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

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Grant support: This material is the result of a project supported by the American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF).

Financial Conflict: Forms submitted as required.

IRB approval: This study did not involve human subjects and, therefore, approval from Human Studies Committees was not required.

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Word count (excluding references, acknowledgement): TBD

Keywords: Treatment guideline, recommendations, psoriatic arthritis, psoriasis, spondylitis, enthesitis, dactylitis, symmetric polyarthritis, asymmetric polyarthritis, asymmetric oligoarthritis, spondyloarthritis, arthritis mutilans, nail abnormalities, NSAIDs, DMARDs, biologic, oral small molecules, tumor necrosis factor inhibitors, interleukin 12/23 inhibitors, IL17 inhibitors, abatacept, tofacitinib

ABSTRACT

Objective: This collaboration between the American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF) developed an evidence-based guideline for the pharmacologic and nonpharmacologic treatment of psoriatic arthritis (PsA).

Methods: We identified critical outcomes in PsA and clinically relevant patient-intervention-comparison-outcome (PICO) questions. A literature review team performed a systematic literature review to summarize evidence supporting the benefits and harms of available pharmacologic and non-pharmacologic therapies for PsA. Grading of Recommendation Assessment Development and Evaluation (GRADE) methodology was used to rate the quality of the evidence. A voting panel including rheumatologists, dermatologists, other health professionals and patients achieved consensus on the direction and the strength of the recommendations.

Results: The guideline covers the management of patients with active PsA who are treatment-naïve, those who continue to have active PsA despite treatment and addresses the use of oral small molecules (OSMs), tumor necrosis factor inhibitors (TNFi), interleukin 12/23 inhibitor (IL12/23i), IL17 inhibitors (IL17i), CTLA4-Ig (abatacept), and a JAK inhibitor (tofacitinib). We also developed recommendations for psoriatic spondylitis, predominant enthesitis, and concomitant inflammatory bowel disease, diabetes, or serious infections. We formulated recommendations for a treat-to-target strategy, vaccinations and non-pharmacologic therapies. Six percent of the recommendations were strong and 94% conditional, indicating the importance of active discussion between the health care provider and the patient to choose the optimal treatment.

Conclusion: The 2017/2018 ACR/NPF PsA guideline serves as a tool for health care providers and patients for selection of appropriate therapy in common clinical scenarios. Best treatment decisions consider each individual patient situation. The guideline is not meant to be proscriptive and should not be used to limit treatment options for patients with active PsA.

INTRODUCTION

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

PsA affects men and women equally. The distribution of the peripheral arthritis varies from asymmetric oligoarthritis involving fewer than four joints to symmetric polyarthritis involving five or more joints. Distal interphalangeal joints are commonly affected and, in some patients, are the only affected joints. Axial disease, when present, usually occurs together with peripheral arthritis. Some patients present with rapidly progressive and destructive PsA – arthritis mutilans. Nail lesions, including pitting and onycholysis, occur in ~80-90% of patients with PsA. PsA is associated with an adverse impact on health-related quality of life (3-5) and higher cost and health care utilization (6, 7). Greater disease activity is associated with progressive joint damage and a higher mortality (8-11). Early identification of PsA and early initiation of therapy are important for improving long-term outcomes (12).

Both non-pharmacologic and pharmacologic treatment can ameliorate symptoms and can occasionally result in disease remission (**Figure 1**). Clinicians and patients can now choose from a wide variety of pharmacologic treatments, including symptomatic treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular injections as well as immunomodulatory therapies.

Patients with PsA and their health care providers frequently face challenges when considering the various treatment options. Our objective was to develop evidence-based treatment recommendations for the management of adults with active PsA using pharmacologic and non-pharmacologic therapies. These PsA treatment recommendations can help guide both clinicians and patients to arrive at optimal management decisions.

METHODS

Methodology Overview

This guideline followed the American College of Rheumatology (ACR) guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines). This process includes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (www.gradeworkinggroup.org) to rate the quality of the available evidence and to develop the recommendations (13-15). ACR policy guided disclosures and the management of conflicts of interest (insert link here to full participant disclosure list just before publication). **Supplementary Appendix 1** presents the full methods in detail.

This work involved four teams: 1) a Core Leadership Team, which supervised and coordinated the project and drafted the clinical questions and manuscript; 2) a Literature Review Team, which completed the literature search and abstraction; 3) an Expert Panel, composed of patient/patient advocates, rheumatologists, one dermatologist rheumatologist, dermatologists and one rheumatology nurse practitioner, which developed the clinical questions (PICO [population/intervention/comparator/outcomes] questions) and decided on the scope of the guideline project; and 4) a Voting Panel, which included rheumatologists, one dermatologist, one dermatologist-rheumatologist, one rheumatology physician assistant, and two patients (one

of whom was also a physical therapist), who provided input from the patient perspective and voted on the recommendations. Additionally, a Patient Panel consisting of nine adults with PsA reviewed the evidence and provided input on their values and preferences. **Supplementary Appendix 2** presents rosters of the team and panel members. In accordance with ACR policy, the principal investigator and the leader of the literature review team were free of conflicts, and all teams had >50% members free of conflicts.

Framework for the PsA Guideline Development and Scope of the Guideline

Because there are numerous topics within PsA that could be addressed, the guideline panels made several decisions up front regarding what to address and what not to address and how to define aspects of the disease (e.g., active disease). At an initial scoping meeting, the Voting Panel and Expert Panel agreed that the project would include the management of patients with active PsA defined as symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining health care provider to be due to PsA based on the presence of at least one of the following: actively inflamed joints; dactylitis; enthesitis; axial disease; active skin and/or nail involvement; and/or extra-articular manifestations, such as uveitis or inflammatory bowel disease (IBD). The health care provider may, in deciding if symptoms are due to active PsA, consider – in addition to core information from the history and physical examination - adjunctive information that includes inflammatory markers (C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)), and imaging. At the scoping meeting, the panels decided that the guideline would address both pharmacologic and non-pharmacologic therapies for the treatment of PsA. We examined the evidence for vaccinations, treatment in the presence of common comorbidities, and a treat-to-target strategy.

In addressing pharmacologic agents, we focused on immunomodulatory agents for long-term management rather than addressing acute symptom management (i.e. through intra-articular

injections and the use of systemic glucocorticoids). Tofacitinib and ixekizumab have been submitted for review and potential approval by the U.S. Food and Drug Administration (FDA) for the treatment of PsA and both might be approved (16, 17). For this reason, these drugs were included in this guideline. Tofacitinib is not included within the OSM category since it's benefit/risk profile differs from the rest of the OSMs, consistent with being considered separately in other treatment guidelines (18, 19). Additionally, the panel addressed alternatives in patient subpopulations (e.g., patients with predominant enthesitis, axial disease, dactylitis, comorbidities), and greater versus lesser disease severity.

There are currently no widely agreed upon definitions of disease severity in PsA or psoriasis. Thus, health care providers and patients should judge PsA and psoriasis severity on a case-by-case basis. For the purposes of these recommendations, severity includes not only the level of disease activity at a given time point, but also the presence or absence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of one or more of the following: a poor prognostic factor (erosive disease, elevated markers of inflammation such as ESR and CRP attributable to psoriatic arthritis), long-term damage that interferes with function (e.g. joint deformities), a highly active disease that causes a major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease (**Figure 2**). In clinical trials, severe psoriasis has been defined as a psoriasis area and severity index (PASI) score of greater than or equal to 12 and a body surface area score of at least 10 (20). However, because it is cumbersome,, physicians seldom use the PASI in their clinical practice. Examples of definitions of severe PsA and severe psoriasis are shown in Figure 2. Finally, because the National Psoriasis Foundation and American Academy of Dermatology are concurrently developing psoriasis treatment guidelines, the treatment of skin

psoriasis separately from the inflammatory arthritis was not included in the current ACR/NPF PsA guideline.

Systematic Synthesis of the Literature

Systematic searches of the published English-language literature included OVID Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Health Technology Assessments) from the beginning of each database through November 15, 2016 (**Supplementary Appendix 3**); we conducted updated searches on May 2, 2017. DistillerSR software (https://distillercer.com/products/distillersr-systematic-reviewsoftware/) (**Supplementary Appendix 4**) facilitated duplicate screening of literature search results. Reviewers entered extracted data into RevMan software (http://tech.cochrane.org/revman), and evaluated the risk of bias of primary studies using the Cochrane risk of bias tool (http://handbook.cochrane.org/). We exported RevMan files into GRADEpro software to formulate a GRADE summary of findings table (**Supplementary Appendix 5**) for each PICO question (21). Additionally, a network meta-analysis was performed when sufficient studies were available. GRADE criteria provided the framework for judging the overall quality of evidence (13). The panels chose the critical outcomes for all comparisons at the initial scoping; these included the American College of Rheumatology Criteria 20% response (ACR20, the primary outcome for most PsA clinical trials), the Health Assessment Questionnaire Disability Index (HAQ-DI, a measure of physical function) Psoriasis Area and Severity Index 75% response (PASI75, a measure of skin psoriasis improvement), and serious infections. Serious infections are among the most concerning for patients and physicians when selecting among therapies. Other specific harms (e.g., liver toxicity for methotrexate) were included as critical outcomes for individual comparisons. We included other outcomes, such as total infections, when appropriate.

Moving from Evidence to Recommendations

GRADE methodology specifies that panels make recommendations based on the balance of benefits and harms, the quality of the evidence (i.e., confidence in effect estimates) and patients' values and preferences. Deciding on the balance between desirable and undesirable outcomes requires estimating the relative value patients place on those outcomes. When the literature didn't clearly guide recommendations, recommendations were based on the experience of the Voting Panel members (including both physicians and the two patients present), and values and input from the members of the Patient Panel.

Consensus Building

The Voting Panel voted on the direction and strength of the recommendation related to each PICO question. Recommendations required a 70% level of agreement as used previously in other similar processes (22) and in the previous ACR guidelines (18, 23, 24); if 70% agreement was not achieved during an initial vote, the Panel members held additional discussions before re-voting. For all conditional recommendations, a written explanation is provided, describing the reasons for this decision, and conditions under which the alternative choice may be preferable.

Moving from Recommendations to Practice

These recommendations are designed to help health care providers work with patients in selecting therapies. The presence or absence of conditions, such as IBD, uveitis, diabetes, and serious infections, and the knowledge of previous therapies, influence decisions regarding optimal management. In the context of PsA, the physical examination, which is also required for selecting therapy, includes assessment of the peripheral joints (including dactylitis), the entheses, the spine, the skin and nails. Health care providers and patients must take into

consideration all active disease domains, comorbidities and the patient's functional status in choosing the optimal therapy for an individual patient at the given point in time.

RESULTS/RECOMMENDATIONS

How to Interpret the Recommendations

1. A **strong recommendation** means that the panel was **confident** that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion would not want to follow the recommendation. We use the phrase "**should use"** or **"should be used**" for strong recommendations.
2. A **conditional recommendation** means that the panel believed that the desirable effects of following the recommendation **probably** outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. We use the phrase "**is recommended over**" or "**is/would be recommended**" for conditional recommendations. We specify conditions under which the less preferred drug may be used by using the phrase "**may be used**" or "**Y (less preferred drug) may be used instead of X (preferred drug)**" for conditional recommendations.
3. Conditional recommendations were usually based on low- to very-low-quality evidence (in rare instance, moderate quality evidence). Strong recommendations were typically based on moderate- or high-quality evidence.
4. For each recommendation, **Supplementary Appendix 5** provides details regarding the PICO questions and the GRADE evidence tables.

Recommendations

Recommendations for Pharmacologic Interventions

Treatment-Naïve Patients with Active PsA (Table 1; Figure 3)

All recommendations for treatment-naïve patients with active PsA are conditional low- to very-low level quality evidence.

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

For treatment-naïve patients with active PsA, the use of a TNFi biologic or OSM is recommended over an IL17i biologic or IL12/23i biologic. An IL17i biologic or IL12/23i biologic may be used instead of TNFi biologics in patients with severe psoriasis or contraindications to TNFi biologics. An IL17i biologic or IL12/23i biologic may be used instead of OSMs in patients with severe psoriasis or severe PsA. MTX is recommended over NSAIDs in treatment-naïve patients with active PsA. NSAIDs may be used instead of MTX after consideration of possible contraindications and side effect profile in patients without evidence of severe PsA or severe psoriasis and in those at risk for liver toxicity (**Table 1; Figure 3**). An IL17i biologic is recommended over an IL12/23i biologic. IL12/23i biologics may be used in patients with concomitant IBD or who desire less frequent drug administration.

Active PsA Despite Treatment with an OSM (Table 2; Figure 4)

All recommendations for patients with active PsA despite treatment with OSM are conditional based on mostly low- to very-low quality evidence, and, in a few instances, moderate-quality evidence.

In patients with active PsA despite OSM therapy, switching to a TNFi, an IL-17i biologic or an IL12/23i biologic is recommended over switching to a different OSM (**Table 2; Figure 4**). A different OSM may be used rather than a TNFi, IL-17i or IL12/23i biologic in patients who prefer an oral medication or those without evidence of severe PsA or severe psoriasis; a different OSM may be used rather than a TNFi, in the presence of contraindications to TNFi biologics. A TNFi biologic is recommended over an IL-17i, an IL12/23i, abatacept or tofacitinib. An IL17i biologic is recommended over an IL12/23i, abatacept or tofacitinib. An IL12/23i biologic is recommended over abatacept or tofacitinib. In patients with contraindications to TNFi biologics, an IL12/23i, an IL17i, abatacept or tofacitinib may be used instead of a TNFi. In patients with severe psoriasis, an IL12/23i biologic or an IL17i biologic may be used instead of a TNFi biologic. Tofacitinib may be used instead of a TNFi biologic in patients preferring oral medication who do not have severe psoriasis.

Switching to another OSM is recommended over adding another OSM to the current treatment (except in the case of apremilast). Adding another OSM (except apremilast) to current treatment may be considered if the patient has demonstrated partial response to the current OSM. Adding apremilast to the current OSM therapy is recommended over switching to apremilast monotherapy since most evidence for benefits exists for apremilast combination therapy but not for apremilast monotherapy. Switching to apremilast monotherapy may be considered instead of apremilast combination therapy, if patient has intolerable side effects to the current OSM.

Biologic monotherapy is recommended over biologic combination therapy with MTX (the most commonly used OSM in combination therapy). When switching to biologic monotherapy, either stopping the OSM or tapering of the OSM are both reasonable options and depend on patient and health care provider preferences. Biologic combination with MTX may be used instead of biologic monotherapy, if the patient has severe psoriasis, has had a partial response to current MTX therapy, has concomitant uveitis (since uveitis may respond to MTX therapy), or in patients receiving treatment with a TNFi monoclonal antibody biologic, especially infliximab and adalimumab to potentially delay or prevent the formation of anti-drug antibodies.

Active PsA Despite Treatment with a TNFi Biologic Monotherapy or a TNFi Biologic Combination Therapy (Table 3; Figure 5)

All recommendations for patients with active PsA despite TNFi biologic treatment are conditional based on low- to very-low-quality evidence.

In patients with active PsA despite treatment with a TNFi biologic monotherapy, switching to a different TNFi biologic monotherapy is recommended over switching to an IL12/23i, an IL17i, abatacept or tofacitinib monotherapy, or adding MTX to the current TNFi biologic **(Table 3; Figure 5)**. An IL12/23i biologic, IL17i biologic, abatacept or tofacitinib may be used instead of a different TNFi biologic monotherapy, in case of a primary TNFi biologic failure, or a serious adverse event due to the TNFi biologic. An IL17i or IL12/23i biologic may be used instead of a TNFi biologic, particularly in the presence of severe psoriasis. Abatacept may be used instead of a TNFi biologic in patients with recurrent or serious infections in the absence of severe psoriasis. Tofacitinib may be used instead of a TNFi biologic, if oral therapy is preferred.

In patients with active PsA despite treatment with TNFi biologic monotherapy, an IL17i biologic is recommended over an IL12/23i, abatacept or tofacitinib, and an IL12/23i biologic is recommended over abatacept or tofacitinib. An IL12/23i may be considered instead of an IL17i if the patient has IBD or desires less frequent drug administration. Abatacept may be considered instead of an IL17i or an IL12/23i in patients with recurrent or serious infections. Tofacitinib may be considered instead of an IL17i biologic in patients who prefer an oral therapy or have a history of recurrent or severe candida infections. Tofacitinib may be considered instead of an IL12/23i biologic in patients who prefer an oral therapy. For each biologic (TNFi, IL12/23i or IL17i), monotherapy is recommended over biologic and MTX combination therapy. A biologic and MTX combination therapy may be used instead of biologic monotherapy in the presence of severe psoriasis, partial response to current MTX therapy, concomitant uveitis (since uveitis may respond to MTX therapy), and if the current TNFi biologic is infliximab or adalimumab.

Under circumstances in which combination therapy of TNFi biologic and MTX is used and patients continue to have active PsA, switching to a different TNFi biologic with MTX is recommended over monotherapy with a different TNFi biologic. Continuing MTX during TNFi biologic transition was seen as beneficial because TNFi biologics may have more sustained efficacy when used in combination with MTX but limited evidence exists. Monotherapy with a different TNFi biologic may be used if the patient has had MTX-associated adverse events, prefers fewer medications or perceives MTX as a burden. IL12/23i biologic monotherapy or IL17i biologic monotherapy is recommended over respective biologic combination with MTX. An IL17i biologic and MTX combination therapy or an IL12/23i and MTX combination therapy may be used instead of switching to biologic monotherapy, if patient had a partial response to the existing regimen and/or concomitant uveitis that might respond to MTX therapy.

Active PsA Despite Treatment with an IL17i Biologic Monotherapy (Table 4; Figure 6)

All recommendations for patients with active PsA despite IL17i biologic treatment are conditional based on very-low-quality evidence.

In patients with active PsA despite an IL17i, switching to a TNFi biologic is recommended over an IL12/23i, adding MTX to the current IL17i, or switching to a different IL17i **(Table 4; Figure 6)**. Switching to an IL12/23i biologic is recommended over adding MTX to the current IL17i, or switching to a different IL17i. Treatment may be switched to an IL12/23i instead of a TNFi biologic if patient has severe psoriasis or a contraindication to TNFi. Another IL17i biologic may be used instead of switching to a TNFi or IL12/23i biologic, if the patient had a secondary efficacy failure to the current IL17i, severe psoriasis, or a contraindication for TNFi. MTX may be added to the current IL17i instead of switching to a TNFi or an IL12/23i biologic in patients who have had a partial response to the current IL17i.

Active PsA Despite Treatment with an IL12/23i Biologic Monotherapy (Table 4; Figure 6)

All recommendations for patients with active PsA despite an IL12/23i biologic treatment are conditional based on very-low-quality evidence.

In patients with active PsA despite treatment with an IL12/23i, switching to a TNFi biologic is recommended over adding MTX to the current regimen or switching to an IL17i biologic **(Table 4; Figure 6)**. Switching to an IL17i biologic is recommended over adding MTX to the current therapy. MTX may be added to the current IL12/23i biologic therapy instead of switching to a

TNFi or an IL17i biologic in patients with a partial response to the current therapy; MTX may also be added to the current IL12/23i biologic therapy instead of switching to a TNFi biologic in the presence of contraindications for TNFi biologics. One may switch to an IL17i biologic instead of a TNFi biologic in the presence of severe psoriasis or contraindications to TNFi biologics.

Treat-to-Target (Table 5)

This recommendation for patients with active PsA is conditional, based on low-quality evidence.

In patients with active PsA, using a treat-to-target strategy is recommended over a not treat-to-target strategy. One may consider not using a treat-to-target strategy in patients in whom higher adverse events, higher cost of therapy and higher patient burden of medications with tighter control is a concern.

Active PsA with Psoriatic Spondylitis/Axial Disease Despite Treatment with NSAIDs (Table 5)

All recommendations for patients with active PsA with psoriatic spondylitis/axial disease despite NSAIDs are conditional, based on very-low-quality evidence.

The ACR/SAA/SPARTAN recommendations for patients with axial spondyloarthritis should be followed for patients with axial PsA; OSMs are not effective for axial disease (25). In patients with axial PsA despite NSAIDs, a TNFi biologic is recommended over an IL17i or IL12/23i biologic and an IL17i biologic is recommended over an IL12/23i biologic. An IL17i biologic may be used instead of a TNFi biologic, if the patient has contraindications to TNFi biologics or severe psoriasis (**Table 5**). An IL12/23i biologic **may not** be used since a trial of an IL12/23i biologic in patients with axial PsA was recently stopped (personal communication).

Active PsA with Predominant Enthesitis in Treatment-Naïve Patients and Despite Treatment with an OSM (Table 5)

All recommendations for patients with active PsA with predominant enthesitis are conditional, based on low- to very-low-quality evidence. This section names apremilast among all OSMs specifically for recommendations, since of the OSMs, only apremilast has shown efficacy for enthesitis)

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

In patients with active PsA with predominant enthesitis despite treatment with an OSM (used for other manifestations of PsA), a TNFi biologic, an IL17i biologic or an IL12/23i biologic is recommended over switching to another OSM. Apremilast may be used by patients who prefer oral therapy or have contraindications to TNFi biologics or have recurrent infections. A TNFi biologic is recommended over an IL17i biologic or an IL12/23i biologic. An IL17i biologic or IL12/23i biologic may be used instead of a TNFi biologic in patients with severe psoriasis or contraindications to TNFi. An IL12/23i biologic may be used instead of a TNFi biologic in

patients who prefer less frequent drug administration. An IL17i biologic is recommended over an IL12/23i biologic. An IL12/23i biologic may be used instead of an IL17i biologic in patients with concomitant IBD or who desire less frequent drug administration.

Active PsA Patients with Concomitant active IBD (Table 5)

All recommendations for patients with active PsA with concomitant active IBD are strong based on moderate-quality evidence, except for two conditional recommendations based very low quality evidence.

Active PsA in patients who are OSM- and biologic-treatment-naïve with concomitant active IBD

In patients with active PsA with concomitant active IBD who are both OSM- and biologic-treatment-naïve, a TNFi monoclonal antibody biologic (excludes etanercept, which is a fusion molecule/soluble receptor biologic) is recommended over an OSM (**Table 5)**. An OSM may be used in patients without severe PsA, who prefer oral therapy or have contraindications to TNFi biologics.

Active PsA despite treatment with an OSM in patients with concomitant active IBD

In patients with active PsA with concomitant active IBD despite treatment with an OSM, a monoclonal antibody TNFi biologic or an IL12/23i biologic **should be used** over an IL-17i and a monoclonal antibody TNFi biologic **should be used** over a TNFi soluble receptor biologic (etanercept; **strong recommendations; Table 5).** A monoclonal antibody TNFi biologic is recommended over an IL12/23i biologic (conditional recommendation). An IL12/23i biologic may be used instead of monoclonal antibody TNFi biologic in patients with contraindications to TNFi biologics or who prefer less frequent drug administration.

Active PsA Patients with Comorbidities (Table 6)

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

Active PsA in patients who are OSM- and biologic-treatment-naïve with concomitant diabetes

For OSM- and biologic-treatment-naïve patients with active PsA and concomitant diabetes, an OSM other than MTX is recommended over a TNFi biologic, due to the concern about the higher prevalence of fatty liver disease and liver toxicity with MTX use in this patient population(26, 27) (**Table 6**). A TNFi biologic may be used instead of an OSM in the presence of severe PsA, severe psoriasis or when diabetes is well controlled (i.e., with a potentially lower risk of infections).

Active PsA in patients who are OSM- and biologic-treatment-naïve with frequent serious infections

For patients with active PsA who are OSM- and biologic-treatment-naïve and have frequent serious infections, an OSM **should be used** over a TNFi biologic as a first-line treatment since there is a black box warning against the use of a TNFi biologic in patients with frequent serious infections (**strong recommendation**). An IL12/23i or an IL17i biologic is recommended over a TNFi biologic (conditional recommendations; **Table 6**). A TNFi biologic may be used instead of IL12/23i biologic in patients with severe PsA and instead of IL17i biologic in patients with concomitant IBD.

Active PsA Patients Requiring Killed or Live Attenuated Vaccinations When Starting Biologics (Table 7)

All recommendations for vaccinations in patients with active PsA are conditional based on very-low-quality evidence.

It is recommended to start the biologic and administer the killed vaccines (as indicated based on patient age, gender and immunization history per recommendations of the Centers for Disease Control and Prevention (28)) in patients with active PsA over delaying the biologic to give the killed vaccines. Delaying the start of the biologic is recommended over not delaying to administer a live attenuated vaccination in patients with active PsA **(Table 7)**. If PsA manifestations are severe and delaying the start of the biologic is not desirable, one might consider starting the biologic and administering the live attenuated vaccines at the same time.

Recommendations for Non-Pharmacologic Interventions: Active PsA Patients Regardless of Pharmacologic Treatment Status **(Table 8)**

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

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

who prefer the former and have no contraindications to high-impact exercises **(Table 8)**. Clinicians **should** encourage patients to stop smoking, offering cessation aids, due to a demonstrated effectiveness of smoking cessation in randomized trials in other conditions and in the general population (29-31) (**strong recommendation**). In PsA patients who are overweight or obese, weight loss is recommended to potentially increase pharmacologic response.

DISCUSSION

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

A Patient Panel meeting was held prior to the Voting Panel meeting to gain insight into patients' values and preferences for the pharmacologic/non-pharmacologic intervention comparisons being addressed. Findings from the Patient Panel meeting were discussed throughout the Voting Panel meeting to ensure that patient input was incorporated into the final PsA guideline. Examples of patient feedback included strong values for therapies that are effective (e.g.,

prevent further damage, improve quality of life, social participation and function), safe (i.e., particularly have low adverse event profiles. Adverse events, such fatigue, nausea and malaise, had a negative effect on quality of life and social participation and thus weighed heavily on patients' decision-making. The concept of treat-to-target was challenging for patients. While they saw value in improved outcomes, they also thought that this strategy could increase costs to the patient (e.g., copayments, time traveling to more frequent appointments, etc.) and potentially increase adverse events. Therefore, a detailed conversation with the patient is needed to make decisions regarding treat-to-target. Finally, to help ensure that the recommendations are patient-centered, two patients were Voting Panel members.

The ACR/NPF PsA guideline is the first treatment guideline to recommend a TNFi biologic as a first-line agent in patients with active PsA. This is a conditional recommendation. The lack of data on efficacy for OSMs – in particular regarding their impact on the prevention of disease progression or joint damage – and the favorable benefit/harm profile of TNFi biologics drove the final decision. OSMs, except MTX and apremilast, have limited efficacy for psoriasis. Nevertheless, this was a challenging decision that required an extensive discussion by the Voting Panel, and is based on their consensus. During the development of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and European League Against Rheumatism (EULAR) recommendations for the treatment of PsA, panel members also challenged the decision to put OSMs first in those recommendations – the final decision was made based on the lower cost of these medications (32, 33).

Because the use of a TNFi biologic may not be the optimal choice for all patients, we note several conditions in which an OSM may be preferred. These include patients without severe PsA, those without severe psoriasis, who prefer oral therapy, who have concerns over starting a biologic as the first therapy or who have contraindications to TNFi biologics, including recurrent

infections, congestive heart failure or demyelinating disease. This guideline provides recommendations for early and aggressive therapy of newly diagnosed PsA patients.

In patients with concomitant IBD, the Voting Panel made strong recommendations favoring a TNFi monoclonal antibody or an IL12/23i biologic over an IL17i biologic or a TNFi receptor biologic (etanercept). This was based on moderate-quality evidence that showed that TNFi antibody biologics and ustekinumab (an IL12/23i biologic) are effective for the management of IBD, whereas etanercept and secukinumab were not effective for IBD (34, 35).

We recognize that our recommendations do not account for the full complexity of PsA nor the full range of possible therapies (e.g., glucocorticoids were not addressed); however, the varied reporting of disease measures and differences in inclusion/exclusion criteria in PsA clinical trials makes it difficult to compare therapies across trials. The impact of alternative therapies on important outcomes such as joint damage still remains uncertain.

The ACR has decided to use GRADE methodology in the development of guidelines for the management of rheumatic diseases. The GRADE methodology specifies that panels make recommendations based on a consideration of the balance of relative benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the evidence based on the lowest quality of the critical outcomes – high, moderate, low or very low), and patients' values and preferences. The rating of the quality of evidence for each clinical situation (PICO question), helped to inform the strength of the recommendation (strong or conditional) (36).

The use of GRADE (not used in other PsA treatment recommendations) allowed an explicit consideration of the overall evidence including the balance of benefits and harms of treatments

(including cost), and the incorporation of patient values and preferences to judge the tradeoff. This approach led to transparency in decision-making by the Voting Panel for each clinical scenario and the formulation of these recommendations. Consistent with GRADE guidance, the Voting Panel usually offered a strong recommendation in the presence of moderate- or high-quality rating of the evidence, and a conditional recommendation in the presence of very-low or low-quality evidence, although recommendations can also be conditional in the setting of moderate quality evidence (15).

The other merits of the ACR/NPF process undertaken included: a comprehensive literature search; the consideration of each comparison in light of the available evidence; the diverse composition of the Voting Panel; the inclusion of all of the available therapies (e.g., IL17i biologics, an IL12/23i biologic, abatacept and tofacitinib) in the decision-making process (including those approved for psoriasis or rheumatoid arthritis, but not yet for PsA, ensuring that the guideline would not be out of date by the time it was published); and the inclusion of population subsets, such as those with predominant enthesitis and/or IBD.

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

In PsA, we often used indirect comparisons among trials/therapies, frequently relying on network meta-analysis. Stratified analyses among subgroups (e.g., treatment naïve, a TNFi

biologic inadequate responder) were rarely reported separately in primary trials, limiting our ability to perform network meta-analyses in these important subgroups. There were few or no head-to-head comparison studies identified in the literature review for most clinical scenarios (PICO questions). Thus, the quality of evidence was most often low or very low and only occasionally moderate. This led to nearly all recommendations being "conditional," with few "strong" recommendations in cases in which there was sufficient evidence (including that from outside of PsA) to make the Voting Panel confident in selecting one option over the comparator. A flow chart or ranking of treatments requires strong recommendation; when recommendations are conditional/ weak it means that the right course of action differs between the patients. When the right course of action differs between patients, it is inappropriate to make the flow chart and establish treatment ranking or a hierarchy of treatment options (14).

The 2017/18 ACR/NPF treatment guideline for patients with PsA will assist patients and their health care providers in making challenging treatment decisions. More comparative data are needed to inform treatment selection. Several ongoing trials, including a trial to compare a TNFi biologic combination therapy with a TNFi biologic monotherapy and MTX monotherapy (37), will inform treatment decisions. We anticipate future updates to the guideline, when new evidence is available.

ACKNOWLEDGMENTS

We thank Ms. Emily Boyd with the NPF for her involvement throughout the guideline development process. We thank Dr. Maureen Dubreuil for leading the Patient Panel meeting, as well the patients who participated in this guideline project – Eddie Applegate, Steve Bishkoff, Christy Gephart, Lisa Medlin, Gail C. Richardson, Richard F. Seiden, Delores Teddleton and Hilary Wilson. We thank the ACR staff, including Ms. Regina Parker for assistance in organizing

the face-to-face meeting and coordinating the administrative aspects of the project, and Ms. Robin Lane for assistance in manuscript preparation. We thank Ms. Janet Joyce for help in developing the literature search strategy and performing the literature search and updates, and Ms. Tamara Rader for peer-reviewing the literature search strategy. We thank Dr. Jonathan Treadwell for his statistical contributions to the network meta-analyses that were done as part of the literature review.

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