Treatment of psoriatic arthritis: management recommendations

L. Gossec¹, J.S. Smolen²

¹Sorbonne Universités, UPMC Univ Paris 06, Institut Pierre Louis d’Épidémiologie et de Santé Publique, GRC-UPMC 08 (EEMOIS); AP-HP, Pitie Salpêtrière Hospital, Department of Rheumatology, Paris, France;
²Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, and 2nd Department of Medicine, Hietzing Hospital, Vienna, Austria.

Laure Gossec, MD, PhD
Josef S. Smolen, MD

Please address correspondence to:
Prof. Laure Gossec,
Hôpital Pitie-Salpêtrière,
Service de Rhumatologie,
47-83, boulevard de l’Hôpital,
75013 Paris France.
E-mail: laure.gossec@aphp.fr

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ABSTRACT
Given the varied therapeutic options available for the management of psoriatic arthritis (PsA), recommendations for the management of PsA have been developed by several expert groups. These recommendations deal mainly with pharmacological treatments.

At the international level, 2 recommendations sets are available: these have been developed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and by the European League against Rheumatism (EULAR). These recommendations were published in 2009 and in 2012, respectively; and updates of these recommendations are currently ongoing. The first sets of recommendations dealt with non-steroidal anti-inflammatory drugs, glucocorticoids, conventional synthetic disease modifying drugs and tumour necrosis factor inhibitors; the 2015 sets of recommendations also deal with new drugs with other mechanisms of action, namely ustekinumab, secukinumab and apremilast. In the present paper, we will review these management recommendations.

Introduction
The management of psoriatic arthritis (PsA) rests on pharmacological and non-pharmacological measures. The main pillar of pharmacological treatment is represented by disease-modifying anti-rheumatic drugs (DMARDs). There are three major classes of DMARDs, loosely grouped according to different mechanisms of action: conventional synthetic (cs) DMARDs such as methotrexate, sulfasalazine and leflunomide; biological agents (bDMARDs) including tumour necrosis factor inhibitors (TNFi) as well as those with other mechanisms of action, and targeted synthetic (ts) DMARDs, such as phosphodiesterase inhibitors (e.g. apremilast) or JAK-inhibitors (e.g. tofacitinib) (1). With several therapeutic options available and insufficient information on differential efficacy and safety, treatment decisions in clinical practice remain challenging; this is why recommendations for the management of PsA are of use. Such recommendations are usually developed by a group of experts, and are based on the data available (collated through a systematic literature review) as well as on expert consensus (2). When high-quality, low-bias trials are available, these studies may give evidence of efficacy and - in the best of cases - negligible toxicity for a given drug; this will then be reflected by authorisations for use of the drug, delivered by agencies such as the Food and Drug Administration or the European Medicine Agency. Such studies will not however allow to hierarchise the new drug into an algorithm, in the lack of head-to-head trials and strategy trials. Therefore, recommendations for management are developed by experts to help guide clinicians and other stakeholders, including people with the disease who can use these recommendations for information and other stakeholders e.g., governments or reimbursement agencies.

As regards management recommendations for PsA, various sets of recommendations have been developed by several expert groups, either at the national level or at the international level (3). At the international level, 2 recommendations sets are available: these have been developed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and by the European League against Rheumatism (EULAR) (4, 5). These recommendations were published in 2009 and 2012 respectively, and both sets of recommendations are currently undergoing updates.

In the next paragraphs, we will present these recommendations.
The published management recommendations from GRAPPA and EULAR

These recommendations deal mainly with pharmacological treatments, although an optimal management of patients with PsA should also include non-pharmacological strategies with patient education and regular exercise (6).

Both recommendation sets propose a graduated, overlapping approach to the treatment of PsA (Fig. 1). However, the GRAPPA recommendations have an equal dermatology/rheumatology outlook whereas the EULAR recommendations put the primary emphasis on the musculoskeletal aspects of the disease, given that EULAR is a rheumatology-oriented organisation (2).

The first set of recommendations to be published were the GRAPPA recommendations (5). Based on systematic literature reviews and the expert opinion of both dermatologists and rheumatologists, these recommendations proposed different therapeutic pathways according to the predominant clinical manifestation (Fig. 2) (5).

The EULAR recommendations for the management of PsA were developed in 2011 (4) based on 2 systematic literature reviews (7) and on the results of the discussions and votes of an expert committee comprising rheumatologists, methodologists, health professionals, patients and a dermatologist. Compared to the GRAPPA recommendations, on top of a greater rheumatology focus, the presentation of the recommendations is different, and includes a Table with 5 overarching principles and 10 recommendations, as well as an algorithm (Fig. 3).

Both of these sets of recommendations propose non-steroidal anti-inflammatory drugs as first treatment for joint inflammation then, if necessary, introduction of csDMARDs such as methotrexate, and finally, if inflammation persists, introduction of TNFis (4, 5).

The ongoing update of the EULAR recommendations

Recently, novel therapies with utility in PsA have emerged: these are bDMARDs, namely secukinumab or ustekinumab, and a tsDMARD: apremilast (8-10). Moreover, new trials have addressed therapeutic strategies (11) and treat-to-target recommendations have been developed for PsA (12, 13). Because of the advent of these new drugs and these new strategies, over 2014-2015, EULAR has updated the PsA recommendations. The results of this update have been presented at the EULAR 2015 congress and are currently under review before publication (14).

We will present here a brief summary of the main points of the new EULAR recommendations, since this Supplement is scheduled to be available at the American College of Rheumatology annual meeting in November 2015. Final information will however be available only after the recommendation main paper is published, hopefully by the end of 2015 (14).

The EULAR Taskforce consisted of 34 persons from 14 European countries: 27 rheumatologists, 3 people affected with PsA, 2 health professionals, 1 dermatologist and 1 rheumatology fellow. Thus again for these recommendations, the main focus is on musculoskeletal manifestations (15). The process was both evidence-based and consensus-based and included, between June 2014 and February 2015, 2 expert meetings, a systematic literature review of drug efficacy and tolerance based on randomised controlled trials (8) and extensive discussions.

The updated recommendations comprise 5 overarching principles and 10 recommendations, covering pharmacological therapies for PsA from non-steroidal anti-inflammatory drugs, to all...
the disease-modifying drugs, whatever their mode of action, taking articular and extra-articular manifestations of PsA into account, but focusing on musculoskeletal involvement.

The overarching principles put forward the importance of “shared decision” with the patient, which refers to the necessity to discuss and record treatment aims, management plans and reasons for the recommended approaches with the patient. Treatment objectives and the importance of considering comorbidities, in particular, cardiovascular diseases and metabolic syndrome (16, 17) are also dealt with in the overarching principles.

Importantly, the EULAR recommendations insist at the general principle of targeting remission or at least low disease activity (LDA)/minimal disease activity (MDA) in a treatment-to-target approach (12), as outlined in part in the overarching principles and in part in the individual recommendations (14). The feasibility and effectiveness of this approach has recently been confirmed by the randomised controlled strategy-trial TICOPA which indicated patients treated with tight control aiming at MDA had better outcomes than patients in the standard care group (18). The target to aim for in PsA remains not perfectly determined. MDA has been defined by using not only joint involvement, but also other musculoskeletal characteristics and skin disease as well as patient-reported outcomes (19). Very recently, criteria for remission and LDA have been validated for the Disease Activity index for Psoriatic Arthritis (DAPSA) which focuses solely on joint assessment (20).

**csDMARDs**

The recommendations address csDMARDs as an initial therapy after failure of non-steroidal anti-inflammatory drugs and local therapy for active disease. Based on the available literature (8) and similarly to the 2012 recommendations, the experts recommended methotrexate as the first-choice csDMARD. Although there are few randomised controlled trials of methotrexate in PsA and one is a negative trial for the primary outcome (7, 21), there are observational data on the wide use and good treatment maintenance of methotrexate in PsA (22, 23). The first csDMARD prescribed is usually methotrexate because of its effects on joints and skin, but can also be leflunomide, sulfasalazine or others.

**TNFi**

In some cases the first csDMARDs is either not well tolerated or not/incompletely efficacious even though the treatment has been taken for an appropriate length of time (usually 3–6 months), i.e. the treatment target of at least low disease activity is not reached. In such cases, a second csDMARD or a bDMARD can be considered. The experts felt that given the long-term experience, the well-established efficacy/safety balance in PsA, and usual practice, TNFis would usually be the first bDMARD. All the available originator TNFis (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) have demonstrated efficacy in PsA, both for skin and joint involvement, as well as in preventing radiographic damage (7, 8, 24). Biosimilars if licensed may also be used (25).

**Other bDMARDs and tsDMARDs**

The EULAR recommendations then also address the use of bDMARDs targeting two novel mechanisms of action, namely the IL12/23 (ustekinumab) and IL17 pathways (secukinumab) (8, 10, 26–29, 9, 30, 31). These drugs are useful additions to the pharmacopea of...
PsA. Importantly, the Taskforce felt that at the present time TNFı would usually be prescribed preferentially to these new bDMARDs in most cases (14).

A first tsDMARD has been approved for PsA: apremilast is a phospho-diesterase-4-inhibitor and the task force also addressed this agent in more detail; it has a significant though moderate efficacy on joints, skin and entheses in PsA (32-34), but structural data and studies comparing it with methotrexate, other csDMARDs or bDMARDs are lacking, although there is a good overall safety profile (8). The new recommendations state this drug would usually be prescribed in patients who failed csDMARDs and for whom bDMARDs are not appropriate (14). For more detailed information on the recommendations, readers are referred to the main publication (14).

Patients with predominant axial or enthesal manifestations
For these patients, the algorithm is slightly different, since csDMARDs are not effective. This is detailed in the main publication.

Switches
If the first bDMARD strategy fails, any other bDMARD or tsDMARD may be used.

Discussion
The authors of the EULAR recommendations are aware that the placements of the various agents in the algorithm will be a topic of intense discussions in the rheumatology community. However, with more long-term and especially registry data, the day-to-day efficacy, safety, and tolerability will become better known and allow for further insights. Until recently, patients who had failed or incomplete responses to csDMARDs only had TNFıs available and cycling through TNFıs was the only option if the first TNFı was ineffective. At this time, several options have become available – a major advance in the treatment armament of PsA (35).

The ongoing update of the GRAPPA recommendations
Over the last 2 years, GRAPPA has also undertaken an update of PsA management recommendations (36). These recommendations are now finalised and have been submitted for publication, but have not been officially released. The new recommendations are based on several systematic literature reviews focusing on the different manifestations of PsA (37-43). The format of these new recommendations is much closer to the format of the EULAR recommendations, since it now includes overarching principles, as well as a Figure giving indications for order of treatments according to the predominant manifestation.

The exact order of the drugs has not been officially released; however, it appears apremilast will be in a more prominent position in the GRAPPA recommendations than in the EULAR recommendations. Readers are referred to the new GRAPPA recommendations when published for more information concerning the matter.

Conclusion
Management recommendations provide physicians and other stakeholders who treat patients with PsA with a practical approach to prescribing the optimal treatment for PsA patients based on the most recent insights. They also inform patients with PsA about current treatment goals, strategies and opportunities. Such recommendations are undoubtedly useful. In particular, the newly-proposed EULAR algorithm addresses relevant issues related to an indirect ‘comparison’ of drugs, namely efficacy, safety, tolerability, ease of use, costs and long-term experience (14). These considerations should also be taken into account in the new GRAPPA recommendations.

Management recommendations have strengths: they give an updated consensus view on how to manage a disease in terms of treatment choices, in a simple format (usually a table and/or an algorithm/figure). Management recommendations also have limitations, which must be recognised: they may become quickly out-of-date if new studies are published (since the systematic literature review is then obsolete); they rest on the consensus of a limited number of persons thus cannot represent the opinion of all physicians; they may be wittingly or unwittingly influenced by conflicts of interest with pharmaceutical companies; and they represent group-level general outlines which may not apply to a specific, individual patient. However, if the conclusions are based on thorough systematic literature reviews that account for the quality of the individual papers and adhere to stringent criteria, these recommendations remain of value in patient care. It should also be recognised that international recommendations may not be applicable in some countries, through either lack of availability, or lack of reimbursement opportunities for some medications.

In any case, recommendations generally give a range of options, as a single optimal intervention is usually not identified. Physicians must therefore use clinical knowledge and gestalt when applying management recommendations. Finally, the process of developing management recommendations often leads to also developing a research agenda (4, 14). In the field of PsA, the research agenda is extensive, since the evidence base for many recommendations is low. As new data become available, management recommendations will continue to evolve, towards better care and better outcomes for people with PsA.

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