporal relationships of arthritis with other variables are less clear. A further limitation is the self-report nature of the data. However, self-reported arthritis has been shown to have reasonable sensitivity and specificity (18). Further, as arthritis was measured using a single item in the survey, it was not possible to examine associations between child maltreatment and specific types of arthritis.

This study expands on the findings from the study of Afifi et al (1) in that it shows that the greater the frequency and severity of childhood maltreatment, the greater the likelihood of adulthood arthritis. In addition to possible biomechanical factors related to physical injury, the mechanism of how this might be mediated by neurologic or immunologic changes is unknown and deserves further study, particularly in the light of emerging evidence for an immune or metabolic pathogenesis of OA, the most common type of arthritis.

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. Badley had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Badley, Shields, O'Donnell, Hovdestad, Tonmyr.

Analysis and interpretation of data. Badley, Shields, O'Donnell, Hovdestad, Tonmyr.

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BRIEF REPORT

Repetitive Knee Bending and Synovitis in Individuals at Risk of and With Knee Osteoarthritis: Data From the Foundation for the National Institutes of Health Osteoarthritis Biomarkers Consortium

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Objective. To investigate associations between engagement in knee bending (stair climbing, kneeling, squatting, heavy lifting, getting in/out of a squatting position) and synovitis prevalence on noncontrast magnetic resonance imaging (MRI) in individuals at risk of and with knee osteoarthritis.

Methods. We included baseline data from 594 participants (mean ± SD age 61.5 ± 8.9 years, 61% had Kellgren/Lawrence grade ≥2; 59% were female; mean ± SD body mass index was 30.7 ± 4.8 kg/m^2) of the Osteoarthritis Biomarker Consortium Foundation for the National Institutes of Health project. Knee bending activities were queried by a standard questionnaire, and the severity of Hoffa synovitis and effusion synovitis (surrogate outcomes of synovitis) were graded using the MRI OsteoArthritis Knee Scoring system. Logistic regression was used, unadjusted and adjusted, for metabolic syndrome, physical activity level, and sex. A grade ≥1 defined synovitis prevalence, with a grade ≥2 cutoff implemented in sensitivity analyses.

Results. The prevalence of grade ≥1 Hoffa synovitis and effusion synovitis equaled 59% (n = 353) and 62% (n = 366), respectively. Adjusted for confounders, kneeling for ≥30 minutes during a single day was associated with grade ≥1 Hoffa synovitis prevalence (odds ratio [OR] 1.65 [95% confidence interval (95% CI) 1.11–2.47]). Participants engaging in this activity ≤1 day per week had greater odds for prevalent Hoffa synovitis than those who did not perform the activity (OR 1.88 [95% CI 1.11–3.18]). No other significant associations were found. Sensitivity analyses yielded similar findings.

Conclusion. In this selected sample with a preponderance of grade ≥1 Hoffa and/or effusion synovitis on noncontrast MRI, only prolonged kneeling was associated with Hoffa synovitis prevalence. Replication in other samples is warranted.

INTRODUCTION

Repetitive knee bending is a well-recognized risk factor of knee osteoarthritis (OA). Frequent squatting, kneeling, and heavy lifting have been shown to increase the likelihood of worse cartilage defects both in men with symptomatic knee OA and in healthy women (1,2). Although cartilage loss and radiographic disease severity are typically monitored to ascertain disease

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SIGNIFICANCE & INNOVATIONS

- In this sample of individuals at risk of and with definite knee osteoarthritis and the majority presenting with grade ≥1 synovitis on noncontrast magnetic resonance imaging, participation in kneeling for ≥30 minutes was significantly associated with a greater likelihood of ≥ grade 1 Hoffa synovitis.
- Specifically, participants who kneeled ≤1 day per week had significantly greater odds of Hoffa synovitis prevalence compared with those reporting no such activity.
- No associations were found for Hoffa synovitis prevalence with stair climbing, squatting, heavy lifting, or getting in/out of a squatting position, nor did any of the knee bending activities show a significant association with effusion synovitis prevalence.
- Sensitivity analyses using a more restrictive cutoff to define synovitis prevalence (grade ≥2) and reducing interference from potential misclassification errors yielded similar findings.

progression, synovial inflammation or synovitis has gained interest as a hallmark feature of OA pathogenesis.

Synovitis is common in knee OA, manifests across all stages of the disease, and likely also acts as a precursor of disease rather than just a consequence of underlying structural damage (3). That is, low-grade systemic inflammation and activation of synovial macrophages may also be induced by metabolic syndrome, a comorbidity prevalent among individuals with knee OA (4). In an exploratory study of 100 individuals with knee OA, however, Roze et al (4) suggested that Hoffa synovitis as detected on noncontrast magnetic resonance imaging (MRI) was more prevalent in participants who were lean and physically active than in those with metabolic syndrome. Additionally, effects of moderate-intensity knee bending loads, or exercise therapy, on inflammatory wet biomarkers appeared variable in individuals at risk or with knee OA (5,6). Thus, whether, and to what extent, repetitive knee bending is associated with the prevalence of synovitis in individuals at risk or with knee OA remains unclear. The purpose of this study was to investigate the association between repetitive knee bending and the prevalence of synovitis in individuals at risk of and with definite knee OA.

MATERIALS AND METHODS

Study design. We conducted a cross-sectional analysis with baseline data from the Foundation for the National Institutes of Health (FNIH) Osteoarthritis Biomarkers Consortium project (7,8). This project investigated biomarkers of knee OA progression over 48 months in a nested case–control design using public data and images from the Osteoarthritis Initiative (OAI) (7). Briefly, 600 participants were selected from the OAI cohort and grouped based on whether persistent pain and/or radiographic disease progression had occurred in the index knee, with 1 index knee identified per subject. A prespecified number of participants was selected across strata and frequency-matched for radiographic disease severity and body mass index (Figure 1).

Participants. The OAI is a multicenter observational cohort study of knee OA consisting of men and women ages 45 to 79 years, including all ethnic minorities and subdividing participants into 3 subcohorts: the progression subcohort with symptomatic tibiofemoral OA (n = 1,390), the incidence subcohort at risk of OA (n = 3,284), and a nonexposed control group (n = 122). The main exclusion criteria were the presence of inflammatory arthritis, contraindications to 3T MRI, and bilateral end-stage knee OA. The detailed eligibility criteria for each of the subcohorts are available elsewhere (https://data-archive.nimh.nih.gov/oai/). To qualify specifically for the FNIH substudy, participants had at least 1 knee with a Kellgren/Lawrence grade of 1, 2, or 3 at baseline and complete data at all relevant time points. Complete data at all relevant time points included biochemical as well as imaging biomarker data, such as knee radiographs and MRIs suitable for analysis, and clinical data (7). Participants were excluded from the FNIH data set if they had knee/hip replacements or metallic

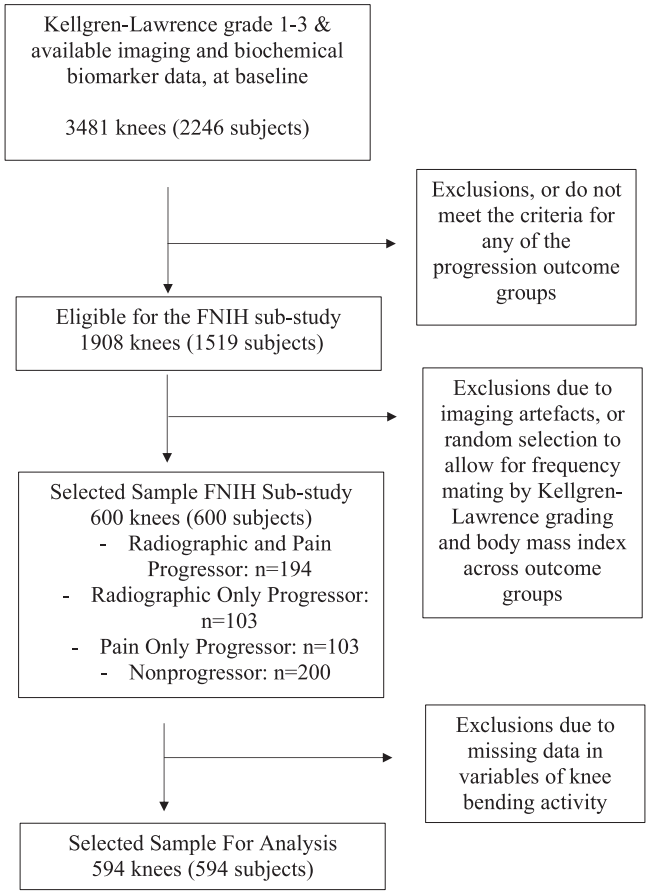

Figure 1. Participant flow diagram. Adapted from Osteoarthritis Biomarkers Consortium Foundation for the National Institutes of Health (FNIH) Project: Study Design, version 1.0 (with permission).

bone implants from baseline to 24 months, minimum medial joint space width of <1.0 mm, and/or a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score of >91 (range 0–100) at baseline, indicating ceiling effects of disease progression, radiographic and pain progression by the 12-month follow-up, predominant lateral joint space narrowing at baseline or during follow-up, and insufficient follow-up times to ascertain persistent pain progression (7). Finally, from a total of 600 participants in the FNIH project selected, we retained 594 participants with complete data on knee bending activities (99% of the original FNIH sample) for the present analyses.

MRI. The OAI consortium used 3 Tesla MRI Trio systems (Siemens Healthcare). The pulse sequences consisted of sagittal and coronal intermediate-weighted turbo spin-echo sequences, a sagittal 3-dimensional dual-echo in the steady state sequence with water excitation, and the axial and coronal multiplanar reformats of the latter (7). The semiquantitative MRI Osteoarthritis Score system was implemented to grade the severity of Hoffa and effusion synovitis, as surrogate outcomes of synovial thickening or synovitis (9). Images were read sequentially by 2 experienced musculoskeletal radiologists not blinded to time points, but unaware of clinical characteristics and disease progression status (7,9).

Hoffa synovitis was evaluated by ascertaining the presence of signal alterations in the intercondylar region of Hoffa's fat pad and scored from 0 (normal) to 3 (severe). Similarly, the degree of effusion synovitis was determined by estimating the distention of the synovial cavity, with grade 0 representing a normal physiologic amount of joint effusion and grade 3 a large effusion with evidence of capsular distention (9). Intrarater and interrater reliability for Hoffa synovitis have both been reported to have a weighted $\kappa = 0.68$ (95% confidence interval [95% CI] 0.38–0.99), while reliability estimates for effusion synovitis attained $\kappa = 0.95$ (95% CI 0.61–1.00) and $\kappa = 0.91$ (95% CI 0.57–1.00), respectively (7,8). We used a grade ≥1 cutoff to define Hoffa and/or effusion synovitis prevalence as well as a more restrictive cutoff of grade ≥2 to reduce interference from potential misclassification errors in sensitivity analyses (8).

Repetitive knee bending. Occupational and nonoccupational knee bending activities were queried at enrollment using a standard questionnaire adapted from the literature (10). Questions assessed whether participants had performed the following activities during the past 30 days and during a single day (yes/no): taking a flight of stairs ≥10 times, kneeling for ≥30 minutes, squatting or deep knee bending ≥30 minutes, lifting or moving weights of ≥25 pounds, and getting in or out a squatting position ≥10 times. Additionally, the frequency by which each activity occurred in a typical week was categorized as none, ≤1 day/week, 2–3 days/week, 4–5 days/week, or nearly every day.

Participant characteristics. Data of age, sex, radiographic disease severity, physical activity level, knee pain severity, and metabolic syndrome were collected at screening or enrollment using standardized measurements and/or questionnaires. Specifically, we used scores from the Physical Activity Scale for the Elderly, assessing the level of physical activity, as well as from the knee-specific WOMAC pain subscale reporting knee pain. Finally, as per Roze et al (4), the International Diabetes Federation diagnostic criteria were used to generate a surrogate marker for metabolic syndrome. Participants with signs of central obesity (abdominal circumference of 88 cm in women and 102 cm in men and/or a body mass index of >30 kg/m^2) were classified as having metabolic syndrome if ≥2 of the following criteria were also present: drug treatments for raised triglycerides, drug treatments for cholesterol abnormalities, systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or antihypertensive drug treatments, and type 2 diabetes mellitus and/or treatment, as per the Charlson Comorbidity Index.

Statistical analysis. Descriptive statistics were calculated, and baseline comparability assessed using chi-square tests (for categorical variables) and independent *t*-tests (for continuous variables) as appropriate. To investigate the association between engagement in, and frequency of, knee bending activities (exposures) and the prevalence of either Hoffa or effusion synovitis (outcomes), unadjusted and adjusted multivariate logistic regression was performed, calculating crude and adjusted odds ratios (ORs) and 95% CIs accordingly. Analyses were adjusted for the presence of metabolic syndrome, physical activity level, and sex as potential confounders. Confounders were selected considering causal diagrams as well as changes in ORs of the exposure variables when adding confounders separately to the models. The Hosmer-Lemeshow test was implemented to evaluate model calibration ($P > 0.05$). Sensitivity analyses were performed using an alternative definition of synovitis prevalence (≥ grade 2) according to a similar statistical approach. All analyses were performed in Stata software, version 15.1. *P* values less than 0.05 were considered significant.

RESULTS

The mean ± SD age of the participants was 61.5 ± 8.9 years, and 59% (n = 348) were female. Approximately 60% (n = 364 [61%]) had evidence of radiographic tibiofemoral OA, and features of metabolic syndrome appeared common (n = 490 [83%]). Similarly, the presence of grade ≥1 Hoffa synovitis (n = 353 [59%]) and/or effusion synovitis (n = 366 [62%]) was established in two-thirds of the sample. While stair climbing (n = 352 [59%]) and heavy lifting (n = 414 [70%]) were frequently performed, only up to one-fourth of participants on average reported squatting (n = 82 [14%]), kneeling (n = 151 [25%]), or getting in/out of a squatting position (n = 160 [27%]). Participants with effusion synovitis exhibited sig-

Table 1. Participant characteristics, with synovitis measured as grade ≥1*

Characteristics	All (n = 594)	No Hoffa synovitis (n = 241)	Hoffa synovitis (n = 353)	No effusion synovitis (n = 228)	Effusion synovitis (n = 366)
Demographics and symptoms					
Age, mean ± SD years	61.5 ± 8.9	60.8 ± 9.1	62.0 ± 8.7	61.2 ± 8.7	61.8 ± 9.0
Female	348 (59)	149 (62)	199 (56)	127 (56)	221 (60)
WOMAC pain, mean ± SD (range 0–20)†	2.4 ± 3.1	2.12 ± 2.85	2.60 ± 3.28	1.97 ± 2.84	2.68 ± 3.26‡
Metabolic syndrome	490 (83)	203 (84)	287 (81)	181 (79)	309 (84)
Body mass index, mean ± SD kg/m†	30.7 ± 4.8	31.0 ± 4.7	30.5 ± 4.8	30.5 ± 4.8	30.9 ± 4.8
Structural parameters					
K/L grade ≥2	364 (61)	155 (64)	209 (59)	128 (56)	236 (65)§
Hoffa synovitis					
Grade 0	241 (41)	241 (100)	0 (0)‖	117 (51)	124 (34)§
Grade 1	301 (51)	0 (0)	301 (85)‖	104 (46)	(54)§
Grade 2	47 (8)	0 (0)	47 (13)‖	7 (3)	40 (11)§
Grade 3	5 (1)	0 (0)	5 (1)‖	0 (0)	5 (1)§
Effusion synovitis					
Grade 0	228 (38)	117 (49)	111 (31)‖	228 (100)	0 (0)§
Grade 1	249 (42)	102 (42)	147 (42)	0 (0)	249 (68)§
Grade 2	97 (16)	21 (9)	76 (22)‖	0 (0)	97 (27)§
Grade 3	20 (3)	1 (0)	19 (5)‖	0 (0)	20 (6)§
Knee bending and physical activity					
≥1 frequent knee bending activity	441 (75)	174 (73)	267 (76)	168 (74)	273 (75)
Stair climbing (≥10 flights)#	352 (59)	141 (59)	211 (60)	140 (61)	212 (58)
None	242 (41)	100 (42)	142 (40)	88 (39)	154 (42)
≤1 day/week	20 (3)	7 (3)	13 (4)	4 (2)	16 (4)
2–3 days/week	54 (9)	25 (10)	29 (8)	21 (9)	33 (9)
4–5 days/week	49 (8)	21 (9)	28 (8)	18 (8)	31 (9)
Nearly every day	229 (39)	88 (37)	141 (40)	97 (43)	132 (36)
Kneeling (≥30 minutes)#	151 (25)	47 (20)	104 (30)‖	63 (28)	88 (24)
None	443 (75)	194 (81)	249 (71)‖	165 (72)	278 (76)
≤1 day/week	81 (14)	23 (10)	58 (16)‖	33 (15)	48 (13)
2–3 days/week	37 (6)	12 (5)	25 (7)‖	14 (6)	23 (6)
4–5 days/week	14 (2)	7 (3)	7 (2)‖	6 (3)	8 (2)
Nearly every day	19 (3)	5 (2)	14 (4)‖	10 (4)	9 (3)
Squatting (≥30 minutes)#	82 (14)	29 (12)	53 (15)	30 (13)	52 (14)
None	512 (86)	212 (88)	300 (85)	198 (87)	314 (86)
≤1 day/week	33 (6)	10 (4)	23 (7)	11 (5)	22 (6)
2–3 days/week	34 (6)	13 (5)	21 (6)	14 (6)	20 (6)
4–5 days/week	8 (1)	4 (2)	4 (1)	3 (1)	5 (1)
Nearly every day	6 (1)	2 (1)	4 (1)	2 (1)	4 (1)
Lifting/moving objects ≥25 pounds#	414 (70)	161 (67)	253 (72)	164 (72)	250 (68)
None	180 (30)	80 (33)	100 (28)	64 (28)	116 (32)
≤1 day/week	132 (22)	54 (22)	78 (22)	50 (22)	82 (22)
2–3 days/week	152 (26)	65 (27)	87 (25)	58 (25)	94 (26)
4–5 days/week	61 (10)	19 (8)	42 (12)	26 (11)	35 (10)
Nearly every day	69 (12)	23 (10)	46 (13)	30 (13)	39 (11)
Getting in/out of squatting position ≥10 times#	160 (27)	60 (25)	100 (28)	60 (26)	100 (27)
None	434 (73)	181 (75)	253 (72)	168 (74)	266 (73)
≤1 day/week	39 (7)	16 (7)	23 (7)	10 (4)	29 (8)
2–3 days/week	64 (11)	22 (9)	42 (12)	28 (12)	36 (10)
4–5 days/week	32 (5)	15 (6)	17 (5)	12 (5)	20 (6)

(Continues)

Table 1. *(Cont'd)*

Characteristics	All (n = 594)	No Hoffa synovitis (n = 241)	Hoffa synovitis (n = 353)	No effusion synovitis (n = 228)	Effusion synovitis (n = 366)
Nearly every day	25 (4)	7 (3)	18 (5)	10 (4)	15 (4)
Physical activity score, mean ± SD (range 0–400)**	163.9 ± 83.0	159.8 ± 84.1	166.6 ± 82.3	165.5 ± 79.7	162.8 ± 85.2

* Values are the number (%) unless indicated otherwise. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; K/L = Kellgren/Lawrence.
† Higher scores indicate worse pain.
‡ Significantly different at $P < 0.05$ compared with participants without effusion synovitis in an independent *t*-test.
§ Significantly different at $P < 0.05$ compared with participants without effusion synovitis in a chi-square test.
⁋ Significantly different at $P < 0.05$ compared with participants without Hoffa synovitis in a chi-square test.
Participation in knee bending activity during a single day, during the past 30 days.
** Higher scores indicate greater physical activity levels.

nificantly worse WOMAC pain ($P = 0.007$) and greater proportion of definite knee OA ($P = 0.042$) compared to those without effusion synovitis, while no such differences were established between participants with and without Hoffa synovitis (Table 1).

Hoffa synovitis. Among individuals with Hoffa synovitis (n = 353), the majority (n = 301 [85%]) were assigned mild grade 1 Hoffa synovitis. Of all activities studied, kneeling for ≥30 minutes was associated with grade ≥1 Hoffa synovitis prevalence, in both unadjusted and adjusted analyses (Table 2). Adjusted for confounders, kneeling was associated with 65% greater odds of Hoffa synovitis (OR 1.65 [95% CI 1.11–2.47]; $P = 0.014$). When compared with participants who did not kneel for ≥30 minutes during a single day, participants who had engaged in this activity ≤1 day per week had significantly greater odds for prevalent Hoffa synovitis on MRI (adjusted OR 1.88 [95% CI 1.11–3.18]; $P = 0.018$). No other significant associations were found between frequency of knee bending activities and Hoffa synovitis prevalence (data not shown). Sensitivity analyses yielded similar findings (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23760/abstract).

Effusion synovitis. Of the participants with prevalent effusion synovitis (n = 366), 68% (n = 249) presented with small grade 1 effusion. There were no significant associations between any of the knee bending activities and the prevalence of effusion synovitis, either in unadjusted or adjusted analyses (Table 2). Frequency of knee bending activities also did not significantly associate with prevalence of effusion synovitis (data not shown). Results remained unchanged in sensitivity analyses (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23760/abstract).

DISCUSSION

In individuals at risk of and with knee OA and a considerable proportion presenting with surrogate markers of synovitis on noncontrast MRI, we found that kneeling for at least 30 minutes during a single day was the only knee bending activity to associate with a greater likelihood of grade ≥1 Hoffa synovitis. To the best of our knowledge, we were the first to investigate the association between specific knee bending activities and synovitis prevalence in a relatively large sample of knee OA. Our observation partly agrees with Roze et al (4), showing a greater prevalence of Hoffa synovitis in active and lean individuals with knee OA than in those with metabolic syndrome. Although prolonged kneeling was associated with a surrogate MRI outcome of synovitis, Hoffa synovitis readings in particular are known to be nonspecific, also portraying other pathologies, such as Hoffa disease (9). Indeed, knee bending beyond 90° of flexion causes increased pressures within the infrapatellar (Hoffa) fat pad (11). Thus, prolonged deep knee flexion during kneeling may have induced fat pad inflammation, increasing signal on fluid-sensitive MRI (9,12). Although crosstalk between the infrapatellar fat pad and cartilage/synovium likely exists, furthering inflammatory processes in OA, we cannot conclusively discern synovitis from Hoffa disease due to the lack of contrast-enhanced imaging or biopsy results (9,12). Furthermore, semiquantitative assessments of Hoffa synovitis are also known to be less reliable than measurements of effusion synovitis (8,9). Given that dissociating grade 0 from grade 1 synovitis is challenging (8), analyses may have been prone to misclassification errors (likely independent from exposure status) and may have underestimated, rather than overestimated, associations observed. Notably, however, reliability estimates from the FNIH substudy were improved compared with previous endeavors (8,9), and sensitivity analyses revealed similar findings overall.

Kneeling for ≤1 day per week increased the likelihood of Hoffa synovitis prevalence compared with no such activity at all. While only a few participants (n = 70 [12%]) indicated prolonged kneeling for >1 day per week, one may consider that a risk of misclassification existed, particularly between categories indicating engagement for ≤1 day per week or none at all. Although impossible to clearly apprehend the extent of such errors, the probability of misclassification was unlikely to be conditional on

Table 2. Association between knee bending activities and prevalence of Hoffa synovitis (grade ≥1) and effusion synovitis (grade ≥1)*

	Unadjusted	Adjusted†	LH test
Hoffa synovitis‡			
Stair climbing ≥10 flights	1.05 (0.76–1.47)	1.01 (0.72–1.41)	0.58
Kneeling ≥30 minutes	1.72 (1.16–2.55)§	1.65 (1.11–2.47)§	0.95
Squatting ≥30 minutes	1.29 (0.79–2.09)	1.23 (0.75–2.01)	0.62
Lifting/moving objects of ≥25 pounds	1.26 (0.88–1.79)	1.17 (0.80–1.70)	0.50
Getting in/out of squatting position ≥10 times	1.19 (0.82–1.73)	1.13 (0.76–1.67)	0.49
Effusion synovitis‡			
Stair climbing ≥10 flights	0.87 (0.62–1.21)	0.90 (0.64–1.27)	0.83
Kneeling ≥30 minutes	0.83 (0.57–1.21)	0.87 (0.60–1.27)	0.92
Squatting ≥30 minutes	1.09 (0.67–1.77)	1.15 (0.70–1.88)	0.86
Lifting/moving objects of ≥25 pounds	0.84 (0.58–1.21)	0.89 (0.61–1.31)	0.93
Getting in/out of squatting position ≥10 times	1.05 (0.72–1.53)	1.13 (0.76–1.68)	0.89

* Values are the odds ratio and 95% confidence interval, unadjusted and adjusted for confounders, unless indicated otherwise. Model fit is expressed using the *P* value from the Losmer-Hemeshow (LH) test.
† Adjusted for presence of metabolic syndrome, physical activity level, and sex.
‡ Participation in knee bending activity during a single day, during the past 30 days.
§ Significant at $P < 0.05$.

synovitis prevalence. Nevertheless, bias of this nature, if any, may have exaggerated the respective effect estimate. Replication in other samples is needed to better understand the relationship between knee bending frequency and synovitis prevalence.

We were unable to support any other associations between knee bending activities and the prevalence of either Hoffa synovitis or effusion synovitis. Our findings agree with a study by Helmark et al (5) reporting that in 11 individuals with knee OA, no changes were observed in synovial fluid concentrations of proinflammatory cytokines following a moderate-intensity weight-bearing knee bending exercise. Indeed, depending on the duration and type of muscle contractions as well as the amount of activated muscle mass, quadriceps muscle contractions, as required during knee bending activities, may induce a significant release of muscle interleukin-6 with a net antiinflammatory, rather than proinflammatory, effect as a result (13).

Our results overall suggest that knee bending may not play a significant role in synovitis prevalence in individuals at risk of and with knee OA. Nevertheless, issues of selection bias should be considered when interpreting these findings. Indeed, we analyzed baseline data from the FNIH substudy, a selected sample drawn from the OAI cohorts. Briefly, participants with severe joint space narrowing and high levels of pain at baseline were excluded from the study. First, this exclusion may partly explain the relatively small proportion of individuals with moderate and severe synovitis on MRI as well as our inability to establish significant differences in pain severity between individuals with and without Hoffa synovitis. Second, selection as such may have indirectly influenced the extent to which individuals engaged in knee bending and exhibited synovitis on MRI. Notably, however, 75% (n = 441) of the current sample reported ≥1 knee bending activity during the past 30 days, similar to the level of the main OAI cohort serving as a model for the target population of individuals at risk of and with knee OA (n = 3,460 [73%]). Additionally, the current prevalence of Hoffa and effusion synovitis (59% and 62%, respectively) lies within ranges reported previously using data from cohorts other than the OAI that investigated individuals at risk (8–11%) (14) or with symptomatic knee OA (69–79%) (15). However, exploration of our data revealed that 63% and 57% of the individuals at risk of knee OA presented with Hoffa and effusion synovitis (data not shown), respectively, much higher than previously reported (14,15). Partly due to our definition of synovitis prevalence (grade ≥1) being prone to misclassification errors, individuals without synovitis may well have been under-sampled, potentially attenuating associations investigated. Notably, sensitivity analyses using a cutoff grade ≥2 for synovitis prevalence led to increased proportions of individuals without synovitis and generally greater effect-size estimates but with similar findings overall. Finally, due to the lack of availability of relevant data, we as well as others (4) implemented a proxy definition for the presence of metabolic syndrome, potentially underestimating its true impact in the associations under study (4).

In conclusion, in individuals at risk of and with definite knee OA and a preponderance showing grade ≥1 Hoffa and/or effusion synovitis on noncontrast MRI, only kneeling for at least 30 minutes during a single day was associated with a greater likelihood of Hoffa synovitis. Because this was a selected sample, replication is warranted to better understand the role of repetitive knee bending in synovitis prevalence.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final ver-

sion to be published. Dr. Van Ginckel 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. Van Ginckel.

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Strategies for Managing the Costs of Chronic Illness in the Context of Limited Financial Resources: A Qualitative Study in Dominican Persons With Arthritis

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Objective. Persons who reside in low- and middle-income countries often have insufficient resources to pay for treatments prescribed for their medical conditions. The aim of this study was to determine, using qualitative methods, how patients with arthritis in the Dominican Republic manage the costs associated with chronic illnesses.

Methods. We conducted individual interviews with 17 Dominican adults with advanced arthritis who were undergoing total knee replacement or total hip replacement at a hospital in Santo Domingo, Dominican Republic. Interviewers followed a moderator's guide with questions pertaining to the financial demands of arthritis treatment and the strategies participants used to pay for treatments. Interviews were audio recorded, transcribed verbatim, and translated into English. We used thematic analysis to identify salient themes.

Results. The thematic analysis suggested that health system factors (such as the extent of reimbursement for medications available in the public health care system) along with personal factors (such as disposable income) shaped individuals' experiences of managing chronic illness. These systemic and personal factors contributed to a sizeable gap between the cost of care and the amount most participants were able to pay. Participants managed this resource gap using a spectrum of strategies ranging from acceptance (or, "making do with less") to resourcefulness (or, "finding more"). Participants were aided by strong community bonds and religiously oriented resilience.

Conclusion. This qualitative study illuminates the range of strategies Dominican individuals with limited resources use to obtain health care and manage chronic illness. The findings raise hypotheses that warrant further study and could help guide provider–patient conversations regarding treatment adherence.

INTRODUCTION

Chronic medical conditions, such as arthritis, are the leading cause of illness, disability-associated life-years, and mortality in both high- and low-income countries (1–4). It is estimated that osteoarthritis (OA), the most prevalent form of arthritis, affects 10–15% of adults ages >60 years worldwide (5–8). Individuals living in resource-limited countries typically manage arthritis with a combination of analgesics, antiinflammatory medications, home remedies (9), and behavioral coping mechanisms (10). In the latter category, religion often plays an important role in dealing with illness (10,11). Purchasing treatments places a sizeable financial burden on individuals in low- and middle-income countries (12–14), leaving them to forego part of the treatment or identify additional resources (15–19). Higher out-of-pocket costs contribute to lower adherence (16,20–22), and individuals with lower socioeconomic status are less likely to adhere to treatment regimens (23–26).

There is limited research on the manner in which individuals living in resource-limited settings manage the costs of chronic illness given scant personal resources (27,28). In particular, only a few qualitative studies have addressed this topic (16,29,30). The findings of these studies suggest that individuals with limited financial resources may delay care, substitute alternative medicine, and/or draw on social resources for transportation or financial support (16,29,30). A need remains to understand how these individuals make decisions about whether to utilize care and, when deciding to seek care, how they bridge any gaps in available resources. Further qualitative research can help provide nuanced insights into the coping and payment strategies used by patients

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SIGNIFICANCE & INNOVATIONS

- In a middle-income country with stark income inequality (Dominican Republic), there is societal decision-making that perpetuates a lack of access to health care.
- When available resources are insufficient for accessing health care, there is a range of strategies used by Dominican individuals to manage chronic illness.
- Knowledge regarding strategies that patients may use to manage chronic illness when lacking resources for medications is beneficial for clinicians working in resource-limited settings.
- There is a need for policies that address underinsurance and transportation-related barriers to care.

with chronic illness in a resource-limited setting, identify obstacles to care, and generate hypotheses for future studies. The objective of this study was to use qualitative methods to examine how individuals with arthritis living in the Dominican Republic, a middle-income country with stark income inequality (31), make decisions about utilizing health care given the scant resources available to them. The study's guiding questions were "How do Dominican individuals living with arthritis and other chronic conditions manage the costs of chronic illness?" and "How do they make health care utilization decisions?"

SUBJECTS AND METHODS

Setting. The Dominican Republic occupies the eastern portion of the Caribbean island of Hispaniola. Approximately 30.5% of the population lives below the international poverty line (32). The government spends roughly 4.4% of the per capita gross domestic product of $6,722 on health care (33,34). The government-subsidized health insurance plan (the "subsidized regime"), Seguro Nacional de Salud (SENASA), is the most widely used among impoverished, unemployed, or disabled Dominican individuals (31). SENASA covers much less expenditure than the plans covering salaried workers ("contributive regime"), and the quality and reliability of services is known to be lower (31). SENASA benefits typically cover the costs of catastrophic care, some medications, and ambulatory care, but provide limited coverage for specialty care, including joint replacement and multiple medications.

Subjects. Seventeen participants were selected from among the 42 patients chosen for Operation Walk Boston (OpWalk Boston) in 2017. OpWalk Boston is a nonprofit, volunteer organization that has conducted annual trips since 2008 to provide total hip replacement (THR) and total knee replacement (TKR) surgeries to financially limited individuals in the Dominican Republic. Because there were no exclusions for this study, a random assortment of OpWalk participants was approached either before surgery (at least 2 hours) or postoperatively (not on the same day as surgery). Patients learn about OpWalk through advertisement, word of mouth, or physician referral and are selected based on financial and medical criteria.

Patients are considered financially eligible if they do not have sufficient health insurance or personal funds to cover the costs of surgery. Medical eligibility criteria include symptomatic radiographically advanced hip and/or knee arthritis and otherwise stable health status. All participants were assured that their participation was voluntary, anonymous, and would not affect the care administered to them by OpWalk. All participants provided verbal consent. The study was approved by the Partners HealthCare Institutional Review Board (protocol no. 2010P_000082).

Procedures. During OpWalk Boston 2017, two interview teams, each including at least 1 native Spanish speaker, performed 17 interviews over 3 days. Interviews were conducted in Spanish and audio recorded. Interviewers followed a moderator's guide (Table 1) that was developed and reviewed by Boston members and Dominican members of the research team, in order to ensure that all questions were comprehensible and appropriate. Interviews were organized to flow as a conversation might, beginning with general questions about experiences with arthritis and progressing to more specific probes about coping with the financial demands of health care. Recordings were transcribed and translated into English by one of the authors, who is bilingual (CC), and verified by a second bilingual colleague. Participant identifiers were removed from the transcripts, and speakers are identified by study ID number alone.

Thematic analysis. Using data from all transcripts, we conducted thematic analysis, a commonly used inductive method of qualitative analysis (35). First, investigators coded a portion of the transcript text, using words or phrases to identify the most basic segments of data deemed meaningful in relation to the guiding questions of the study, which included, "How do Dominican individuals living with arthritis and other chronic conditions manage the costs of chronic illness?" and "How do they make health care utilization decisions?" Comparing the transcripts coded by each investigator, a single coding scheme was developed. Two co-authors (JN, CC) then coded the remaining data according to this scheme, adding codes when necessary to reflect relevant ideas that had not been identified in the first portion of data coding.

Next, themes were generated. Themes express patterns in the data in relation to the guiding questions of the study, often by grouping codes or otherwise expressing relationships among them. The investigators met to develop an initial thematic scheme comprising themes, subthemes, and ideas about the relationships among them. Two investigators (JN, CC) linked all transcript excerpts with the appropriate themes

Table 1. Moderator's guide

Topics	Questions
Demographics	1. Level of education? (None, elementary complete/incomplete, high school complete/incomplete, university complete/incomplete) 2. What kind of setting do you live in? (city, town, or small village)
Arthritis experiences	1. For how many years have you experienced pain or problems related to arthritis? 2. How many years ago was your arthritis diagnosed? 3. Tell me about your arthritis. How has it affected your life? 4. Do you take daily medication for your arthritis?
Affording arthritis medication	1. Where do you get your medicine from? Have you ever had limited access to medications due to transportation issues? 2. Do you know the cost of your medication? Do you have insurance that covers it? a. If you are short of money for medications, do you find other ways of getting the money or do you have to miss doses? How can you ask for money if you need more than you have? 3. Do you ever have to make choices between paying for medication and something else (food, school, clothes, housing, etc.)? 4. Have you ever skipped doses, stopped taking your medication, or switched to a lower dose because you were unable to pay for the prescribed amount?
Affording medication in general	1. Are you on any other medications? a. If so, have you had problems paying for these medications? b. If you have had problems paying, what do you do? Find the money somehow? Miss doses? Get medications donated from community members? 2. If you have difficulty paying for medications, do you try other treatments that are less expensive? a. Probe: for example, switching to a different medication for the same disease without consulting your doctor, herbal remedies, teas, prayer, song, spiritual healing?
Visiting a doctor	1. What do you see a doctor for? In the last year, how many times did you see a doctor for arthritis pain? 2. Is there any reason why you would not see the doctor more often (payment, travel distance, work requirements, etc.)? 3. Can you think of times when you had to miss a visit because you could not afford to pay for it, or when you could not find transportation? 4. If you cannot pay for a visit, do you usually miss it or do you find the money somehow? How?
Insurance	1. Do you have insurance that covers your doctors' visits? 2. If yes: a. What type of insurance do you have (national/private)? b. Does the insurance cover the whole visit, or do you have to pay for part? How much do you pay for? Does anyone help you pay for these visits? c. How do your friends and family pay for medications and doctors' visits? 3. If no: a. How do you pay for these visits? b. Does the doctor ever charge less for people who can't pay as much? 4. Do you think that difficulty with paying for medications and doctors' visits has worsened your health?

using qualitative data analysis software (Dedoose). Themes and their interrelationships were portrayed visually in a thematic map (Figure 1). All investigators met to refine the thematic scheme and the thematic map, and all approved the final versions.

RESULTS

Of the 42 individuals participating in OpWalk 2017, 17 were approached for interviews and all consented. Two were male and 15 were female, and all were between 32 and 86 years of age. Nine had experienced joint pain for 5–15 years, and 8 had experienced joint pain for >15 years. One participant had rheumatoid arthritis, while the rest had OA (risk factors among the participants with OA included prior injury, obesity, and older age). Nine of the participants lived in Santo Domingo (where the hospital is located) and 8 were from outside of the capital city.

Themes were identified and grouped into 2 broad categories, including factors that contribute to an imbalance between participants' resources and their health care needs (Figure 1), and the spectrum of coping mechanisms addressing this imbalance (Figure 1). The following section describes each theme or subtheme and presents supporting interview data. A comprehensive list of supporting quotations is provided in Supplementary Appendix A, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23742/abstract.

Factors contributing to imbalance between available and needed resources. *Health care systems*. Participants noted that private health care has a variety of advantages over public health care but is not affordable for the majority of

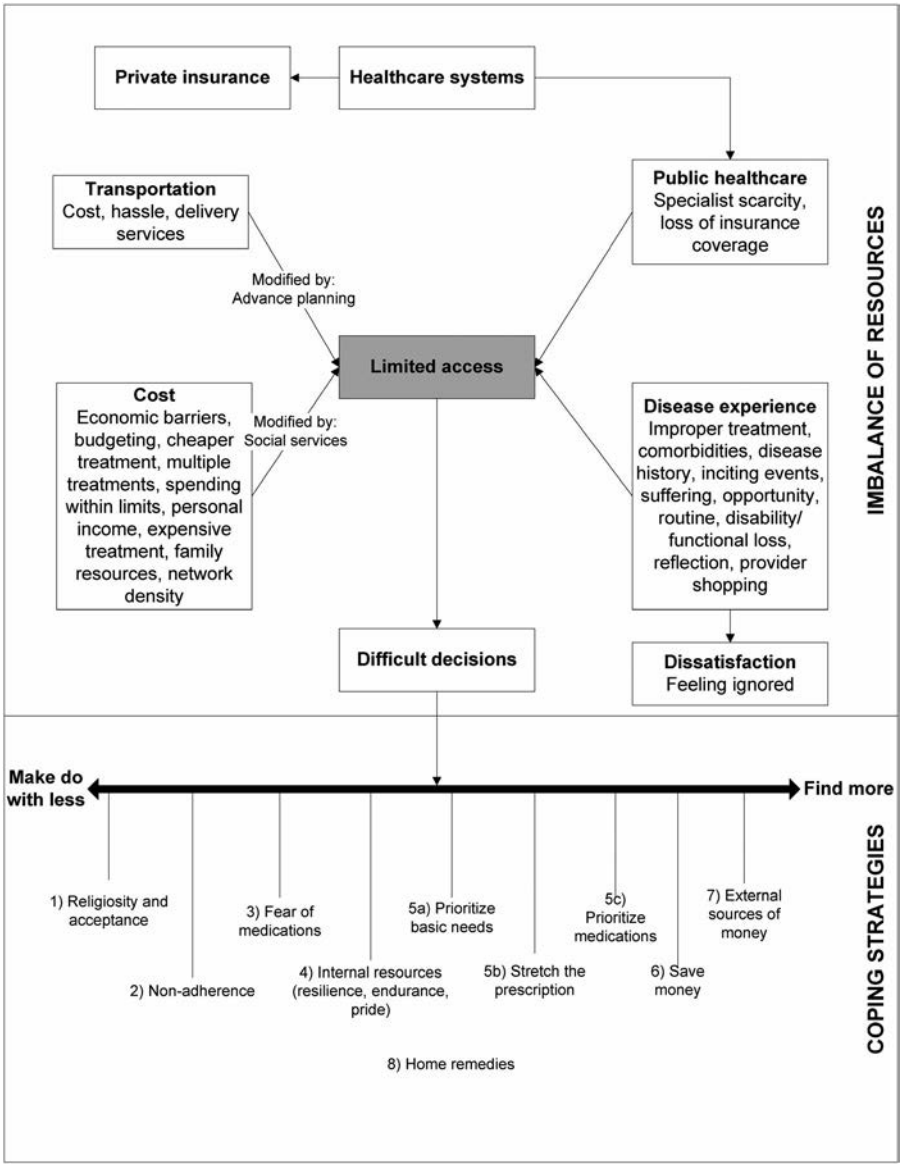

Figure 1. Thematic map.

Dominican citizens. The individuals selected for OpWalk were all insured by government-subsidized SENASA, which does not cover costly elective procedures such as THR and TKR. Many participants talked about the barriers arising from lack of adequate insurance or personal resources: "With the insurance I had he charged me 500 pesos… But…they took my insurance away, and when I returned to him I had to pay 1,500. I no longer have that so I go home" (Subject 1021) (Note: At the time of the interview, 500 Dominican pesos was worth approximately 12 US dollars at an exchange rate of 40 pesos per dollar).

Others mentioned quality issues, including specialist scarcity, in the public hospitals that they used when private clinics were not accessible: "I don't worry about going to doctors that are good. Because if I don't have money I go to the Goico [a public hospital], I go to the medical dispensaries that are in the poor neighborhoods, you see?" (Subject 1021).

Cost. A major contributor to limited access was the cost of health care, which inhibited both care and treatment:

> Moderator: Ok. If you can't pay for a medical appointment, generally do you lose the appointment, or try to find the money somehow?
> Subject 1073: No—well sometimes I lose it…
> Moderator: Have you ever had problems to—to buy those medications?
> Subject 1073: Of course! Of course.

Often, the inability to afford medicine offered at an ordinary pharmacy drove participants to seek cheaper options at economy pharmacies. These boticas (or, economy pharmacies) offer a variety of alternative treatments (e.g., menthol) as well as reduced doses of standard over-the-counter painkillers. However, some of

the participants expressed distrust in these pharmacies because the medicine purchased there may be less effective: "I don't like medications from the economy pharmacy because…[they] don't have many …components" (Subject 1063).

In order to manage financial limitations, some participants received discounts from social services: "There, you go and after they give you the little paper you go to a department that they send you to, Social [services], and…if you can prove with your information that you don't have the capacity to pay what is needed to pay, they reduce the price" (Subject 1031).

Transportation. Lack of transportation also emerged as an important barrier. Sometimes the burden of finding a ride to the hospital proved immense. Furthermore, not all participants lived within the vicinity of the hospital: "Sometimes I was late, because from here in the city to where I live takes about two hours" (Subject 1076).

Some sought rides with family members or friends, but others were restricted to public transportation, which in some cases became another financial burden:

> Subject 1015: I have to get around in a taxi.
> Moderator: Ok and if you don't have enough for the fare…
> Do you lose the appointment?
> Subject 1015: I lose the appointment.

Some participants mentioned being unable to make the trip to the pharmacy due to limited physical function. Participants called on family members to make these trips or utilized pharmaceutical delivery services.

Disease experience. Most participants had been reporting joint pain for several years. Many also reported having comorbidities that required medical attention, with hypertension being especially common. Some used wheelchairs to move around. Many reported severe limitations in daily routine: "It has affected my life… immeasurably. Because… it has deteriorated my knees, everything, and I can't walk" (Subject 1054).

While some participants were able to obtain analgesics for their joint pain, others lacked the necessary resources: "If you get sick, and you don't have medications, what are you going to do, tell me? You have to stay that way because you don't have medications" (Subject 1021).

Ultimately, many were dissatisfied with their situations. Some expressed frustration with the system or felt ignored due to lack of coverage:

> Subject 1029: The Hippocratic oath does not exist anymore.
> Moderator: You think [doctors] are insensitive?
> Subject 1029: Totally.

Together, these first 4 themes portray an imbalance between participants' health care needs and the resources required for access to health care. Due to this imbalance, participants faced difficult decisions, which included how to expend resources, prioritize treatments, and manage their illnesses without added costs.

Strategies to cope with an imbalance between available and needed resources. Participants adopted coping strategies in response to lacking the resources needed to acquire health care. We identified eight themes, which encompass 6 additional sub-themes, regarding these strategies. We plotted these on a spectrum, in which the left end represents strategies employed to "make do with less" and the right end represents acquiring additional resources (Figure 1). We note that some of these strategies represent deliberate choices by participants (e.g., decisions to miss doses of medications to make a fixed supply last longer), while in other circumstances the strategies seemed less deliberate but ultimately served the same purpose of stretching resources (e.g., genuine fear of medications).

Religiosity and acceptance. On the far left of the spectrum are the strategies derived from acceptance of one's condition (as opposed to actively trying to change it). Religiosity was a means of support: "One prays, 'God help me take away this pain,' because, He is the one who can do everything" (Subject 1008).

Others ascribed to their deity the power to improve their condition: "Well, that's how I held on until God wanted… waiting to find something someday" (Subject 1063).

Acceptance allowed participants to feel as if they had adapted to the circumstances of their illness: "I adapt to my–my circle of poverty… that exists" (Subject 1076).

Nonadherence. Moving to the right on the spectrum, some participants were deliberately nonadherent to their treatment regimens (22). This nonadherence caused a reduction in the gap between needed and available resources. As noted earlier, some participants described being nonadherent for reasons other than conserving resources. Some felt that treatment was either unnecessary because their condition was not debilitating enough, or useless due to the advanced degree of their disease: "I no longer use anything because it hurts all over" (Subject 1011). Others were nonadherent less purposefully, due to forgetfulness: "Sometimes I don't take it because I forget to" (Subject 1073).

Fear of medications. Several participants expressed fears that commonly prescribed arthritis medications would impact their health negatively if taken too frequently. Such fears provided another, distinct motivation (in addition to lack of resources) for using less medication. Some described a fear of addiction that motivated deliberate underdosing: "I take [medication] when it hurts, when I feel too much pain. I don't like to get myself addicted" (Subject 1015).

Others discontinued use of arthritis medications because they feared side effects: "I don't want to saturate my liver and my kidneys" (Subject 1029).

Having comorbidities, such as gastritis, diabetes mellitus, and/or hypertension made some participants more wary of

medication side effects: "I go to the doctor for rheumatism, the muscle pains. I go for my stomach… eh… I go… you know that, the stomach is something that is harmed by those medications you take" (Subject 1031).

Internal resources (resilience, endurance, pride). Many participants used internal resilience, endurance, and other emotional resources to cope with advanced disease:

> Moderator: Last year you didn't see any doctors for your legs?
> Subject 1063: Mmm no. I put up with it.
> Moderator: And why…do you prefer to not go to the doctor?
> Subject 1063: Well, because the solution was an implant and I couldn't get it.

Some emotional resources, such as pride, discouraged participants from searching for additional material resources: "Because if a poor person doesn't have [money] they're not going to do what they can't afford because then they lose their merit and dignity" (Subject 1021).

Prioritization. Participants commented on the challenge of balancing different financial responsibilities. The low socioeconomic status of many participants placed them in the position of choosing among basic needs.

Prioritize basic needs. Some participants chose to use their scant economic resources to cover basic needs, such as food and housing, with the awareness that it would impact their treatment regimen: "I have had times where I have enough to buy the medication but not to eat the food I need on a daily basis. So I have to take out from what I saved for my medication in order to buy the week's food" (Subject 1031).

Stretch the prescription. Unwilling to forego treatment entirely, some participants employed strategies to make their medications last longer, either skipping doses, using an incomplete course of treatment, or using lower doses of their prescribed medications.

> Moderator: Have you ever omitted doses or stopped taking the medication, or used a lower dose because you couldn't pay for the prescribed amount?
> Subject 1049: Well, sometimes, because sometimes you have limitations and I've had to lower [the dose]. I've put up with this pain, due to not having [medication] in those moments.

Prioritize medications. Some participants were steadfast in prioritizing their medications above other necessities.

> Moderator: Would you stop buying other things, like clothes?
> Subject 1029: Of course yes. I even stopped buying quality food.

Save money. Another strategy toward the right of the spectrum was saving money for medications. Some participants did so by allocating resources for medications immediately after receiving their monthly income: "At least I almost never miss [my medication], because every month I take money to buy it…I set that money [aside]. I take it out first" (Subject 1054).

Others sought less costly treatments, even if they were less effective: "Sometimes I take more acetaminophen, which is another thing for the pains. Because it is less expensive, you see? If I don't have money then I have to buy what's least expensive to always maintain myself" (Subject 1021).

External sources of money. We placed strategies focused on finding additional resources on the far right of the spectrum. External sources of money, those that would not be within the participant's immediate reach under other circumstances, were a significant help for many in accessing health care.

Family. Perhaps the most important external source of money was the participant's own family, whether small or large, nuclear or extended, near or far. Larger families provided more security in this regard. When asked what they would do if they needed more money, one participant answered: "I ask for it. That's what I have four boys for. Four daughters and four boys, I have eight" (Subject 1063).

Other social networks. Participants described calling on additional social networks, such as employers or religious communities: "I belong to the church of the Adventists, and they have helped me with a prescription" (Subject 1011). One woman who worked as a domestic employee recalls: "I have worked in a house. They helped me a lot… I am alive today because of them. However many times I got sick, they would lay me down, call their doctor, and they would take care of me" (Subject 1051).

Some even utilized their social connections to obtain medications on credit: "The people at the pharmacy are very good friends of mine. I never have to worry about the payment. I pay my last bill and I take a medication" (Subject 1029).

Loans. Others deferred to more formal mechanisms and applied for loans: "Well I took loans. Since we teachers have a cooperative bank that we save up in, so I had to take a loan… Later they discount it from my own salary" (Subject 1049).

Home remedies. One strategy that was employed throughout the entire spectrum was the use of home remedies as adjunctive, lower-cost therapies (9). Thirteen of the participants described some type of home remedy in their treatment repertoire. Home remedies varied in their composition and use, from soursop leaf teas to sesame seed mixtures with honey: "I wash the sesame seeds, leave them to dry, and then I heat them in a pot and I pour in the honey to eat it. It works for your bones" (Subject 1053).

Thematic map. The thematic map (Figure 1) depicts relationships among the themes and subthemes described above. Themes in the top half represent contributors to an imbalance between participants' health care needs and the resources available. The remaining themes represent the strategies that

participants report using in response to this imbalance. These range from strategies that decrease utilization of health care (whether intentionally or coincidentally) at the left, to strategies that involve actively seeking additional resources at the right (summarized by the principles of "make do with less" and "find more," respectively).

DISCUSSION

We conducted 17 interviews to understand how individuals in resource-limited settings cope with chronic arthritis and other comorbid illnesses and seek resources to obtain health care. We found that systemic factors related to the public health care system, insurance access, and transportation contributed to an imbalance between what the health care participants could afford and their perceived needs. In response, participants developed diverse coping mechanisms and resource acquisition strategies.

Our qualitative approach allowed us to identify a range of strategies that underinsured Dominican individuals may use to manage chronic illness in the context of low resource availability. Two previous qualitative studies in the same setting (Hospital General de la Plaza de la Salud, Santo Domingo) investigated modes of coping with arthritis. Yu and colleagues found that participants coped with pain while utilizing relatively little pain medication, in part by using nonpharmacologic therapies and social support networks (12). Niu et al similarly identified strategies that patients used to manage pain without medication (e.g., prayer) and to obtain medication (e.g., family financial support) (11). Recognizing that comorbid conditions present competing demands for a patient's resources, we elicited a more complete picture of factors that influence participants' utilization decisions by asking participants about how they obtain medication and other health care in general, not exclusively for treatment of arthritis. We note, for example, that hypertension and diabetes mellitus are common among Dominican individuals with OA; thus, patients' needs often include therapy for these comorbid illnesses.

A similar suite of strategies emerged in a qualitative study of individuals in a medically underserved area of the US, in which participants described the prioritization of their basic living expenses, drawing on social networks for financial and transportation help and delaying care or managing conditions independently for as long as possible (30). The results of previous studies also have suggested that individuals with limited financial resources compensate with social resources to access health care (27), and that alternative medicine plays an important role (29).

Elaborating on findings of previous studies, we found that individuals' coping strategies could be viewed along a spectrum (Figure 1), from accepting limited resources to seeking additional resources. The strategies toward the left of this spectrum are generally more passive. Religious beliefs, for example, were often cited as helping participants accept their illnesses, reflecting the well-documented importance of religion in Dominican culture (11). Moving further to the right on the spectrum, participants harnessed their resilience, creativity, and entrepreneurialism to find additional resources for receiving health care.

The findings of our qualitative analysis should be viewed as hypothesis-generating. These qualitative data suggest a set of themes related to managing chronic illness in persons with scant resources; however, further detailed quantitative studies are needed to confirm these observations. Additionally, participant characteristics limit the extent to which we may generalize findings. Our participants were all Dominican individuals with advanced arthritis who were scheduled to undergo joint replacement surgery. The majority of the participants were women. Coping strategies might differ in individuals with less severe arthritis, men, and those living in countries with different cultural practices and policy contexts.

The findings of the present study suggest avenues for further research and also have implications for clinical practice and policy. For clinicians working with low-income populations, it would be valuable to understand the strategies that patients may use when managing chronic illness, such as skipping doses or eliminating certain medications entirely, and why they may use these strategies. Participants reported that coverage under SENASA was often insufficient even for basic medications and office visits. In addition, transportation was a significant barrier for many participants. The present study demonstrates the need for policies that address underinsurance and transportation-related barriers to care. Without changes in the cost of services or the level of support provided to patients, the trends noted in our work will likely persist.

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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. Ms Nascimben 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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Changes in Lipid Levels and Incidence of Cardiovascular Events Following Tofacitinib Treatment in Patients With Psoriatic Arthritis: A Pooled Analysis Across Phase III and Long-Term Extension Studies

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Objective. The risk of cardiovascular disease (CVD) is higher in patients with psoriatic arthritis (PsA) compared to the general population. Tofacitinib is an oral Janus kinase inhibitor for the treatment of PsA. Because tofacitinib increases circulating lipid levels in some patients, we evaluated CVD risk factors and major adverse cardiovascular events (MACE) in patients with active PsA receiving tofacitinib 5 or 10 mg twice daily plus conventional synthetic disease-modifying antirheumatic drugs.

Methods. Data were pooled from 2 phase III studies (Efficacy and Safety of Tofacitinib in Psoriatic Arthritis [OPAL Broaden] and Tofacitinib in Patients with Psoriatic Arthritis With Inadequate Response to TNF Inhibitors [OPAL Beyond]) and 1 ongoing long-term extension (Open-Label Extension Study of Tofacitinib in Psoriatic Arthritis [OPAL Balance], data cutoff January 2017; database not locked). Outcomes included fasting lipid levels, blood pressure, hypertension-related adverse events (AEs; including hypertension, high blood pressure, and increased blood pressure), and MACE.

Results. Overall, 783 tofacitinib-treated patients were included. Percentage increases from baseline in low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c) levels ranged from 9% to 14% for tofacitinib 5 mg and 10 mg at 3 and 6 months; no meaningful changes in LDL-c:HDL-c or total cholesterol:HDL-c ratios were observed. Blood pressure remained stable for 24 months. Fifty-eight patients (7.4%) had hypertension-related AEs; none were fatal (incidence rate [IR] per 100 patient-years 4.81 [95% confidence interval (95% CI) 3.65–6.22]). Five patients (0.6%) had MACE (IR 0.24 [95% CI 0.05–0.70]); 2 were fatal.

Conclusion. Serum lipid level increases at month 3 following tofacitinib treatment in PsA were consistent with observations in rheumatoid arthritis and psoriasis. The IR of hypertension-related AEs and MACE was low; long-term follow-up is ongoing.

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SIGNIFICANCE & INNOVATIONS

- The magnitude and dose dependency of increases in lipid levels to month 6 in patients with psoriatic arthritis (PsA) receiving tofacitinib were consistent with findings in patients with rheumatoid arthritis (RA) and psoriasis.
- As increases in low-density lipoprotein cholesterol were paralleled by increases in high-density lipoprotein cholesterol (HDL-c), no meaningful changes in the total cholesterol:HDL-c ratio were observed.
- The incidence of major adverse cardiovascular events in patients with active PsA was within the range reported in prior tofacitinib studies in RA and psoriasis, and was generally consistent with data reported in the literature for other PsA treatments.
- There is no evidence at this time that treatment of PsA with tofacitinib is associated with increased cardiovascular risk.

INTRODUCTION

Psoriatic arthritis (PsA) is an immune-mediated systemic inflammatory disease with multiple disease manifestations, including peripheral arthritis, enthesitis, dactylitis, and spondylitis, together with skin and nail psoriasis (1). The risk of cardiovascular disease (CVD) and cardiometabolic disorders is higher in patients with PsA compared with the general population (2,3) and is considered comparable with rates in patients with rheumatoid arthritis (RA) and diabetes mellitus (4–7). Therefore, management of CVD risk factors is recommended (2,8,9). In addition, an association has been suggested between peripheral joint inflammation and lipid dysregulation in PsA (10).

Treatment options for PsA aim to achieve optimal control of disease activity through the suppression of inflammation (11). Tofacitinib is an oral Janus kinase inhibitor for the treatment of PsA. The efficacy and safety of tofacitinib have been demonstrated in 2 phase III studies (Efficacy and Safety of Tofacitinib in Psoriatic Arthritis [OPAL Broaden] [12] and Tofacitinib in Patients with Psoriatic Arthritis With Inadequate Response to TNF Inhibitors [OPAL Beyond] [13]) and 1 ongoing long-term extension (LTE) study (Open-Label Extension Study of Tofacitinib in Psoriatic Arthritis [OPAL Balance] [14]).

The objective of this post hoc analysis was to better understand the changes in cholesterol levels and other selected CVD risk factors as well as to evaluate the incidence of major adverse cardiovascular events (MACE), a composite of CVD deaths, nonfatal myocardial infarction, and nonfatal stroke in patients with active PsA receiving tofacitinib 5 and 10 mg twice daily (BID) in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) using data from 2 phase III studies (OPAL Broaden [12] and OPAL Beyond [13]) and 1 ongoing LTE study (OPAL Balance [14]).

PATIENTS AND METHODS

Data were analyzed for patients who received ≥1 dose of tofacitinib 5 or 10 mg BID or placebo, pooled across 2 phase III studies and 1 LTE study of the 2 phase III studies in patients with active PsA. OPAL Broaden (12) was a phase III, 12-month, double-blind, placebo- and active-controlled parallel-group study in adult patients with active PsA who were naive to tumor necrosis factor inhibitors (TNFi), who were receiving 1 background csDMARD, and who had a prior inadequate response to ≥1 csDMARD. Patients were randomized 2:2:2:1:1 to tofacitinib 5 mg BID, tofacitinib 10 mg BID, adalimumab 40 mg subcutaneously every 2 weeks, placebo advancing to tofacitinib 5 mg BID after 3 months, or placebo advancing to tofacitinib 10 mg BID after 3 months. OPAL Beyond (13) was a phase III, 6-month, double-blind, placebo-controlled, parallel-group study in adults with active PsA who were receiving 1 background csDMARD and who had an inadequate response to ≥1 prior TNFi. Patients were randomized 2:2:1:1 to receive tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo advancing to tofacitinib 5 mg BID after 3 months, or placebo advancing to tofacitinib 10 mg BID after 3 months. OPAL Balance (14) is an ongoing, open-label LTE study that enrolled patients who had participated in OPAL Broaden or OPAL Beyond. Data up to January 2017 (database not locked; data may change) were included in the current analysis, which included up to 3 years of tofacitinib exposure per patient. All patients received open-label tofacitinib 5 mg BID upon entry into OPAL Balance. The tofacitinib dosage could be increased to 10 mg BID at the investigator's discretion after 1 month, and could be decreased from 10 mg BID to 5 mg BID for safety reasons at any time. (For information on data sharing, see Supplementary Appendix 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23930/abstract.)

Patient eligibility and disposition. Eligible patients were age ≥18 years, had been diagnosed with PsA for ≥6 months prior to study participation, fulfilled the Classification criteria for Psoriatic Arthritis (15), and had active plaque psoriasis at screening and active arthritis (≥3 swollen and ≥3 tender/painful joints) at both screening and baseline (defined at the initiation of OPAL Broaden and OPAL Beyond) (12,13).

Assessments. Baseline demographics and patient characteristics from the corresponding qualifying study were used as baseline in the LTE. Pooled phase III data comprised phase III studies only and included placebo data up to month 3; pooled phase III and LTE data comprised tofacitinib data from the phase III and LTE studies (patients who were originally randomized to placebo were included, but only from the day that treatment with tofacitinib was initiated). Continuous

laboratory measurements such as fasting lipid levels and C-reactive protein (CRP) level analyses included pooled data from months 0 to 6 of phase III studies only (including tofacitinib 5 mg BID, tofacitinib 10 mg BID, and placebo up to month 3 only). Blood pressure measurements and data on hypertension were pooled across the phase III and LTE studies using tofacitinib-exposed patients only and were identified using a Standardized Medical Dictionary for Regulatory Activities (MedDRA, version 19.1) query for hypertension (narrow). All hypertension-related events were reported as adverse events (AEs) and included the terms hypertension, high blood pressure, and increased blood pressure.

Table 1. Baseline demographics and characteristics from the phase III studies OPAL Broaden and OPAL Beyond*

Characteristics	Tofacitinib 5 mg BID (n = 238)	Tofacitinib 10 mg BID (n = 236)	Placebo (n = 236)
Baseline demographics			
Female, no. (%)	121 (50.8)	136 (57.6)	136 (57.6)
Age, years	49.5 ± 12.4	49.4 ± 11.7	48.4 ± 12.5
White, no. (%)	226 (95.0)	221 (93.6)	222 (94.1)
Body mass index, kg/m^2	29.8 ± 6.3	30.2 ± 6.3	29.2 ± 5.6
Smoking history, no. (%)			
Never smoked	139 (58.4)	140 (59.3)	158 (66.9)
Smoker	37 (15.5)	45 (19.1)	39 (16.5)
Ex-smoker	62 (26.1)	51 (21.6)	39 (16.5)
Baseline medical history, no. (%)			
Diabetes mellitus†	29 (12.2)	37 (15.7)	34 (14.4)
Hypertension‡	99 (41.6)	81 (34.3)	87 (36.9)
Dyslipidemia§	60 (25.2)	67 (28.4)	55 (23.3)
Metabolic syndrome¶	99 (41.6)	101 (42.8)	94 (39.8)
Lipid laboratory values			
HDL-c, mg/dl	55.7 ± 16.9	56.5 ± 19.6	55.7 ± 17.5
LDL-c, mg/dl	116.8 ± 32.4	119.1 ± 37.2	114.6 ± 33.1
Triglycerides, mg/dl	146.7 ± 93.9	144.2 ± 150.4	137.3 ± 74.6
Baseline disease characteristics			
Psoriatic arthritis duration, years	8.6 ± 7.9	7.5 ± 6.6	8.1 ± 7.5
Baseline PASDAS#	6.1 ± 1.2	6.2 ± 1.2	6.0 ± 1.2
Baseline HAQ DI	1.2 ± 0.7**	1.2 ± 0.6	1.2 ± 0.7
Baseline CPDAI with baseline BSA ≥3%††	10.0 ± 2.5	10.4 ± 2.7	9.8 ± 2.8
Baseline swollen joint count	12.5 ± 10.3	12.3 ± 9.8	10.9 ± 8.9
C-reactive protein, mg/liter	12.3 ± 20.5	12.0 ± 21.9	11.3 ± 20.2
Baseline total psoriatic BSA, mean % ± SD‡‡	10.0 ± 14.1	10.0 ± 12.6	12.0 ± 16.5
Relevant prior and concomitant medication, no. (%)			
Prior TNFi	131 (55.0)	132 (55.9)	132 (55.9)
Prior non-TNFi bDMARDs§§	11 (8.4)	14 (10.6)	11 (8.4)
TNFi naive	107 (45.0)	104 (44.1)	104 (44.1)
Concomitant methotrexate	186 (78.2)	180 (76.3)	193 (81.8)
Concomitant corticosteroid (day 1)¶¶	67 (28.2)	37 (15.7)	49 (20.8)
Concomitant NSAIDS (day 1)	144 (60.5)	125 (53.0)	132 (55.9)

* Values are the mean ± SD unless indicated otherwise. BID = twice daily; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; PASDAS = Psoriatic Arthritis Disease Activity Score; HAQ DI = Health Assessment Questionnaire disability index; CPDAI = Composite Psoriatic Disease Activity Index; BSA = body surface area; TNFi = tumor necrosis factor inhibitor; bDMARD = biologic disease-modifying antirheumatic drug; NSAID = nonsteroidal antiinflammatory drug.
† Included patients who met ≥1 of the following criteria: diagnosis of diabetes mellitus recorded at screening; receiving any concomitant antidiabetic medication; glycosylated hemoglobin (HbA_{1C}) ≥6.5% at baseline, or baseline fasting plasma glucose ≥126 mg/dl, if HbA_{1C} data were not available.
‡ Patients who were reported as having hypertension on the Cardiovascular Risk Factor case report form at baseline.
§ Defined as HDL-c <40 mg/dl (male) and <50 mg/dl (female) from baseline/screening data.
¶ Defined as patients with ≥3 components of the metabolic syndrome: obesity (waist circumference for male and female, respectively: US, Canada, Europe, Russia: ≥102 cm and ≥88 cm; Asian, including Japanese: ≥90 cm and ≥80 cm; ethnic central and South American: ≥90 cm and ≥80 cm); dyslipidemia: triglycerides ≥150 mg/dl, including patients receiving medications for lowering triglycerides, and HDL-c <40 mg/dl (male) and <50 mg/dl (female); elevated blood pressure: systolic ≥130 mm Hg or diastolic ≥85 mm Hg, including patients receiving antihypertensive medication; and fasting glucose ≥100 mg/dl, including patients receiving antidiabetic medication.
# For this subset of patients, n = 229, 230, and 231, respectively.
** n = 237.
†† For this subset of patients, n = 160, 147, and 166, respectively.
‡‡ For patients with BSA >0% at baseline.
§§ Patients who were treated with any non-TNFi bDMARD or both TNFi bDMARDs and non-TNFi bDMARDs were included in the prior non-TNFi bDMARDs category. For this subset of patients, n = 131, 132, and 132, respectively.
¶¶ Oral systemic corticosteroid use at baseline (maximum allowed dose of 10 mg/day of prednisone equivalent).

MACE were pooled across the phase III and LTE studies and were evaluated and classified by an external, independent adjudication committee, who were blinded to treatment; events were confirmed using prespecified criteria (see Supplementary Appendix 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23930/abstract).

Disease activity was measured using the Psoriatic Arthritis Disease Activity Score (PASDAS) (16), the Composite Psoriatic Disease Activity Index (CPDAI) (17), and the Disease Activity Index for Psoriatic Arthritis (18). In the pooled CVD event analyses across phase III and LTE studies, patients who received ≥1 dose of tofacitinib were considered as a single group (all tofacitinib doses). The average tofacitinib 5 mg BID treatment group consisted of patients with an average total daily dose of <15 mg from day 1 with tofacitinib; the average tofacitinib 10 mg BID treatment group consisted of patients with an average total daily dose of ≥15 mg from day 1 with tofacitinib.

Ethics approval. The institutional review boards and/or independent ethics committees approved the studies at each investigational center. Studies were conducted in compliance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written, informed consent.

Statistical analysis. Continuous data were summarized descriptively. In addition, changes from baseline in the CRP level were analyzed using a mixed model for repeated measures (MMRM), with the fixed effects of treatment, visit, treatment-by-visit interaction, geographic location, study, and baseline value; an unstructured covariance matrix was used and *P* values were unadjusted. Two separate MMRM analyses were performed, using data from week 2 to month 3, and for month 4 to month 6 using data from week 2 to month 6.

Discrete data were summarized using proportions and/or incidence rates (IRs) adjusted for person-time using the study drug. IR estimates (patients with events per 100 patient-years [PYs]) were calculated and included events occurring up to 28 days beyond the last dose (or to the data cutoff date for the ongoing LTE study). Exposure was defined as the total follow-up time calculated up to the day of the first event within the event counting period for patients who experienced the event or the last dose day plus an additional risk period of 28 days beyond the last dose (or to the data cutoff date for the ongoing LTE study, whichever was earlier) for patients without events. These definitions were chosen because the active reporting period for AEs was up to and including 28 calendar days after the last administration of the investigational product, and because reporting to the company safety database may occur at any time regardless of the time elapsed from the last administration of the study drug or since study completion. Inclusion of all events (numerator) without regard to elapsed time may inflate IR estimations, because the exposure time (denominator) is not similarly increased. Exact Poisson 95% confidence intervals (95% CIs, adjusted for PYs) are provided for the IR data (19,20).

RESULTS

Patients. Overall, 783 tofacitinib-treated patients were included in the analysis, pooled across the phase III and LTE studies. The total exposure to tofacitinib (all tofacitinib doses) was 1,237.9 PYs, with a median duration of exposure of 594.0 days (range 1–1,196 days). Baseline demographics and characteristics, including CVD risk factors, were generally similar between treatment groups in the phase III studies. Baseline demographics and characteristics from the pooled phase III studies are shown in Table 1. The mean age ranged from 48.4 to 49.5 years across treatment groups and the majority of patients were white (range 93.6–95.0%) and female (range 50.8–57.6%). At baseline, the duration of diagnosed PsA ranged from 7.5 to 8.6 years, and patients had high disease activity (PASDAS range 6.0–6.2; CPDAI range 9.8–10.4).

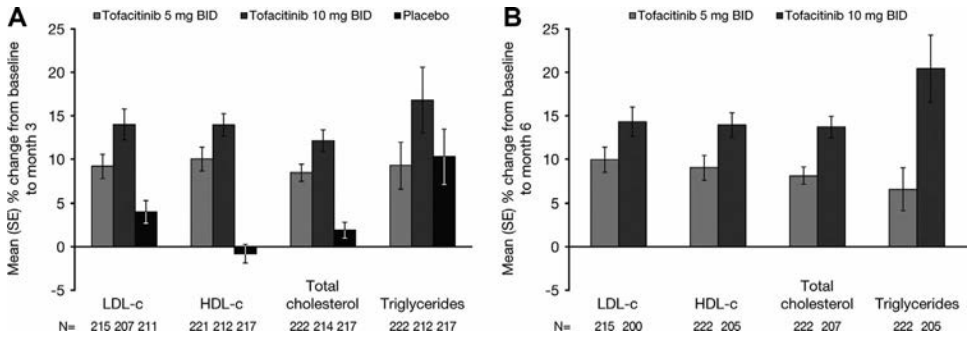

Figure 1. Mean percentage change from baseline in lipids at **A**, month 3 and **B**, month 6 (pooled phase III data), based on patients with a baseline and ≥1 postbaseline measurement. Patients randomized to placebo were advanced to tofacitinib 5 or 10 mg twice daily (BID) at month 3. LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol; N = number of patients with value at the given time point.

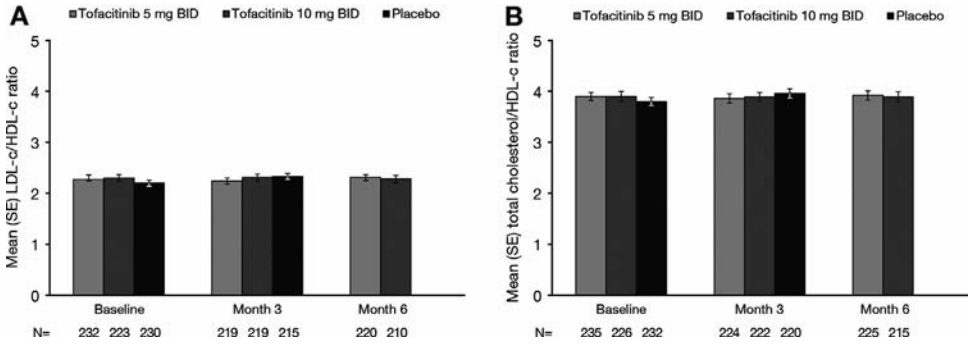

Figure 2. Mean lipid ratios at baseline, month 3, and month 6 for **A**, low-density lipoprotein cholesterol (LDL-c):high-density lipoprotein cholesterol (HDL-c) and **B**, total cholesterol:HDL-c (pooled phase III data), based on patients with a baseline and ≥1 postbaseline measurement. Patients randomized to placebo were advanced to tofacitinib 5 or 10 mg twice daily (BID) at month 3. N = number of patients with value at the given time point.

Outcomes. Mean percentage increases from baseline in low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c) ranged from ~9% to 14% for tofacitinib 5 and 10 mg BID at 3 months (LDL-c 9.2% and 14.0%; HDL-c 10.0% and 14.0%, respectively) and stabilized through month 6 (LDL-c 9.9% and 14.3%; HDL-c 9.0% and 13.9%, respectively; pooled phase III data) (Figure 1). Percentage changes from baseline to month 3 or month 6 in LDL-c and HDL-c appeared to be greater with the 10 mg BID dose than the 5 mg BID dose. Similar mean percentage changes from baseline were also seen for total cholesterol and triglycerides at both time points (3 months: total cholesterol 8.5% and 12.1%; triglycerides 9.3% and 16.8%; 6 months: total cholesterol 8.2% and 13.7%; triglycerides 6.6% and 20.4%, respectively). No meaningful changes were observed in lipid ratios (3 months: LDL-c:HDL-c 2.2 and 2.3; total cholesterol:HDL-c 3.9 and 3.9; 6 months: LDL-c:HDL-c 2.3 and 2.3; total cholesterol:HDL-c 3.9 and 3.9 for tofacitinib 5 mg and 10 mg BID, respectively) (Figure 2).

Treatment with tofacitinib 5 mg and 10 mg BID provided a significant least squares mean reduction in CRP levels from baseline versus placebo as early as week 2 (tofacitinib 5 mg –6.3 mg/liter; tofacitinib 10 mg –7.0 mg/liter; both $P < 0.001$ versus placebo [0.2 mg/liter]; pooled phase III data). Significant reductions from baseline in CRP level were also reported for both doses of tofacitinib versus placebo at month 3 (tofacitinib 5 mg –5.1 mg/liter; tofacitinib 10 mg –5.8 mg/liter; both $P < 0.001$ versus placebo [0.4 mg/liter]), and reductions were maintained to month 6 (tofacitinib 5 mg –6.4 mg/liter; tofacitinib 10 mg –8.3 mg/liter; no placebo comparison at month 6) (Figure 3). There was no dose response to tofacitinib treatment in terms of mean systolic and diastolic blood pressure over 24 months (pooled phase III and LTE data); neither dose of tofacitinib was associated with meaningful changes from baseline (Figure 4).

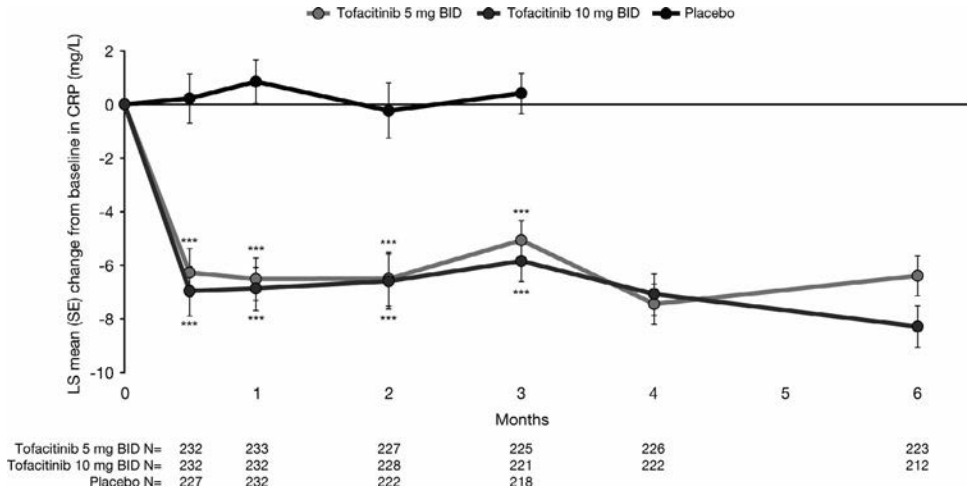

Figure 3. Least squares (LS) mean change from baseline in C-reactive protein (CRP) level over time (pooled phase III data). Two separate analyses were performed. A mixed model for repeated measures (MMRM) was used to generate results with data from week 2 to month 3, as well as results from week 2 to month 6. Each analysis was based on an MMRM with the fixed effects of treatment, visit, treatment-by-visit interaction, geographic location, study, and baseline value; an unstructured covariance matrix was used. BID = twice daily; N = number of patients with value at the given time point; *** = $P < 0.001$ versus placebo.

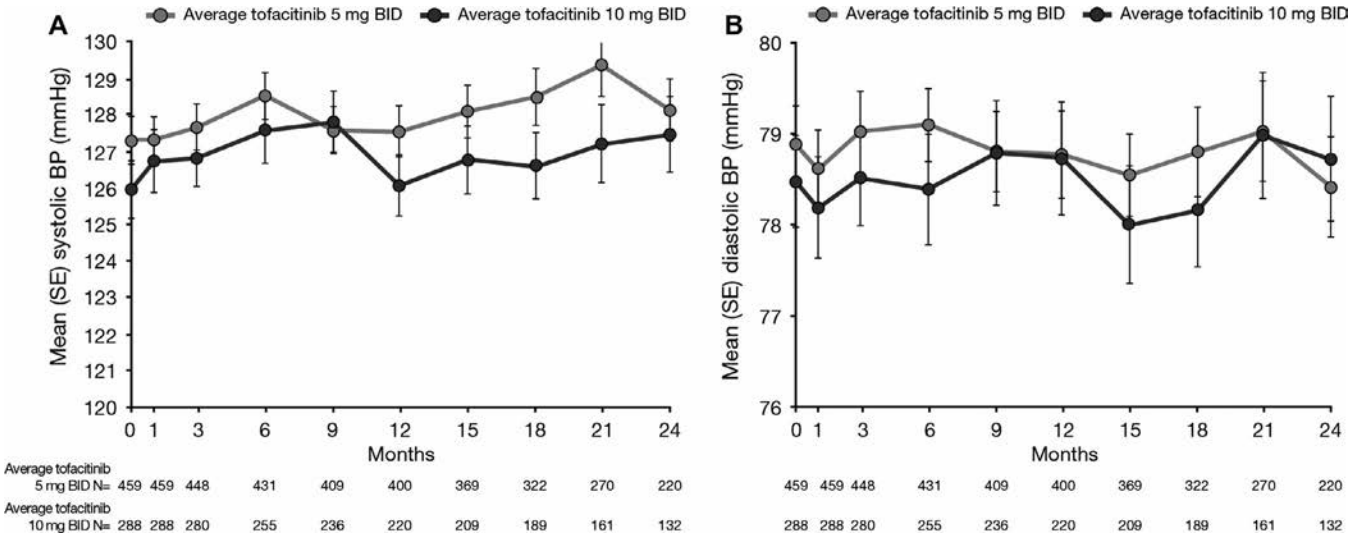

Figure 4. **A**, Mean systolic, and **B**, mean diastolic sitting blood pressure (BP) over 24 months (pooled phase III and long-term extension data). Includes all tofacitinib-exposed patients who had both a baseline and ≥1 postbaseline observation; baseline values are from the OPAL Broaden and OPAL Beyond studies. Average tofacitinib 5 mg twice daily (BID) comprised patients with an average total daily dose of <15 mg from day 1 using tofacitinib. Average tofacitinib 10 mg BID comprised patients with an average total daily dose of ≥15 mg from day 1 using tofacitinib. N = number of patients with value at the given time point.

Across the phase III and LTE studies, 58 patients with hypertension-related AEs (including the terms hypertension, high blood pressure, and increased blood pressure) were reported and none were fatal (Table 2). Of these, 2 hypertension events led to patient discontinuation (both receiving tofacitinib 5 mg). A further 2 events were classified as serious AEs (one each receiving tofacitinib 5 mg and 10 mg at the time of the event). When comparing doses, the IRs of hypertension events were similar between those patients receiving an average dose of tofacitinib 5 mg BID and those receiving 10 mg BID.

Table 2. Patients with hypertension-related AEs and treatment-emergent adjudicated MACE (pooled phase III and LTE data)*

	Pooled phase III data (0–3 months)			Pooled phase III and LTE data		
	Tofacitinib 5 mg BID (n = 238)	Tofacitinib 10 mg BID (n = 236)	Placebo (n = 236)	Average tofacitinib 5 mg BID (n = 482)	Average tofacitinib 10 mg BID (n = 301)	All tofacitinib (n = 783)
Total hypertension-related AEs, no. (%)	5 (2.1)	6 (2.5)	5 (2.1)	36 (7.5)	22 (7.3)	58 (7.4)
Exposure, PYs†	54.0	53.3	52.8	758.3	447.9	1,206.1
Total hypertension-related AEs‡	9.26 (3.01–21.61)	11.26 (4.13–24.50)	9.48 (3.08–22.12)	4.75 (3.33–6.57)	4.91 (3.08–7.44)	4.81 (3.65–6.22)
Total MACE, no. (%)	0	0	0	2 (0.4)	1 (0.3)	3 (0.4)
Ischemic stroke	0	0	0	0	1 (0.3)	1 (0.1)
Myocardial infarction	0	0	0	1 (0.2)	0	1 (0.1)
Sudden cardiac death§	0	0	0	1 (0.2)	0	1 (0.1)
Exposure, PYs†	54.6	54.4	53.7	788.6	469.8	1,258.44
Total MACE¶	0 (0–6.75)	0 (0–6.78)	0 (0–6.87)	0.25 (0.03–0.92)	0.21 (0.01–1.19)	0.24 (0.05–0.70)

* Values are the incidence rate (95% confidence interval) unless indicated otherwise. Hypertension-related adverse events (AEs; including the terms hypertension, high blood pressure, and increased blood pressure) were defined using a Standardized Medical Dictionary for Regulatory Activities query (version 19.1). All causalities included all defined events regardless of treatment relatedness. MACE = major adverse cardiovascular event; LTE = long-term extension; BID = twice daily; PYs = patient-years.

† PY exposure was the time to the day of the first hypertension-related AE, subject to an observation period of 28 days beyond the last dose or to the data cutoff date.

‡ Defined as the number of patients with events per 100 PYs.

§ Two additional events in the pooled phase III and LTE population, both in patients receiving tofacitinib 5 mg, were reported beyond the observation period and were not included in the incidence rate calculation.

¶ Defined as the number of patients with events per 100 PYs. Two additional events in the pooled phase III and LTE population, both in patients receiving tofacitinib 5 mg, were reported beyond the observation period and were not included in the incidence rate calculation.

In total, 5 patients (0.6%) experienced a MACE across the phase III and LTE studies (Table 2), of which 2 were fatal (both adjudicated to be unrelated to treatment) and 3 were nonfatal. In 2 patients, MACE (1 fatal and 1 nonfatal) were outside the 28-day observation period and were therefore not included in the IR calculation. The overall IR for MACE events, excluding the 2 patients where the event took place beyond the 28-day observation period, was 0.24 (95% CI 0.05–0.70) patients with events per 100 PYs. No patients had congestive heart failure. Further details of the fatal and nonfatal MACE can be found in Supplementary Appendix 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23930/abstract.

DISCUSSION

In the OPAL Broaden and OPAL Beyond phase III studies in patients with active PsA, dose-dependent increases in lipid levels of 10–15% were observed following treatment with tofacitinib 5 and 10 mg BID at month 3, with no appreciable further changes at month 6. HDL-c increased concurrently with other lipids, and no meaningful changes in LDL-c:HDL-c or total cholesterol:HDL-c ratios were observed. These changes are consistent with observations of lipid levels in other tofacitinib studies in patients with RA and psoriasis (21–24). Furthermore, both tofacitinib 5 and 10 mg BID provided significant and consistent reductions in CRP level from baseline compared with placebo over 3 months, and the proportion of patients reporting hypertension, as defined by the MedDRA Hypertension Standardized MedDRA Query, was similar between treatment groups, with comparable IRs. Although the risk of CVD and cardiometabolic disorders is higher in patients with PsA compared with the general population (2,3,25), and as lipid ratios, CRP levels, and blood pressure/hypertension are known CVD risk factors (26–28), taken together, this analysis showed no further increase in CVD risk following treatment with tofacitinib 5 or 10 mg BID. This conclusion is consistent with the observed IR of MACE, which was found to be generally consistent with that seen in a population-based longitudinal study of PsA (IR 0.57) (29), and in those patients receiving either secukinumab (IR 0.6) (30) or ustekinumab (IR 1.23) (31) for the treatment of PsA or psoriasis. In addition, IRs were similar to those observed in patients who received tofacitinib treatment in pooled analyses of patients with RA (IR range 0.19–0.58) (21,24) and psoriasis (IR 0.37) (22).

Suppression of circulating cholesterol levels in the setting of active systemic inflammation, such as in RA, has long been recognized (26,32–34). However, compared with controls, elevated LDL-c and triglycerides have been observed (35) in PsA, with rates of hypertriglyceridemia and metabolic syndrome higher in patients with PsA than in patients with RA (36). Dyslipidemia in PsA is possibly a consequence of skin and joint inflammation in PsA associated with elevations of inflammatory cytokines such as TNF and interleukin-6 (37), which can induce hepatic synthesis of CRP (2). Other factors, such as obesity and diet, may also be involved. The insidious onset of PsA may also mean that patients with PsA are exposed to active disease for longer than patients with other inflammatory diseases, putting them at greater risk for lipid changes (36). In addition, the burden of systemic inflammation, along with oxidative stress and disease activity, have been demonstrated to play a role in increasing the risk of CVD and therefore MACE in patients with PsA (3,38). To further understand the link between lipids and CVD risk in patients with PsA, investigating nontraditional lipid risk factors such as HDL-associated paraoxonase 1 activity and HDL-associated serum amyloid A may be beneficial. Indeed, paraoxonase 1 activity has been found to be decreased in patients with PsA compared with healthy controls (38), and in patients with psoriasis, treatment with tofacitinib has been found to both increase paraoxonase 1 activity and decrease HDL-associated serum amyloid A (23).

Of note, both the US product information and European Union (EU) summary of product characteristics (SmPC) state that maximum increases in lipid parameters, including total cholesterol, LDL-c, and HDL-c, were generally observed within 6 weeks of treatment initiation. Furthermore, both the product information and SmPC recommend that lipid parameters should be assessed 8 weeks after starting treatment (and approximately 4–8 weeks thereafter in the US, or 8 weeks in the EU), and that patients should be managed according to clinical guidelines (39,40). Increases in total cholesterol and LDL-c associated with tofacitinib may be reduced to pretreatment levels with statin therapy (41).

Limitations of this analysis include the fact that comparisons with placebo were limited to the 3-month placebo-controlled portion of the phase III studies, and thus the overall extent and length of exposure to placebo was less than to tofacitinib. However, since the differences in lipid changes between 3 months and 6 months were minimal, the 3-month placebo-controlled period appears to be a sufficient duration for lipid evaluation. In addition, the evaluation of MACE and hypertension events over time was limited by the sample size and extent of exposure, and consequently, due to the long latency period of MACE, a study of this length may not provide sufficient data. However, when compared with the larger RA and psoriasis data sets of pooled data from randomized trials and LTE studies (6,300 patients with 21,886 PYs of exposure for RA [data cutoff April 4, 2016; database not locked, data may change]); 3,662 patients with 8,537 PYs of exposure for psoriasis [data cutoff May 10, 2016; database not locked, data may change]), the IRs were comparable. Furthermore, in a prospective, observational 5-year study, embedded within the US Corrona RA registry of patients with RA, rates of CVD, which included MACE as part of the definition, were comparable between patients initiating tofacitinib and patients initiating biologic DMARDs (42). Finally, caution should be applied when comparing studies due to different population

characteristics, capture and definition of events, and few events of interest in the PsA tofacitinib development program.

In patients with PsA, the magnitude and dose dependency of increases in lipid levels to month 6 were consistent with findings in tofacitinib studies in patients with RA and psoriasis. Because increases in LDL-c were paralleled by increases in HDL-c, no meaningful changes in total cholesterol:HDL-c ratio were observed. In addition, rates of hypertension were not affected by treatment dose, CRP levels decreased, and the incidence of MACE was low and similar to other PsA therapies. Of note, the incidence of MACE in patients with active PsA was within the range reported in prior tofacitinib studies in RA and psoriasis (21–24) and was generally consistent with data reported in the literature for other PsA treatments (29–31). In conclusion, there is no evidence at this time that treatment of PsA with tofacitinib is associated with increased CVD risk; however, longer-term follow-up is needed and is ongoing. Low numbers of patients with hypertension-related AEs and MACE were noted.

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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. Gladman 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. Gladman, McInnes, Veale, Nurmohamed, Graham, Wang, Jones, DeMasi.

Acquisition of data. Veale.

Analysis and interpretation of data. Gladman, Charles-Schoeman, McInnes, Veale, Thiers, Nurmohamed, Graham, Wang, Jones, Wolk, DeMasi.

ROLE OF THE STUDY SPONSOR

Pfizer Inc. was involved in the study design, data collection, data analysis, and writing of the manuscript. Publication of this article was contingent on the approval of all authors prior to approval of Pfizer Inc.

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LETTERS

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Idiopathic inflammatory myopathy and venous thromboembolic events: comment on the article by Antovic et al

To the Editor:

I read with great interest the article by Antovic and colleagues (1). In a population-based study, the investigators demonstrated an increased risk of venous thromboembolic events (VTEs) in patients with idiopathic inflammatory myopathy (IIM) as compared with the general population. Strikingly, the hazard ratio for VTEs was 26.6 (95% confidence interval [95% CI] 10.4–68.0) in the first year of diagnosis. The authors reported that 34.8% of patients with IIM, versus 0.9% in the control group, were taking glucocorticoids; however, further data analysis might have been conducted to evaluate for possible association of glucocorticoid exposure and increased risk of VTE. There is a growing body of evidence indicating that glucocorticoids, which remain the first-line regimen and standard of care when treating patients with IIM, increase the risk of VTE. The use of glucocorticoids might be a contributing factor to the findings reported in this article.

A previous population-based case–control study using the Danish National Registry of Patients linked the use of glucocorticoids to an increased risk of venous thromboembolism (2). Moreover, the authors found that the risk of VTE is elevated among new users of glucocorticoids, showing a 3-fold greater risk as compared with the general population and with an increasing cumulative dose.

In addition, an epidemiologic prospective study from the UK using the General Practice Research Database revealed a greater risk of VTE, with an odds ratio of 3.1 in current oral glucocorticoid users as compared with nonusers (3). More recently, a retrospective cohort study from a nationwide database in the US demonstrated similar findings, with a 3.33 incidence rate ratio of VTE (4). A possibility that might give insight into the greater risk of VTE in glucocorticoid users is that glucocorticoids increase the levels of procoagulants such as plasminogen activator inhibitor-1 (5). Patients with Cushing's syndrome, a condition characterized by excessive cortisol levels in the blood, have been linked to greater risk of VTE, with an incidence rate of 14.6 (95% CI 10.3–20.1) per 1,000 person-years (6).

It is critical for health care providers to be aware that treatment with glucocorticoids might be a confounding factor for the increased risk of VTE in patients with IIM. This observation underscores the necessity of monitoring for possible VTE patients with IIM who have been treated with glucocorticoids.

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Reply

To the Editor:

I appreciate the interesting review of corticosteroids and their impact on the risk of VTEs that Dr. Parperis provided. Corticosteroid use and its impact on comorbidities definitely should be followed closely in clinical practice. Unfortunately, we only had information on corticosteroid use in a subset of our study

population and therefore could not assess the impact that corticosteroids had on the risk of VTEs.

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Implementation and challenges of training nurse practitioners and physician assistants in a university fellowship program: comment on the article by Smith et al

To the Editor:

In response to the article by Smith et al published in *Arthritis Care & Research* (Smith BJ, Bolster MB, Slusher B, Stamatos C, Scott JR, Benham H, et al. Core curriculum to facilitate the expansion of a rheumatology practice to include nurse practitioners and physician assistants. Arthritis Care Res [Hoboken] 2018;70:672–8) we would like to share the experiences of the Duke Rheumatology Nurse Practitioner/Physician Assistant (NP/PA) fellowship program. After 2 years of discussion and planning, in October 2017 we launched a 1-year fellowship in rheumatology for NP/PAs. The fellowship program director is an NP, trained in rheumatology by our faculty, who has been a member of our group for 10 years. Duke Rheumatology already had employed 3 NPs, all of whom were successfully trained by intensive mentorship, and we realized the value of NPs in providing high-quality rheumatologic care. We developed a fellowship program complete with training manual, structured curriculum, and clinical one-on-one mentoring to ensure that Duke Rheumatology had well-trained, advanced-practice providers (APPs) in all rheumatology clinics. In these settings, we aimed to ensure that our trained APPs could competently evaluate uncomplicated new patients, most undergoing their first rheumatologic evaluation, as well as to share follow-up patient management with physicians, particularly to enhance access for emergent visits as well as routine follow-up (e.g., after a change in therapy). Our program is similar to the Advanced Clinician Practitioner in Arthritis Care (ACPAC) program of the University of Toronto described by Lundon et al (Lundon K, Shupak R. Success of the advanced clinician practitioner in arthritis care program: comment on the article by Smith et al [letter]. Arthritis Care Res [Hoboken] 2019;71:1146–7).

Briefly, our fellowship curriculum consists of the following requirements: 1) Enroll in an advanced rheumatology course. A total of 19 online modules have been developed and supported by the American College of Rheumatology/Association of Rheumatology Professionals. The Duke fellowship paid for enrollment. 2) Complete 2 continuity clinics per week in the first 6 months, and then 3 per week for the remaining 6 months. Clinic patients are "staffed" by dedicated faculty rheumatologists as well as the NP/PA fellowship program director. This is similar to how we precept physician fellows. One half-day clinic per week was also attended by the first-year physician fellows. This structure ensured complete review by the senior care provider of every patient who was seen in continuity clinics, including review of visit documentation. Additionally, some patients with new diagnoses of inflammatory arthritis alternated visits between first-year physician and NP fellows to simulate future practice collaboration. 3) Attendance is mandatory at divisional grand rounds, divisional journal club, case conference, core curriculum as outlined by physician fellows, radiology conference, weekly post-fellows' clinic journal club, weekly topic review with the NP/PA program director, and the Carolinas Fellows Collaborative Conference (summer and winter). 4) Receive an in-person performance review by the NP/PA program director every 8 weeks, with written minutes signed by the fellow. 5) Maintenance of a binder containing all necessary licensure certificates, copies of all completed evaluations (program keeps originals), and a detailed patient log as well as at least 1 completed outpatient note from every month of training. 6) Receive 2 weeks of inpatient exposure in the Duke Hospital rheumatology consult service; shadow the physician fellow in order to gain an understanding of disease complexity and transitioning of care from inpatient to outpatient. 7) Participate in self-study to promote and encourage continuous learning through textbooks and journal articles.

Our first 2 NP fellows have recently successfully completed the 1-year fellowship. As with any new program, adjustments and modifications were anticipated; changes to enhance the fellows' training have been promptly implemented. Both of our graduates were salaried during training and are obligated to Duke University for 2 years of service post-training. Both have expressed a desire to remain at Duke long term.

At the North Carolina Rheumatology Association annual meeting in April 2018, considerable interest in and enthusiasm for our training program was expressed by community rheumatologists, particularly regarding trainee availability post-fellowship. In our program, originally designed to train APPs to meet Duke's needs for providers, and therefore funded by the institution, no consideration was given initially to training APPs for community practice. As with all training programs, funding is an important future consideration, both to train APPs for the training institution and/or for local and regional practices to enhance the rheumatology workforce. The paucity of funding sources for such training

programs has previously led to the discontinuation of another NP/PA fellowship program in the US. More recently, a pharmaceutical company sought applications for competitive funding to support APP training.

Many questions remain outstanding. Would a community practice pay Duke or another training institution to train an APP? This would involve a model different from physician training, in which the institution covers the cost of training for rheumatologists who may then practice elsewhere. If a practice paid for training, how would a trainee be selected? If pharmaceutical companies pay for training, where would the trained APP be expected to work upon completion? Our current NPs attest to the success of the program. Sustainability will depend on answers to the above questions and other components requiring consideration and future modifications.

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Reply

To the Editor:

Caldwell and colleagues describe the establishment of a rheumatology training program for NPs and PAs. We read with interest the training model outlined and applaud their efforts for the work that has been accomplished at their institution. Their plan of immersing NP and PA fellows in the clinical and educational activities of their division, including integrating fellows with the physician first-year fellows, is an approach that will certainly enrich the professional development of NP/PAs who are new to rheumatology practice. Incorporating PA fellows into the clinical and educational activities of their division, including integrating the NP and PA fellows with the physician first-year physician fellows, is an approach that certainly enriches the professional development of NP/PAs who are new to rheumatology practice. It very likely creates a strong affiliation for the trainees, not only clinician to clinician, but also to the specialty of rheumatology. Activities such as completing the American College of Rheumatology (ACR)/Association of Rheumatology Professionals (ARP) Advanced Rheumatology Course, fulfilling outpatient and inpatient clinical responsibilities, receiving regular feedback from mentors, recording individual progress, and performing self-study exercises provide a comprehensive training experience. Completing these activities with physician trainees helps to model and reinforce the principal benefits of interprofessional teams providing patient care, and it provides an impression-making experience during a formative time in the careers of NPs, PAs, and physicians.

Although NPs and PAs have been working in rheumatology since the 1970s, we recognize that there is still much to learn, and many questions remain regarding best practices for the training of NPs and PAs in rheumatology. Federal funding is not available for postgraduate NP or PA training programs; thus, innovative funding sources need to be considered. Potential funding source considerations could include institutions, community practices, industry and/or foundations. At this time of such a critical rheumatology workforce shortage (1), resources must be devoted to the further development of rheumatology NPs and PAs who can be prepared to assist in meeting the needs of patients with rheumatic disease (Battafarano DF, Ditmyer M, Bolster MB, Fitzgerald JD, Deal C, Bass AR, et al. 2015 American College of Rheumatology workforce study: supply and demand projections of adult rheumatology workforce [2015–2030]. Arthritis Care Res [Hoboken] 2018;70:617–26).

The authors of the NP/PA Rheumatology Curriculum Outline envision that the curriculum could be adapted and utilized in both academic institution and community practice training settings, including Duke's NP/PA training program described by Caldwell and colleagues. The Rheumatology Curriculum Outline could serve as a self-study guide for the NP or PA. While academic rheumatology divisions and community-based rheumatology practices can and do train NPs and PAs, a collaborative approach between academic and community-based rheumatology practices during the training period seem to be one approach that could enhance the experience of the trainee. The participation of the NP or PA in academic center conferences and other educational activities would likely be of value. The added coordination of training opportunities with such an arrangement could be of value to both the practice and its practitioners.

Caldwell and colleagues pose an interesting question: "Would a community practice pay Duke or another training institution to train an APP?" While we do not know the answer to this question and are not aware of any such models either current or discontinued, the question merits discussion. Financial considerations would be the primary concern when entering into such an arrangement for all parties. The model of training NPs and PAs in academic institutions paid in full by community practices more than likely is financially impractical for community practices, who instead would opt to train NPs and PAs on the job using many available resources, including the Rheumatology Curriculum Outline. The collaborative nature of NP and PA working arrangements with rheumatologists in all settings may lend itself more towards an on-the-job training model versus training in an academic setting. NPs and PAs trained in academic settings in many cases are hired by the institution (as Caldwell et al mention) or may obtain employment in the same geographic location as their training. Continued discussion of innovative models for training NPs

and PAs in academic settings for community practices could be beneficial to all involved.

NPs and PAs currently receive additional postgraduate training as they enter the workforce. Additionally, engagement in lifelong learning is an activity utilized by NPs and PAs. When NP/PAs begin working in a rheumatology practice (academic or community practice), it would not be unexpected that they would have a reduced clinical load that encourages training and education. The rate at which NPs and PAs progress in their training is variable, and during this period the revenue generated by the NP/PA would not likely initially support his or her own salary. Allowances may be necessary to train and integrate the NP/PA most effectively into a rheumatology practice. While there is a potential cost to do this, the value added may be substantial to the practice particularly for the patients cared for within the practice.

The ACR and ARP continue in their efforts to provide resources supporting those who work in rheumatology. The Advanced Rheumatology Course, an online modular educational tool available since 2008, has undergone updates periodically based on learner feedback and scientific advancements. This educational tool was recently updated and re-launched in December 2018. Additionally, the Rheumatology Research Foundation offers funding to support NP and PA educational training and career development. The Health Professional Online Education Grant covers the cost of registration for rheumatology professionals to complete the ARP online educational tools, including the Advanced Rheumatology Course. The Mentored Nurse Practitioner/Physician Assistant Award for Workforce Expansion is a new award intended to support clinical training activities for NPs and PAs new to the rheumatology practice setting.

To further support NPs and PAs new to rheumatology, intensive in-person bootcamp-style training is currently in development. This hands-on and interactive program, supported through grant funding, will incorporate adult learning styles to teach foundational rheumatology principles. The ACR, ARP, and American Academy of Physician Assistants are working collaboratively to deliver this new experiential educational offering.

Creative approaches are being put in place to train NPs and PAs. Advances in technology and education theory will help to expand our capacity to train NP/PAs; this will be one important facet of expanding the rheumatology workforce to meet increasing societal needs. We recognize that much will be learned in the coming years as our specialty works to further address workforce realties to meet the needs of persons with rheumatic disease. We call upon all stakeholders to join in this effort.

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