RHEUMATOLOGY

Rheumatology 2020;59:i37–i46
doi:10.1093/rheumatology/kez383

Treatment guidelines in psoriatic arthritis

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Abstract

Psoriatic arthritis (PsA) is a complex inflammatory musculoskeletal and skin disease. The treatment of PsA has changed substantially over the past 10 years. Clinical practice guidelines are developed to help busy clinicians rapidly integrate evolving knowledge of therapeutic management into practice. In this review, we compare PsA treatment recommendations or guidelines developed by one national organization [ACR and National Psoriasis Foundation (NPF) in 2018], one regional organization (EULAR in 2015), and one international organization (the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis in 2015). We examine the development of guidelines in PsA more broadly and examine similarities and differences in the three sets of recommendations.

Key words: psoriatic arthritis, therapy, treatment guidelines, treat-to-target, outcomes

Rheumatology key messages

- Developing treatment guidelines for PsA is challenging due to the heterogeneity of the disease.
- Available PsA treatment recommendations differ in methods employed, therapies included and some of the final recommendations.
- More studies are needed to fully inform treatment selection in PsA and overall disease management.

Introduction

The purpose of clinical practice guidelines and/or treatment recommendations is to provide clinicians with the best evidence available in selected scenarios in order to allow physicians to deliver the best health care. This is particularly important as the number of new therapies expands and we learn more about the complexity of diseases and how different disease elements may direct therapy selection. In no disease is this more relevant than psoriatic disease where six new therapies have entered the market in the past 5 years, including four first-in-class therapies.

In this paper, we discuss how treatment recommendations have dealt with the individual features of PsA, the therapies and the relative lack of comparative data in creating a decision-making pathway for physicians. We examine and compare treatment recommendations or guidelines from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [1], the EULAR [2], and the ACR/National Psoriasis Foundation (NPF) [3].

Psoriatic arthritis: a complex disease

Psoriatic arthritis (PsA) is chronic, inflammatory, musculoskeletal disease associated with psoriasis [4]. Up to 30% of patients with psoriasis may develop PsA over the course of their lifetime. Musculoskeletal manifestations of PsA include peripheral arthritis, spondylitis, dactylitis (inflammation of the whole digit) and enthesitis (inflammation where a tendon, ligament or joint capsule inserts onto the bone). Skin manifestations of PsA include psoriasis (which has numerous phenotypes but the most common type associated with PsA is psoriasis vulgaris or plaque psoriasis) and nail disease. Beyond the musculoskeletal and skin features, patients with PsA experience fatigue, physical function limitations, sleep disturbance, as well as diminished work capacity and social participation [5]. In addition to the association with extra-articular manifestations such as uveitis and inflammatory bowel disease (IBD), PsA is also associated with several comorbidities including obesity and metabolic disease (diabetes, hypertension, hyperlipidaemia, fatty liver disease, cardiovascular outcomes), depression and anxiety [6]. All of these factors may play an important role in therapy selection [1].

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Submitted 30 April 2019; accepted 26 June 2019

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REVIEW

Treatment for PsA includes traditional or conventional disease modifying antirheumatic drugs (DMARDs), biologic therapies such as TNF inhibitors (TNFi), IL-17 inhibitors (IL-17i), IL-12/23 inhibitor (IL-12/23i), and new targeted oral agents including a phosphodiesterase-4 inhibitor and a Janus kinase (JAK)/signal transducer and activator of transcription (STAT) inhibitor (Table 1). Additionally, agents are now approved for psoriasis that are not yet approved for PsA including an IL-17 receptor blocker (brodalumab) and three IL-23i (guselkumab, tildrakizumab and rizankizumab) likely to the enter the market in the near future [7, 8]. The fact that therapies and the relevant evidence available are changing rapidly leads to one of the greatest challenges in creating treatment guidelines. Some of the therapies included in the ACR/NPF guidelines, published in January 2019, were not available at the time that evidence synthesis was performed for the GRAPPA and EULAR recommendations that were last updated in 2015.

Purpose of guidelines

As pathophysiology of disease and therapy effectiveness, particularly in specific scenarios, is better understood, physicians may struggle to keep up with the latest evidence. Treatment guidelines are designed with several goals in mind: to educate providers, particularly in a changing therapeutic landscape; to describe 'best care' through processing of the best available scientific evidence and broad consensus and to simultaneously point out where there is little information to guide treatment decisions; to reduce inappropriate variation in care and set standards for quality control; to promote efficient use of resources; and to highlight the research that needs to be done to inform future care.

Terminology and basic components in treatment guideline development

First, the terms 'guidelines' and 'recommendations' are used differently by various groups. The ACR uses the term 'guidelines' to refer to the full set of recommendations within the paper. GRAPPA has chosen to use the term 'recommendations' as treatment scenarios may be varied by health care system and setting and thus the term recommendation leaves up to the physician and patient the final decision instead of imposing a 'guideline', felt to be a more stringent term. EULAR follows the same convention. Regardless of the term used, the decision regarding the selection of a specific therapy for an individual patient is between the physician and the patient [9].

The basic development of a treatment guideline begins with identifying the process that will be used. For example, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) is among the most commonly used methods for developing guidelines (and is used by the ACR and several other organizations in North America and Europe) [10, 11]. Other options include the Strength of Recommendation Taxonomy [12] (used by the American Academy of Dermatology), and the Oxford Centre for Evidence-Based Medicine (OCEBM) (used by EULAR) [13, 14]. All of these methods require selecting a key group of decision makers, which ideally involves multiple stakeholders including content experts and, in many cases, patient representative of those receiving the therapies. These processes depend on systematic literature reviews but vary somewhat in the definitions of the strength of the evidence. After selecting a methodology to be employed and recruiting stakeholders, the scope of the guideline is decided upon. For example, will only pharmacotherapies be examined or will non-pharmacological therapies, treatment strategies or other methods of

Table 1 Psoriatic arthritis treatment toolbox

Therapy Class	Therapies
Oral therapies[a]	MTX, sulfasalazine, cyclosporine, leflunomide, apremilast
TNF inhibitors	Etanercept, infliximab, adalimumab, golimumab, certolizumab pegol
IL-12/23 inhibitor	Ustekinumab
IL-17A inhibitors	Secukinumab, ixekizumab
CTLA-4 Ig	Abatacept
JAK/STAT inhibitor	Tofacitinib
Symptomatic therapies	nonsteroidal anti-inflammatory drugs, glucocorticoids, local glucocorticoid injections
Psoriasis therapies	Topical therapies Phototherapy Other oral therapies: retinoids IL-17R blocker: brodalumab IL-23 inhibitors: guselkumab, tildrakizumab, rizankizumab[b]
Non-pharmacological therapies	Physical therapy, occupational therapy, smoking cessation, weight loss, massage therapy, exercise

[a]Oral therapies are termed 'oral small molecules' in the ACR/NPF treatment guidelines and are split into 'cs-DMARDs' (top row) in the GRAPPA and EULAR recommendations and apremilast in its own group (phosphodiesterase-4 inhibitor). [b]Rizankizumab is approved in Japan and recently approved in the USA (April 2019) and thus was included in the 2019 American Academy of Dermatology/National Psoriasis Foundation (AAD/NPF) treatment guidelines for psoriasis. JAK: Janus kinase; STAT: signal transducer and activator of transcription.

management be considered? This is more formally decided upon in GRADE and similar methods in that the specific questions [i.e. patient–intervention–comparator–outcome (PICO) questions] are designed. Evidence is then gathered to address the questions of interest through systematic literature reviews. Evidence is assembled into a readable format (i.e. tables) and reviewed by the stakeholders. Voting proceeds after evidence review (using a variety of formats). Following voting, recommendations are generated as key action statements and typically a strength and grade of recommendation is also provided. The guideline is then published [15]. Ideally, after publication, the implementation of the guideline is appraised to determine whether the guideline was useful and whether it changed clinician behavior. We will walk through each of these components for the guideline (or set of recommendations) to understand how they are similar and different.

Overview of the PsA guidelines/ recommendations

Overall these guidelines are quite similar but there are differences among them in structure and final recommendations (Table 2) [16, 17]. Differences among the recommendations are in part the result of differing processes for arriving at decisions and the relative weight placed on expert opinion *vs* evidence in the case of low quality evidence. Thus, the key methodologies used contribute to key differences. The ACR/NPF guidelines used GRADE, GRAPPA used a modified GRADE methodology, and EULAR used OCEBM. Additionally, the construction of the panels, in particular, the number of dermatologists, also influenced the structure of the recommendations and the final decisions.

Structure: scope of the guideline and the topics selected

The scope of the guideline is decided upon prior to initiation of the literature search and often leads to the structure of the guideline. GRAPPA is unique in structuring the recommendations by disease domain [18] and including a separate working group to develop questions for patients with specific comorbidities. The GRAPPA treatment recommendations committee included rheumatologists, dermatologists, methodologists and patient research partners. PICO questions were developed for each domain and a number of teams developed the questions and literature search [19–25]. This resulted in an overall grid with treatment selection by disease domain and a separate grid to aid clinicians in making treatment decisions in the setting of 16 comorbidities. ACR/NPF held a scoping meeting to decide which questions and topics to address. The ACR/NPF guideline group included a core group of three rheumatologists, a GRADE expert and a literature review expert and then an expert panel, systematic literature review team and voting panel. A dual dermatologist–rheumatologist was included on the expert panel and a dermatologist and dual dermatologist–rheumatologist were included on the voting panel. The scope of the guideline was created during a scoping meeting combining the expert and voting panels. At this meeting, the group decided to focus on patients with 'active PsA' overall and then included PICO questions related to specific features such as enthesitis and axial disease. The pharmacologic therapies, a handful of non-pharmacological therapies, and the outcomes were selected. The application of GRADE resulted in pairwise comparisons in each category (as PICO questions are phrased as intervention *vs* comparator) and thus a series of individual recommendations rather than a grid or flow chart. For the EULAR recommendations, a steering group consisting of seven rheumatologists, one fellow, one patient research partner and one health professional defined the questions and an Systematic Literature Review was performed. The panel built on the prior PsA recommendations published in 2012 and thus the structure, a flow chart, was relatively similar.

Beyond the specific questions to be addressed, the patient population to which the recommendations apply was mostly similar between the three sets: patients with active PsA. The definition of active disease in the GRAPPA recommendations included activity in the specific domains of the disease. The ACR/NPF guideline defined active PsA based on activity in any of the features, based on the effect on the patient and the physician's attribution of the symptoms to the disease.

Therapies selected

Among the major differences between the ACR/NPF guidelines compared with the EULAR and GRAPPA recommendations were the therapies available for inclusion and the terminology used in the oral therapies. GRAPPA and EULAR maintained the previous terminology: conventional synthetic DMARDs (csDMARDs), though made note that there was limited evidence to support their 'disease modifying' effect as it relates to structural damage. It was for this reason that the ACR/NPF task force decided to rename this category the oral small molecules (OSM). Apremilast was also included in this group given the absence of studies examining radiographic outcomes and the apparent similarity in effectiveness, though there are no data comparing apremilast with the other OSMs. In addition, there were several therapies included in the ACR/NPF guideline for which minimal information was available at the time of the GRAPPA and EULAR recommendations. For secukinumab (an IL-17i) and apremilast (a Phosphodiesterase 4 inhibitor) there were only published abstracts and they were not yet approved therapies at the time of the GRAPPA recommendations. Ixekizumab (an IL-17i), abatacept (CTLA-Ig) and tofacitinib (JAK inhibitor) were relatively new in PsA at the time of the ACR/NPF guidelines and in fact were included while pending US approvals for PsA because of the availability of data and the knowledge that they would eventually be approved. However, for these reasons, tofacitinib and abatacept were included in only a few of the recommendations because of relative paucity of published data at the time of the voting panel meeting. Thus, since 2015, the treatment landscape has changed significantly. This explains some of the differences in the guidelines.

Table 2 Summary of differences in recommendations

	EULAR 2015	GRAPPA 2015	ACR/NPF 2018
Process			
Method	OCEBM	Modified GRADE	GRADE
Composition of the committees	Mainly rheumatologists; patients and allied health professionals	Greater dermatologist involvement including leading two working groups; patients involved in each group	Relatively few dermatologists involved; patients in the expert and voting panels and separate patient panel; allied health professionals involved in the expert and voting panels
Structure of recommendations	Flow diagram with caveats	Flow diagrams for each feature with caveats	Only pairwise comparisons; no flow diagram can be created
Psoriasis management	Minimally addressed except to refer to co-management	Skin and nail disease addressed	Addressed in the conditions with regard to severity of psoriasis in particular; refers to co-management and concurrent AAD/NPF guidelines for management of psoriasis
Axial disease management	Addressed	Addressed	Only a few questions addressed but otherwise refers to ACR/SPARTAN guideline
Enthesitis	Addressed	Addressed	Addressed
Drugs			
MTX	Recommended as csDMARD of choice	Considered alongside other csDMARDs	Generally considered alongside other OSMs
TNF inhibitors	Recommended after failure of csDMARD for peripheral arthritis Earlier use in predominant axial disease or enthesitis. Or if there were prognostic indicators for severe disease Preference for TNFi as first-line biologic	Recommended after failure of csDMARD for peripheral arthritis though can be used first in severe disease, enthesitis or axial disease No clear preference among biologics	Conditionally recommended first in treatment naïve PsA over OSMs Conditional preference for TNFi over other biologics
Secukinumab	Recommended after failure of csDMARD but TNFi preferred as first line biologic	Recommended alongside other biologics	Conditionally recommended after TNFi but may be used earlier in setting of contraindications to TNFi or patients with severe psoriasis or nail disease
Ixekizumab	Not available	Not available	Conditionally recommended after TNFi but may be used earlier in setting of contraindications to TNFi or patients with severe psoriasis or nail disease.
Ustekinumab	Recommended after failure of csDMARD but TNFi preferred as first line biologic	Recommended alongside other biologics	Conditionally recommended after IL-17 except in IBD and in patients who desire less frequent injections
Apremilast	Recommended for use after MTX if biologics are contraindicated	Recommended for use after failure of csDMARDs or if csDMARDs are contraindicated. Conditionally recommended before csDMARD in some cases	Considered alongside other OSMs
Abatacept	Not available	Not available	Generally conditionally recommended after TNFi
Tofacitinib	Not available	Not available	Generally conditionally recommended after TNFi

This table was adapted from Gossec *et al.* [16]. csDMARD: conventional synthetic DMARD; GRADE: Grading of Recommendations Assessment, Development and Evaluation; GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; NPF: National Psoriasis Foundation; OCEBM: Oxford Centre for Evidence-Based Medicine; OSM: oral small molecules; SPARTAN: Spondyloarthritis Research and Treatment Network; TNFi: TNF inhibitors.

Outcomes selected

In comparing therapies, a set of outcomes must be chosen. In GRAPPA, the outcomes were those specific to the individual feature [e.g. American College of Rheumatology 20% response criteria (ACR20) for peripheral arthritis, and so on]. The primary outcomes of interest in the EULAR recommendations were ACR20 for efficacy and withdrawal due to adverse events for safety (additional secondary outcomes are listed in the systematic literature review) [14]. At the scoping meeting, participants in the ACR/NPF process selected ACR20, Psoriasis Area and Severity Index (PASI75), HAQ-Disability Index, minimal disease activity, and adverse events (in particular serious infections) as the primary outcomes of interest.

Managing conflicts of interest

In the EULAR and ACR/NPF processes, participants reported conflicts of interest prior to participation. According to GRADE and the ACR guidelines process, 51% of participants within each group had to be free of conflicts. The participants in the GRAPPA treatment recommendations provided disclosures regarding conflict of interest but there was no limitation on participation.

Inclusion of patients in the process

Patients were involved in the process in all three organizations. Within the GRAPPA process, patient research partners were involved in each panel. In the ACR/NPF process, two patients were included on the voting panel, and a separate patient voting panel was held to solicit patient preferences. Patients were additionally included in the scoping meeting. Patient preferences were addressed with each PICO question during the voting panel meeting. In the EULAR process, two patient research partners were included in the steering committee and the larger task force.

Review of the guidelines

Treatment principles

A set of basic treatment principles is outlined in each of the treatment recommendation papers prior to discussing the more specific recommendations. Overall, the sentiments of these principles were very similar across the three sets of recommendations: (i) the goals of therapy are to improve quality of life and function and prevent structural damage and complications; (ii) this is a disease that requires multidisciplinary care so engage other practitioners as needed (dermatologists, gastroenterologists, etc.); (iii) shared decision making is an important principle of optimizing treatment decisions; (iv) identify and consider comorbidities as they impact treatment selection. The GRAPPA treatment principles include more detailed information about assessment of PsA. The ACR/NPF does not specifically outline basic treatment principles but these same principles are woven throughout the discussion of the individual recommendations.

Definition of disease severity

The ACR/NPF guideline offers specific definitions of severe disease (Table 3). The GRAPPA and EULAR recommendations define disease severity based on the presence of poor prognostic factors. The GRAPPA recommendations suggest that the presence of poor prognostic signs would accelerate treatment. The EULAR recommendations instead note that patients with poor prognostic factors should be treated more aggressively and these included many swollen joints, structure damage in the presence of inflammation, high sedimentation rate or CRP and/or clinically relevant extra-articular manifestations.

Use of NSAIDs and glucocorticoids

Overall, little is included about NSAIDs and glucocorticoids in any of the treatment recommendations with the exception of noting in all three that NSAIDs are a symptomatic treatment and glucocorticoids should be used only when needed and at the lowest dose for the shortest time period. In the EULAR guidelines, there is a note that NSAIDs should be effective within a few weeks and should only be used as a monotherapy up to 3 months. Glucocorticoids can be particularly problematic in PsA because of the risk for flare of psoriasis upon withdrawal but nevertheless may be needed at times.

Order of therapy selection

The structure of the recommendations differs between the three sets and this is particularly notable in order of therapy selection. Both GRAPPA and EULAR use step-up approaches, although both, particularly the GRAPPA recommendations, allow for ‘skipping ahead’ based on the severity of disease or presence of specific disease features such as enthesitis. ACR/NPF, in contrast, offers specific recommendation for each situation (i.e. treatment naïve active PsA, active PsA in the presence of enthesitis, etc.). A flow diagram is not included within the ACR/NPF guideline. Instead several individual figures for a given setting (i.e. treatment naïve active PsA) show the pairwise comparisons for that setting, but the order of therapy selection or prioritization among therapies was not discussed.

First, therapy selection differs between the three disease sets. For the average patient with treatment naïve predominantly peripheral arthritis, the EULAR and GRAPPA recommendations suggest beginning with a csDMARD (although in the GRAPPA recommendations suggest that a biologic may be selected first if the situation warrants more aggressive therapy). In particular, EULAR recommends MTX as the first csDMARD unless there are contraindications. This recommendation was based on the efficacy of MTX in RA, similar persistence among patients with PsA initiating MTX to those with rheumatoid arthritis in a Norwegian study, data from the Tight Control in Psoriatic Arthritis (TICOPA) in which MTX was used as a foundation therapy and expert opinion [26]. The EULAR recommendations acknowledged the weakness of available data at the time to support MTX in

Table 3 Definitions of disease severity

ACR/NPF severe psoriatic arthritis	ACR/NPF severe psoriasis	EULAR poor prognostic factors
Erosive disease Elevated markers of inflammation (ESR, CRP) attributable to PsA Long-term damage that interferes with function (i.e. joint deformities) Highly active disease that causes a major impairment in quality of life Active PsA at many sites including dactylitis, enthesitis Function-limiting PsA at a few sites Rapidly progressive disease	PASI of 12 or more BSA of 5–10% or more Significant involvement in specific areas (e.g. face, hands or feet, nails, intertriginous areas, scalp) where the burden of the disease causes significant disability Impairment of physical or mental functioning can warrant a designation of moderate-to-severe disease despite the lower amount of surface area of skin involved	Many swollen joints Structure damage in the presence of inflammation High ESR or CRP Clinically relevant extra-articular manifestations

BSA: Body Surface Area; NPF: National Psoriasis Foundation; PASI: Psoriasis Area and Severity Index.

clinical trials. In contrast to GRAPPA and EULAR, for the same patient with active peripheral PsA, the ACR/NPF recommends a TNFi first over an OSM (MTX, sulfasalazine, leflunomide, ciclosporin, apremilast). This recommendation is conditional and has several caveats. For example, if the patient prefers an oral drug, has mild disease (absence of severe disease definitions in Table 3), or has contraindications to TNFi, the patient would start an OSM first. In this particular guideline, there was great debate over whether to make TNFi first line. The decision was based on the available data at the time. Using all available trial data from MTX, the odds ratio for response in MTX *vs* TNFi was 0.24 in a network meta-analysis as there was limited direct comparison available. TNFi monotherapy was preferred to combination therapy in the ACR/NPF guideline.

Since the publication of the guidelines, the Study of Etanercept and Methotrexate in Psoriatic Arthritis (SEAM-PsA) trial comparing etanercept to MTX among treatment naïve patients with early PsA was published [27]. There was a significant difference in ACR20 response rates at 24 weeks among patients randomized to etanercept-containing arms (63%) compared with MTX monotherapy (50%). Of note, there was no advantage to combining etanercept with MTX. It is unclear whether this would have changed the recommendation for TNFi first from the voting panel members.

While in both EULAR and GRAPPA recommendations, anti-TNF agents are first choice after csDMARDs, GRAPPA included IL-12/23i and IL-17i as options for first choice after csDMARDs.

Another difference between the recommendations was the placement of apremilast in the treatment algorithm. At the time the EULAR and GRAPPA recommendations were being developed, there was very little published data on apremilast. For this reason and the general recent introduction of the medication class, EULAR placed apremilast at the end of the treatment pathway. GRAPPA left the option open for use of apremilast throughout the treatment pathway to maximize flexibility for the clinician. In the ACR/NPF guideline, apremilast was included with the OSMs and thus could be used first line in patients with mild disease.

Switching therapy among patients who have failed a first TNFi in the EULAR and GRAPPA treatment guidelines is fairly broad. All of the potential biologic therapies (TNFi, IL-12/23i, IL-17i) are listed as options. In the ACR/NPF guidelines, the recommendation is to switch from a first TNFi to a second TNFi prior to switching to a different class and then in general, IL-17i are recommended over IL-12/23i.

Non-pharmacological therapies

The ACR/NPF recommendations note that the following non-pharmacological therapies should be recommended, in the appropriate circumstance: low impact (over high impact) exercise, physical therapy, occupational therapy, weight loss in patients who are overweight or obese, massage and acupuncture. These are all conditionally recommended due to poor evidence specifically in PsA with the exception of weight loss for which there is evidence to support this intervention. One of the few strong recommendations in the ACR/NPF guideline was smoking cessation among those who smoke as smoking is associated with cardiovascular disease and is generally associated with worse treatment outcomes. The EULAR and GRAPPA treatment recommendations do not specifically address use of non-pharmacological therapies. Since the 2015 EULAR PsA treatment recommendations, EULAR subsequently published updated cardiovascular disease recommendations [28] and recommendations for physical activity [29], both of which apply to PsA.

Addressing individual domains

The GRAPPA recommendations are the only set where treatment recommendations for individual domains are provided. However, all three sets of recommendations note that axial PsA should be treated similarly to AxSpA recommendations. The ACR/NPF guideline refers to the ACR/SPARTAN AxSpA recommendations but adds recommendations that refer to IL-17i. All three guidelines also discuss enthesitis. In GRAPPA and EULAR, the recommendations suggest that in the presence of predominant enthesitis, one can skip forward in the treatment paradigm to treat more aggressively (i.e. earlier biologic initiation). In the ACR/NPF guideline, note is made of the

lack of data for OSMs other than apremilast in treatment of enthesitis. In the case of predominant enthesitis in a treatment naïve patient, the ACR/NPF treatment comparisons suggest an NSAID over OSM, TNFi over OSM, and tofacitinib over OSMs. This recommendation is close to that suggested by GRAPPA.

Psoriasis, the most common condition associated with PsA, is addressed in the GRAPPA recommendations in detail. In fact, dermatologists led the work groups for nail disease and skin, and the full range of therapies available in 2015 were included. On the other hand, EULAR recommendations minimally address psoriasis in the treatment pathways but do note that a dermatologist should be involved in management of patients with severe psoriasis and that the preferred csDMARD in patients with psoriasis is MTX. The ACR/NPF task force chose to include severity of psoriasis in many of the conditions that specify the situations in which one would use the recommendation as given *vs* the alternative. However, the management of psoriasis was not addressed in detail. Instead, the guideline refers physicians to the American Academy of Dermatology (AAD)/NPF guidelines, which were being developed in parallel. These guidelines were released in 2019 and include a number of therapies that are not yet approved for PsA (specifically the IL-23i and brodalumab, an IL-17 receptor blocker) [8]. They also published a separate guideline for comorbidities [30].

Comorbidities in treatment selection

A number of comorbidities (e.g. cardiovascular disease, diabetes, fatty liver disease, osteoporosis) and extra articular manifestations (i.e. IBD and uveitis) are associated with PsA. The GRAPPA recommendations are the only set of recommendations to extensively discuss comorbidities related to PsA and the implications for management. A table with comorbidities and the therapies on the opposing axes is included in the GRAPPA recommendations to demonstrate how therapy selection is affected by each comorbidity including in which settings concerns have been raised about specific therapies, whether special monitoring is required, and which therapies are preferred in the setting of a specific comorbidity. In contrast, EULAR includes a statement that notes comorbidities and extra articular manifestations should be taken into account in therapy selection. However, EULAR has released cardiovascular disease recommendations for patients with inflammatory arthritis in general that also apply to PsA. The ACR/NPF has three strong recommendations in the setting of IBD including the avoidance of etanercept (not effective in IBD) and IL-17i (not effective in IBD and a signal that these drugs may bring out or exacerbate IBD).

Treat to target

'Treat to target' is the concept that an outcome (or target) is objectively followed at each visit and therapies are adjusted to get the patient into a state of remission or low disease activity (whichever target is chosen). This concept was tested in a randomized controlled trial, TICOPA which used minimal disease activity as the target [26]. Patients in the intensive management group had a significantly higher likelihood of achieving ACR20 responses, PASI75 and a number of other outcomes. However, in this treatment naïve, early disease population, there were no significant differences in X-ray progression at 48 weeks (though the majority did not progress). All three guidelines recommend using a treat to target approach. One caveat discussed in the ACR/NPF guideline was that patients were reluctant to mandate a treat to target approach as they were concerned it would result in more visits (more costs in terms of travel or copays) as well as higher treatment costs and treatment side effects. Thus, this was a conditional recommendation in the ACR/NPF guideline. In all three guidelines, the target can be decided upon by the physician but may include minimal disease activity or disease activity in PsA [31, 32].

Summary of research agendas from each guideline

All three papers included future research needs in the form of a research agenda or notes in the paper discussion (Table 4) [33]. These included the need for more head-to-head trials, studies of prognostic biomarkers, identification of the best patient reported outcome measures, implications of comorbidities on treatment selection to inform more precise comorbidity-related recommendations, and improved understanding of treatment targets [34].

Limitations of current treatment recommendations

The major limitation of the current treatment recommendations is the paucity of data. Despite many therapies studied in randomized controlled trials *vs* placebo, there are few data to inform how to select one therapy over another. There are several head-to-head trials ongoing and the SEAM trial was recently published [27]. Furthermore, there is no evidence on sequencing of therapy and treatment strategies (beyond treat to target). Next, variability in clinical presentation makes a single overarching guideline difficult to write. These recommendations aim to address the 80% scenarios—the mainstream cases—but this may be inappropriate to implement in all cases and there are many factors to take into account in selecting therapies. Treatment of PsA remains individualized in many cases, creating a difficult scenario in which to create straightforward algorithms. Additionally, the methods by which guidelines are created are somewhat antiquated. GRADE in particular may be very useful in providing evidence-based guidelines in which it is clear how much of the recommendation is based on evidence and how much is based on eminence and/or expert opinion. However, the downside is that the final product is a series of pairwise comparisons that are challenging to directly apply in clinical practice when the clinician is selecting among multiple therapies [35, 36]. Finally, with the rapid evolution in available therapies, the latest treatment guidelines are always somewhat out of date by the time they are published. The GRAPPA and EULAR recommendations are currently in the process of being updated. A preliminary view of the EULAR

Table 4 Research agenda: data needed to inform treatment guidelines in PsA

Topic	Questions to be addressed
Early identification/diagnosis of PsA	Earlier disease identification will improve treatment outcomes
Prognostic factors	Identification of factors that predict more aggressive or destructive disease will assist in selecting therapies
Biomarkers	Prognostic biomarkers, measures of disease activity and response to therapy, and biomarkers that predict response to therapy are needed
Outcome measures	Measures for defining response in trials that are specific to PsA and measures for monitoring response to therapy in clinical practice are needed; patient-specific treatment outcomes would assist in personalizing therapy selection and monitoring
Comparative effectiveness of therapies	Head-to-head randomized controlled trials and pragmatic/real-world trials would inform treatment order
Treatment strategies	Sequencing of therapy (including the importance of first therapy selected), value of combination biologic and oral therapy for therapy persistence, protocols for therapy withdrawal, and identification and management of flares are largely unknown
Therapy personalization	Therapy could be better personalized if biomarkers, genetics and other factors that predict response or non-response to therapy, impact of individual comorbidities on response to therapy, and management of uveitis and inflammatory bowel disease in setting of PsA were better understood

guideline was presented at EULAR in Madrid in 2019 with a publication anticipated in late 2019 [37].

Conclusion

In summary, EULAR, GRAPPA and the ACR/NPF have all created treatment guidelines using three different approaches. Overall, they are quite similar in therapy recommendations with some major differences: the ACR/NPF recommends a TNFi first in the setting of active treatment naïve PsA; the use of the terms csDMARD *vs* OSM and the drugs included in those categories; the drugs available at the time of recommendation development; and the structure of the final recommendations. All three recommend a treat to target approach. Available treatment guidelines have limitations and new methods for guideline development for complex, heterogeneous diseases are needed. There is no one best guideline recommended for all clinicians: GRAPPA was designed for international application and has more information on skin and nail disease management but US and European rheumatologists may benefit from consulting the ACR/NPF and EULAR guidelines, respectively, which take into account local health economies. One of the most useful aspects of these recommendations is the clarity they bring to the available evidence and the identification of the critical gaps for which studies are needed in moving the field forward and improving patient outcomes.

Acknowledgements

A.O. is supported by NIH/NIAMS R01 AR072363. L.C.C. is funded by a National Institute for Health Research Clinician Scientist award.

Funding: This research was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. This paper was published as part of a supplement funded by an educational grant from Novartis.

Disclosure statement: A.O. has served as a consult for Abbvie, Amgen, BMS, Celgene, Corrona, Lilly, Pfizer, Novartis, Takeda and has received grants from Novartis and Pfizer, and her husband receives royalties from Novartis. L.C.C. has received grant funding from Abbvie, Celgene, Lilly, Novartis and Pfizer and honoraria for Abbvie, Amgen, Celgene, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer and UCB. D.D.G. has served as consultant and/or received grant support from Abbvie, Amgen, BMS, Celgene, Eli Lilly, Gilead, Galapagos, Janssen, Novartis, Pfizer and UCB. The other author has declared no conflicts of interest.

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