

European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies

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► Additional supplementary data are published online only. To view these files please visit the journal online (<http://ard.bmj.com/content/71/1.toc>).

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ABSTRACT

Background Psoriatic arthritis (PsA) is a clinically heterogeneous disease. Clear consensual treatment guidance focused on the musculoskeletal manifestations of PsA would be advantageous. The authors present European League Against Rheumatism (EULAR) recommendations for the treatment of PsA with systemic or local (non-topical) symptomatic and disease-modifying antirheumatic drugs (DMARD).

Methods The recommendations are based on evidence from systematic literature reviews performed for non-steroidal anti-inflammatory drugs (NSAID), glucocorticoids, synthetic DMARD and biological DMARD. This evidence was discussed, summarised and recommendations were formulated by a task force comprising 35 representatives, and providing levels of evidence, strength of recommendations and levels of agreement.

Results Ten recommendations were developed for treatment from NSAID through synthetic DMARD to biological agents, accounting for articular and extra-articular manifestations of PsA. Five overarching principles and a research agenda were defined.

Conclusion These recommendations are intended to provide rheumatologists, patients and other stakeholders with a consensus on the pharmacological treatment of PsA and strategies to reach optimal outcomes, based on combining evidence and expert opinion. The research agenda informs directions within EULAR and other communities interested in PsA.

The treatment of psoriatic arthritis (PsA) has changed dramatically over recent years, despite the lack of sufficient knowledge on aetiology and detailed pathogenesis. Observations that pro-inflammatory cytokines may play important pathogenetic roles have led to the evaluation of novel therapies; indeed, new synthetic and biological disease-modifying antirheumatic drugs (DMARD) are widely used,^{1–5} with further treatment options anticipated in the near future.^{6–7} While psoriatic skin and joint disease have many facets in common, the pathways leading to their expression may differ, exemplified in the frequent distinct efficacy of various therapies on skin and joint disease

(eg, phototherapy, fumaric acid or alefacept).^{8–12} PsA in itself is heterogeneous by virtue of its broad phenotypes of joint involvement (peripheral and spinal),¹³ but also its spectrum of extra-articular manifestations, which—aside from skin and nails—comprise dactylitis and enthesopathy.^{14–15}

The complexity of PsA and the relative paucity of randomised controlled clinical studies, let alone strategic trials, contrasts with the situation in rheumatoid arthritis (RA), another chronic and destructive inflammatory joint disease. There are data on the usefulness of synthetic DMARD as well as the efficacy of biological DMARD, particularly tumour necrosis factor (TNF) inhibitors^{1–5 16–18} in PsA, and there exist general recommendations for the use of biological agents.¹⁹ Recently, recommendations for PsA treatment were presented by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).^{20–21} These recommendations are comprehensive, with a special focus on skin disease, providing an initial treatment guidance set. However, clinicians can benefit from concise, easy to follow guidance on the optimal use of available therapies and clear treatment strategies for PsA.

Among other aspects, the efficacy of synthetic DMARD and the role of glucocorticoids remain under debate, and combination therapy of synthetic DMARD or synthetic DMARD with biological agents is relatively underresearched.^{17–22} Moreover, even disease activity assessment of PsA is under scrutiny, given that the measures used in clinical trials are mostly ‘borrowed’ from RA²³ with further methods under evaluation. Furthermore, therapeutic targets require definition.^{24–25}

All of these reasons, as well as more recent insights, provided a rationale for the development of European League Against Rheumatism (EULAR) recommendations for the management of PsA. Rheumatologists require evidence-based guidance for the treatment of PsA with regard to synthetic and biological therapies, including the definition of treatment targets and assessment tools.

To address the set task, EULAR convened a group of experts to produce evidence-based recommendations for the management of PsA with non-topical pharmacological therapies on the basis



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of the EULAR standard operating procedures,²⁶ and to develop a research agenda for future activities.

METHODS

The task force aimed at aggregating available information on disease management in PsA into practical recommendations. The basis of its activities were the respective EULAR standardised procedures,²⁶ which suggest the institution of an expert committee in charge of consensus finding, on the basis of evidence provided by a systematic literature review and expert opinion. The taskforce thus followed a similar path as other management recommendations, such as for RA, ankylosing spondylitis and osteoarthritis.^{27–30} One of the aims of EULAR recommendations is to provide clear guidance that is easy to follow in clinical practice.

The expert committee consisted of 28 rheumatologists, two patients, one infectious disease specialist, one dermatologist, one physiotherapist and two rheumatology fellows. The members of this task force came from 14 European countries and from the USA. This inclusive approach aimed at obtaining broad consensus and applicability of the recommendations. The process was both evidenced based and consensus based, as explained in supplementary text 1 (available online only), and included, between January 2010 and December 2010, two expert meetings, systematic literature reviews and extensive discussions. The literature search is published separately.³¹

A vote was obtained from the experts on the level of agreement with the final recommendations. Votes for agreement or disagreement were performed anonymously, by giving a score from 0 (total disagreement) to 10 (total agreement) for each recommendation; the means and SD of scores from the whole group were calculated.

RESULTS

Overarching principles

Before addressing the actual treatment recommendations, the task force established principles deemed sufficiently important to be conveyed to those affected by PsA or involved with the management of PsA. These principles regarding the care of patients with PsA are of such a generic nature that they were felt to be 'overarching'. The complete wording and level of agreement are shown in table 1, and the explanatory text is in supplementary text 2 (available online only). The task force voted unanimously on these five principles.

Recommendations

The process led to 10 recommendations on drug management and treatment strategies, presented in table 1 with levels of evidence and strengths of recommendations. The 10 recommendations are ordered by means of logical sequence or procedural and chronological hierarchy rather than by any major weight of importance. They also serve as the basis for the algorithm provided in figure 1.

NSAID for relief of signs and symptoms

The task force was unanimous in its view that in the vast majority of PsA patients, NSAID should be used as first-line treatment, although the data regarding the usefulness of NSAID in PsA are limited.^{31–33} NSAID have been shown to be efficacious on joint symptoms, although there is no demonstrated efficacy on skin lesions.³¹ Of course, cardiovascular and gastrointestinal risk^{34–36} should be taken into account when prescribing NSAID, which explains the use of the word 'may' in the wording of the recommendation. Furthermore, not everyone with signs and symptoms

requires NSAID treatment, as some patients may respond well to analgesics or may not feel in need of symptomatic therapy. We encourage the lowest dose and the shortest treatment duration possible with NSAID, in view of their potential toxicity. Data suggest that cyclooxygenase 2 inhibitors are as effective as non-selective NSAID in PsA.³² No data were found regarding the possible worsening of skin lesions following NSAID use.

Treatment with synthetic DMARD

To date, there are few data on which to rest for the decision to start a synthetic DMARD. Who should be treated with DMARD? When to treat with DMARD? This should be addressed by future research. Based on the prognostic factors shown in the literature, the group considered that patients with active disease and potential poor prognosis should be started on DMARD. Active disease was defined globally as one or more tender and inflamed joint and/or tender entheses point and/or dactylitic digit and/or inflammatory back pain; however, for the introduction of synthetic DMARD only joint involvement is taken into account. Poor prognosis refers here to the number of actively inflamed joints (defined here as five or more), elevated acute phase reactants, radiographic damage that is progressing, previous use of glucocorticoids, loss of function and diminished quality of life.^{31 37}

Delay in the start of DMARD therapy may lead to worse outcomes, similar to RA,³⁸ although data are scarce in this respect in PsA.^{20 39} Obviously, patients who have active disease despite previous NSAID therapy should receive a synthetic DMARD (this is stated as 'at an early stage' in the recommendation; although the term 'early' was not precisely defined, it is common to regard 'early' as a few weeks to a maximum of 1 year). Regarding the choice of a DMARD, here again there are few data and almost no head-to-head comparisons. Based on the available literature, the experts recommended methotrexate as the first-choice DMARD. This group decision was based in particular on broad therapeutic dose ranges, different application forms (by mouth, subcutaneous) and available data in PsA and in other inflammatory diseases.^{39–42} It is worth noting here that synthetic DMARD do not appear to be efficacious for treating enthesitis and axial disease (more details under recommendations 6 and 7, see table 1).

When treating with methotrexate, careful consideration must be given to the prescription of an efficacious dose. While the most efficacious dose has not been determined for PsA and low doses may not be effective, it is evident in RA that doses in the order of 25 mg per week are more appropriate than lower doses.⁴³ Other drugs to be considered include sulfasalazine, leflunomide and ciclosporin A (although the use of this latter drug is limited by long-term toxicity issues).^{4 22 31 44–46} The order presented here is not a ranking order. Clinical efficacy on joint involvement has also been published for gold salts and azathioprine, although for these drugs the level of evidence was low.³¹ None of the synthetic DMARD have been tested for (eg, ciclosporin, leflunomide) and/or have demonstrated (eg, methotrexate, sulfasalazine, gold salts, azathioprine) structural efficacy in PsA.³¹ Although there is a lack of evidence on the efficacy of synthetic DMARD combinations, these may be considered.^{47 48}

As a result of the potential for increased hepatic toxicity of methotrexate in PsA compared with other rheumatic conditions,^{49 50} transaminase enzymes should be carefully monitored in patients with PsA who receive treatment with methotrexate or leflunomide, especially in cases of alcohol consumption, obesity, type II diabetes and non-alcoholic steatohepatitis or concurrent therapy with other potentially hepatotoxic drugs (eg, statins). In some patients, a liver biopsy has been recommended.⁵¹

Table 1 EULAR recommendations for the management of PsA, with levels of evidence, grade of recommendations and level of agreement

Overarching principles				Level of agreement (mean ± SD)
A.	Psoriatic arthritis is a heterogeneous and potentially severe disease, which may require multidisciplinary treatment.			9.8 ± 0.5
B.	Treatment of psoriatic arthritis patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.			9.8 ± 0.8
C.	Rheumatologists are the specialists who should primarily care for the musculoskeletal manifestations of patients with psoriatic arthritis; in the presence of clinically significant skin involvement a rheumatologist and a dermatologist should collaborate in diagnosis and management.			9.6 ± 0.8
D.	The primary goal of treating patients with psoriatic arthritis is to maximise long-term health-related quality of life, through control of symptoms, prevention of structural damage, normalisation of function and social participation; abrogation of inflammation, targeted at remission, is an important component to achieve these goals.			9.7 ± 0.6
E.	Patients should be regularly monitored and treatment should be adjusted appropriately.			9.7 ± 0.7

Recommendations	Level of evidence	Grade of recommendation	Level of agreement (mean ± SD)
1. In patients with psoriatic arthritis, non-steroidal anti-inflammatory drugs may be used to relieve musculoskeletal signs and symptoms.	1b	A	9.4 ± 0.9
2. In patients with active disease (particularly those with many swollen joints, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extra-articular manifestations), treatment with disease-modifying drugs, such as methotrexate, sulfasalazine, leflunomide, should be considered at an early stage.	*1b, †4	B	9.4 ± 0.7
3. In patients with active psoriatic arthritis and clinically relevant psoriasis, a disease-modifying drug that also improves psoriasis, such as methotrexate, should be preferred.	1b	A	9.1 ± 1.0
4. Local injections of corticosteroids should be considered as adjunctive therapy in psoriatic arthritis; systemic steroids at the lowest effective dose may be used with caution.	‡3b, §4	C	8.9 ± 1.2
5. In patients with active arthritis and an inadequate response to at least one synthetic disease-modifying antirheumatic drug, such as methotrexate, therapy with a tumour necrosis factor inhibitor should be commenced.	1b	B	8.9 ± 1.5
6. In patients with active enthesitis and/or dactylitis and insufficient response to non-steroidal anti-inflammatory drugs or local steroid injections, tumour necrosis factor inhibitors may be considered.	1b	B	8.5 ± 1.5
7. In patients with predominantly axial disease that is active and has insufficient response to non-steroidal anti-inflammatory drugs, tumour necrosis factor inhibitors should be considered.	2b	C	9.3 ± 0.9
8. Tumour necrosis factor inhibitor therapy might exceptionally be considered for a very active patient naive of disease-modifying treatment (particularly those with many swollen joints, structural damage in the presence of inflammation, and/or clinically relevant extra-articular manifestations, especially extensive skin involvement).	4	D	8.6 ± 1.7
9. In patients who fail to respond adequately to one tumour necrosis factor inhibitor, switching to another tumour necrosis factor inhibitor agent should be considered.	2b	B	8.9 ± 1.8
10. When adjusting therapy, factors apart from disease activity, such as comorbidities and safety issues, should be taken into account.	4	D	9.5 ± 1.0

Recommendations with different levels of evidence within the recommendation are listed below.

The level of agreement was computed as a 0 to 10 scale, based on 28 voters within the group.

*In patients with active disease (particularly those with many swollen joints—usually ≥5, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extra-articular manifestations), treatment with disease-modifying drugs, such as methotrexate, sulfasalazine, leflunomide, should be considered; †at an early stage.

‡ Local injections of corticosteroids should be considered as adjunctive therapy in psoriatic arthritis; §systemic steroids at the lowest effective dose may be used with caution.

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; PsA, psoriatic arthritis.

Choice of synthetic DMARD in the presence of clinically relevant psoriasis

Some DMARD have shown efficacy in psoriasis. This is especially the case with methotrexate, but also ciclosporin A, leflunomide and sulfasalazine.^{51 52} In patients with ‘clinically relevant’ psoriasis, defined as psoriasis with impact on quality of life, these data should be taken into account for the choice of DMARD. In trials, the extent of psoriasis is measured through composite indices such as the PASI (Psoriasis Area and Severity Index). However, these recommendations are mainly aimed at rheumatologists, who usually do not measure psoriasis by PASI. The extent of psoriasis (percentage of skin body surface) is an indicator of psoriasis severity; however, there are cases when the extent may not be important, but the consequences on quality of life are important

(eg, face/hand/genital involvement). Therefore, we suggest considering the choice of DMARD in the light of patient-perceived severity of psoriasis (through its impact on quality of life). This would correspond in dermatological terms to moderate to severe psoriasis. Better understanding the patients’ perspective in PsA was set on the research agenda.

Local and systemic glucocorticoids

Glucocorticoid injections may be a useful adjunctive therapy in localised disease (oligoarticular forms, enthesitis or dactylitis).⁵³ Intra-articular steroids are efficacious for mono/oligoarthritis or single joint flares, in otherwise well-controlled polyarthritides. Glucocorticoid injections may also be performed in dactylitis (tendon sheath/peritendinous injections) and in enthesal

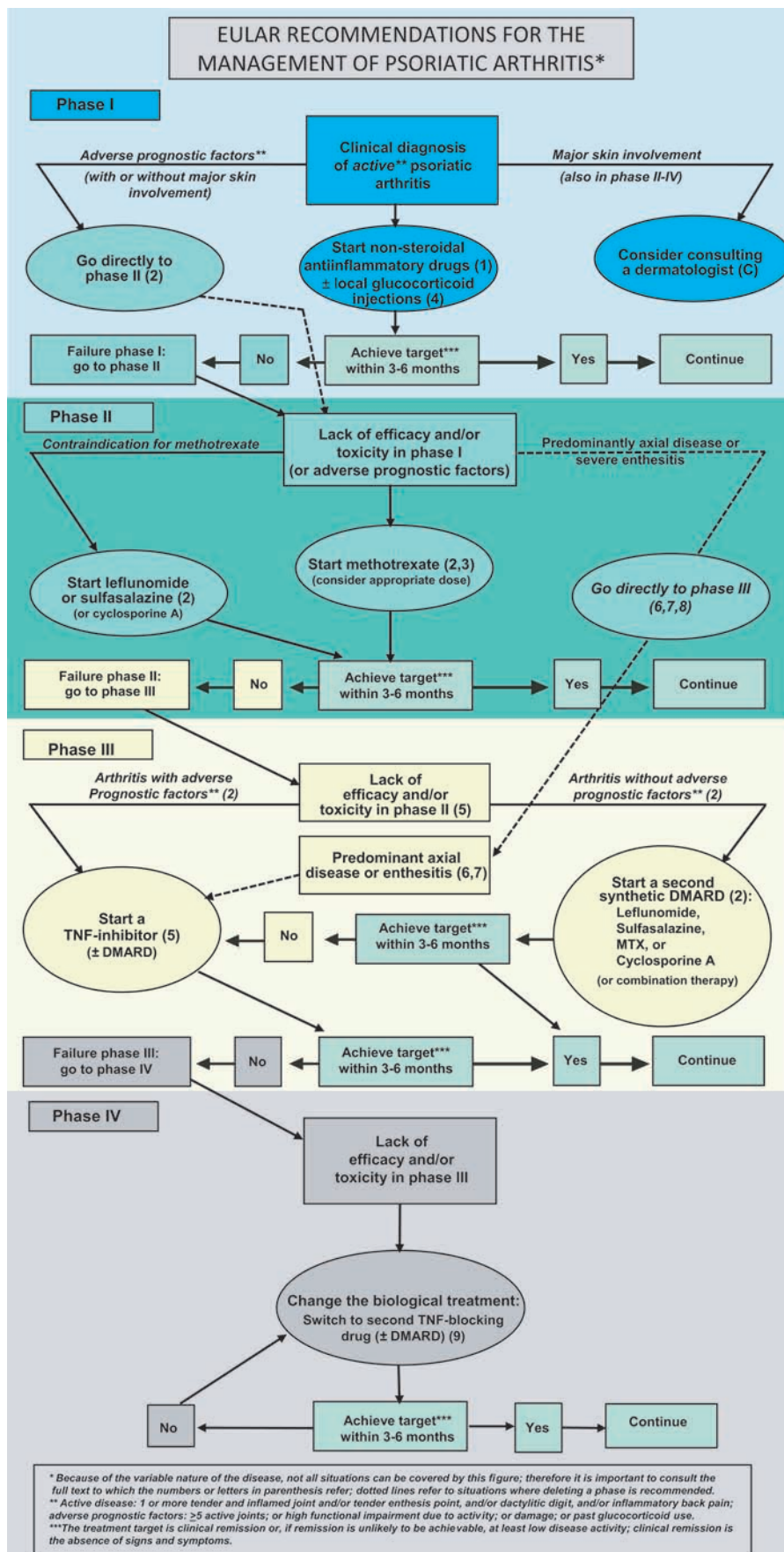


Figure 1 Management of psoriatic arthritis according to the European League Against Rheumatism recommendations. Recommendations have been divided into four phases. Numbers in parentheses indicate the respective items of the recommendation as shown in table 1. Small fonts within the ellipses in phases II and III refer to dose modifications or an alternative therapy, as detailed within the body of the recommendations.

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areas, for example, elbow, or retrocalcaneal bursa in Achilles enthesitis.²⁰

Systemic steroids in psoriasis are feared, as it has been reported that skin flares may occur.⁵⁴ However, the literature search performed to inform the present recommendations found few data (other than case reports) supporting the assertion that skin psoriasis may flare in glucocorticoid-treated PsA patients.³¹ Furthermore, registry data reveal that systemic steroids are, in fact, widely used in PsA (up to 30% of patients in the German national database), usually at low doses (≤ 7.5 mg/day),⁵⁵ although there is no evidence from clinical trials on the efficacy of systemic glucocorticoids in PsA (level of evidence 4; table 1). Nevertheless, the task force considered that systemic glucocorticoids are a therapeutic option, although they should be used with caution, keeping in mind the possibility of a skin flare. Greater caution should perhaps be used in patients with severe/extensive skin involvement, and/or not taking concomitant DMARD (expert opinion). This stems partly from the observation that PASI scores in PsA trials are generally much lower than in clinical trials of psoriasis.

In PsA as in other chronic diseases, the long-term use of glucocorticoids can lead to major adverse events;⁵⁶ therefore, thought should be given to tapering glucocorticoids when feasible. When tapering, attention should be paid to the potential worsening of skin disease (rebound). The safety of glucocorticoids is also an important aspect of the EULAR recommendations on the management of glucocorticoid therapy.⁵⁷

TNF inhibitors

This recommendation deals with patients for whom a synthetic DMARD (usually methotrexate because of its effects on joints and skin, but also leflunomide, sulfasalazine or others, see above) is not efficacious or not well tolerated. A patient should be considered a treatment failure when in spite of therapy for a length of time appropriate to the drug profile (usually 3–6 months), the patient fails to demonstrate achievement of the treatment target low disease activity. Treatment failure could not be defined more precisely given the lack of appropriate trials. In these patients TNF inhibitor treatment (with or without continuation of previous synthetic DMARD therapy) can be considered if the disease is active, ie, if there is evidence of active arthritis in terms of swollen joints and/or at least moderate disease activity by a composite disease activity measure and/or active disease with impaired function or quality of life. However, the definition of (residual) active disease is still pending in PsA, and is part of the research agenda.

This item refers to the use of biological agents. TNF inhibitors (adalimumab, etanercept, golimumab and infliximab) have demonstrated efficacy in PsA, both for skin and joint involvement, as well as in preventing radiographic damage.^{2 5 6 16 31} There were no evident differences regarding the efficacy of the different TNF inhibitors on the joints, although no head-to-head comparisons exist.⁵⁸ However, for skin involvement, it seems that the efficacy of the TNF receptor construct etanercept on psoriasis may be lower, or at least be of slower onset, than for the antibodies targeting TNF (although there are, again, no head-to-head comparisons available).² Also, ustekinumab was tested against etanercept in patients with psoriasis and demonstrated superior skin outcomes after 12 weeks.⁵⁹ This information may be taken into consideration for the choice of TNF inhibitors in patients with clinically significant skin involvement.

Other biological agents have been assessed in PsA but there were too few data (ustekinumab, rituximab, abatacept, tocilizumab) and/or too low response rates (alefacept) to consider these

drugs in this recommendation.³¹ The list of biological agents must of course be updated regularly, as new data are published.

To date, there are no data showing the superiority of TNF inhibitors in combination with synthetic DMARD versus TNF inhibitor monotherapy.^{3 5 31} Of note, in all trials of TNF inhibitors in PsA, methotrexate was allowed but not required, and approximately half the patients in these studies took TNF inhibitor monotherapy without concomitant methotrexate. The data for patients receiving and not receiving methotrexate were comparable.⁶⁰ This was added to the research agenda. TNF inhibitors also improve enthesitis and axial disease (see also recommendations 6 and 7).

Regarding the safety of biological agents in PsA, there are significantly fewer data available than in RA.^{31 61–63} Indeed, there are few data available regarding even the background risk of infectious disease morbidity in PsA/psoriasis. Given the paucity of safety data on biological agents in PsA, one option is to extrapolate from either the RA or psoriasis experience with these therapies. In RA, there is now a wealth of safety data from randomised controlled trials and, most importantly, from large observational studies (registry data). In comparison, however, there is a lack of long-term safety data on TNF inhibitors in the psoriasis setting. Data to date suggest that the biological agents are likely to have a similar risk profile in PsA and psoriasis with regard to serious adverse events (eg, elevated infectious risk), but that the absolute risks of infection and malignancy (and perhaps other serious adverse events) are probably lower than in RA, due to underlying pathophysiological differences between RA and psoriasis. Long-term registry or other observational data will be important to establish the safety profile of these drugs in PsA or psoriasis. However, to date, the literature review did not find any apparent specific safety signals of concern in PsA, compared with RA. As stated in this recommendation, in patients with active arthritis, TNF inhibitors should be ‘considered’; of course, we recommend careful assessment of potential contraindications to TNF inhibitors and careful weighing of the benefit/risk/cost ratio before any treatment decision is made (please see also recommendation 10, see table 1).

Enthesitis and/or dactylitis and TNF inhibitors

This recommendation deals with the subgroup of patients with predominant enthesitis/dactylitis. In these patients, TNF inhibitors might be considered even if no synthetic DMARD have been tried, after failure of local or non-specific anti-inflammatory therapy, because DMARD have not been proved efficacious, even though they have been little studied.³¹ There are very few data regarding this subgroup of patients, but the efficacy of TNF inhibitors on these manifestations of PsA has been reported in several trials, generally as secondary endpoints.³¹ The diagnosis of enthesitis can be challenging; several instruments have been proposed for the assessment of enthesitis.¹⁴ There is no data-driven definition of ‘active’ disease in this case; we suggest to focus on quality of life in this regard. Therefore, physicians must apply clinical judgement when faced with dactylitis/enthesitis, aiming at the improvement of physical disability and quality of life, which can be severely impaired in some situations, such as enthesitis of the Achilles tendon. The group is of course not suggesting that all such patients should be treated with TNF inhibitors, as this would lead to the inappropriate use of TNF inhibitors in some situations. This recommendation, and recommendation 8, received the lowest agreement within the group (see table 1).

Axial disease and TNF inhibitors

Recommendation 7 deals with the subgroup of patients who have predominant axial disease. In these patients, TNF inhibitors

Table 2 Research agenda for PsA

Theme	Research questions
Diagnosis	Defining screening strategies for PsA among psoriasis patients: is screening needed and if so, how and when? Diagnosing PsA versus RA with concomitant psoriasis
Prognosis	Defining prognostic factors related to the risk of progressive disease, structural damage and bad functional outcome in early (and established) PsA Predicting response to treatment (predicting response to NSAID, to DMARD, to biological agents) Assessment of spinal disease: defining the similarities and differences with ankylosing spondylitis Defining disease severity
Pathophysiology	Defining the relationship between inflammation and structural damage in PsA Exploring juvenile PsA: is it different from adult-onset PsA? Identification of new therapeutic targets
Biomarkers	Determining biomarkers related to damage, prognosis and treatment response
Treatment strategy	Defining and evaluating the utility of tight control strategies in PsA Assessing efficacy and safety of combinations of DMARD and of DMARD with biological agents Evaluating the need for early treatment in PsA: who should be treated with DMARD? When to treat with DMARD?
Outcomes	Patient-reported outcomes in PsA (which ones are important?), composite patient-reported scores in PsA, fatigue in PsA Defining treatment targets Defining (residual) active disease Defining remission and predictors of remission
Synthetic DMARD	Need for more RCT with DMARD (eg, methotrexate) to obtain more data on efficacy and toxicity Assessing efficacy and safety of combination therapy of synthetic DMARD Need for DMARD studies in MRI-positive early axial PsA
Biological agents	Efficacy of combining DMARD with biological agents, compared with biological monotherapy and DMARD monotherapy Defining the best indication for biological agents, when to start? Defining the optimal duration of biological therapy, including addressing biological agent discontinuation (need for respective controlled trials) Assessing the possibility of maintenance therapy with lower doses of biological agents Assessing the efficacy and toxicity of new biological agents (including more data on ustekinumab, tocilizumab, abatacept, rituximab) Through registry-based studies, assessing the safety of biological agents in PsA
Systemic glucocorticoids	Assessing the risk of skin flares related to systemic glucocorticoids and in particular at low doses Assessing the benefit/risk ratio of long term glucocorticoid therapy Assessing the efficacy and toxicity of intramuscular glucocorticoids in PsA
Other systemic treatments	Assessing the efficacy of miscellaneous drugs, for example, oral vitamin D ^{73 74}
Local treatments	Radiation synovectomy: evaluating its efficacy in monoarthritis of the knee
Comorbidities	Understanding the risk of cardiovascular disease in PsA and the modification of such risk according to disease activity and therapy Assessing the risk and consequences of metabolic syndrome in PsA Addressing tolerated consumption of alcohol in PsA in particular when treating by methotrexate
Imaging	Defining the optimal use of radiographic scores Evaluating the usefulness of MRI and ultrasonography, as well as developing scoring techniques for these imaging modalities

DMARD, disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomised controlled trial.

can be considered even if no synthetic DMARD have been tried. This was extrapolated from data in ankylosing spondylitis,²⁷ which also included patients with psoriasis. In PsA, the efficacy of TNF inhibitors on axial disease has been reported only in observational studies.⁶⁴ Active disease, here, refers to Bath ankylosing spondylitis disease activity index (BASDAI) levels equal to or above 4.^{65 66} The group suggests following established recommendations for ankylosing spondylitis.^{65 66}

TNF inhibitors exceptionally for a very active patient naive of disease-modifying treatment

In certain, very rare and thus highly selected patients, there may be a place for TNF inhibitors as first-line treatment. This recommendation is mere expert opinion because there are no data in this regard. In TNF inhibitor trials, some patients were in fact DMARD-naive but the results regarding efficacy and safety have never been presented separately for these patients.

Some criteria to help select the patients who may need TNF inhibitors early were discussed, such as contraindications to synthetic DMARD or poor prognostic factors in conjunction with severe skin disease or severe extra-articular manifestations with a professional need for very rapid improvement. This item received the second lowest agreement and warrants further research.

Switching to another TNF inhibitor agent

This recommendation is derived from some studies indicating a good efficacy of a second TNF inhibitor in PsA.^{67 68} The recommendation is also extrapolated from the data available regarding switches in RA.⁶⁹ To date, the group could not identify randomised trials in which switching was appropriately compared between different TNF inhibitors, and therefore a preference for a particular TNF inhibitor in this situation cannot be established.

Accounting for comorbidities and safety issues

Treatment of patients with PsA should be tailored according to the current manifestations of the disease (such as peripheral joint, skin, axial, enthesal symptoms or dactylitis), the level of current symptoms, clinical findings and prognostic indicators; but also according to the general clinical status (age, gender, comorbidity, concomitant medications, psychosocial factors). For each treatment, a careful choice must be made, taking into account efficacy, safety and cost issues.

The recommendations reflect the balance of efficacy and safety and do not deal in detail with the toxicity of DMARD and biological agents. In this regard, the most important pieces of information are provided in the separate publication on the systematic literature reviews,³¹ which indeed are part and parcel of these recommendations, because they provide their bases. Therefore, the recommendations shown here primarily deal with agents whose toxicity appears to be manageable, assuming that users are either aware of the respective risks or will adhere to the information provided in the package inserts. When deemed of particular importance, safety issues were especially mentioned (liver toxicity on methotrexate, infections with biological agents), but clearly safety has not been comprehensively addressed.

Some comorbidities require further exploration and were put on the research agenda; these include the cardiovascular risk in PsA, which has been little studied: cardiovascular diseases and their risk factors appear more common in patients with PsA than in controls.⁷⁰⁻⁷² The contribution of alcohol consumption, type II diabetes, obesity and steatohepatitis to hepatotoxicity in PsA is also a relevant question, particularly

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in the light of the high prevalence of methotrexate use in this disease.⁵⁰

Graphic representation of the recommendations

The recommendations and the algorithm they imply are summarised in figure 1.

The figure attempts to capture the most important aspects of the recommendations and explanatory text. While it does not account for all therapeutic eventualities nor ought to be representative for all variations of the disease, the relatively high level of agreement obtained within the group (see supplementary text 3, available online only) suggests that it has validity for a large majority of patients with PsA.

Research agenda

One of the objectives of this initiative was to develop a research agenda, to guide future research funding by EULAR. An extensive research agenda was developed and the summary is presented in table 2.

DISCUSSION

The task force has formulated 10 statements on the management of PsA. These statements were based on systematic literature reviews, but also on expert opinion with subsequent consensus finding on the wording of the recommendations. By this process and by stating the respective levels of evidence and strength of recommendation for each item, the committee adhered to the EULAR standardised operating procedures for the development of recommendations. Moreover, when evidence was lacking and the task force had to use only expert opinion, a research agenda was formulated to expedite the generation of evidence in the future.

The reasoning behind each statement and, particularly, behind the recommendations' specific wordings is explained in detail in the Results section. Importantly, the overall agreement with these statements, assessed anonymously several weeks after their formulation, was very high.

It is worth noting that the task force felt the best evidence for efficacy was available for three synthetic DMARD (methotrexate, leflunomide and sulfasalazine; statement 2) and four TNF inhibitors (adalimumab, etanercept, golimumab, infliximab; statements 5–7). Some additional synthetic DMARD agents are mentioned in the text only, because although effective in RA, their efficacy appeared to be lower or toxicity higher than that of other agents in their general class, and the data were often sparse.

The task force was convinced that modern therapy of PsA should be target oriented and governed by a strategic treatment approach. Remission or at least low disease activity, if remission cannot be attained, was affirmed as the therapeutic goal, in line with recommendations in RA.³⁰ However, the literature review found few data regarding the natural history, prognosis, treatment targets and treatment strategies in PsA,³¹ contrary to the situation in RA. Still, there are some data supporting low disease activity or minimal disease activity as a therapeutic goal.^{75–79} Furthermore, monotherapy with all TNF inhibitors usually leads to complete cessation of erosion progression at the group level; these agents appear to induce an arrest in disease progression.³¹ Finally, treatment targets constitute yet another part of the research agenda.

Glucocorticoids had a special place in the discussion (statement 4). Although there is a fear of psoriasis flares related to systemic glucocorticoids in PsA (and especially their cessation),

we did not find supportive data in this regard, and the experience of rheumatologists and dermatologists may be different, possibly related to different forms of PsA (with low to moderate skin involvement on the one hand vs important or severe skin involvement on the other). Indeed, the experts in the group did not report their patients having experienced skin flares; and registry data show us that systemic glucocorticoids are in fact widely used at low doses in PsA.⁵⁵

The present EULAR recommendations have been developed by experts (mainly rheumatologists, a dermatologist, an infectious disease specialist, a health professional and two patient representatives) from 14 European countries and the USA. It is therefore a true international document, meant to serve physicians in Europe and the world, although we are aware of the fact that not all agents mentioned here are available or accessible everywhere.

Beyond physicians, the document is also aimed at patients with PsA so they are informed on current treatment goals, strategies and opportunities. Importantly, patient representatives also participated in the task force. Finally, this document is also meant to inform officials in governments, social security agencies and reimbursement agencies.

The recommendations on the management of PsA provided here by the EULAR task force, when compared with those provided by GRAPPA,²⁰ are of lesser complexity and thus more easy to adhere to; moreover, they cover additional aspects of drug therapies as well as therapeutic strategies and goals. A graphic representation (see figure 1) captures most of the important items.

The limitations of the present recommendations include that juvenile PsA and patients with psoriasis and some joint pain but without a definitive diagnosis of PsA are outside their scope; that topical treatments including topical NSAID and topical steroids are not taken into account and that non-pharmacological therapy is not considered. However, the group did state that non-pharmacological therapy was an important component of PsA treatment.

These recommendations reflect the current state of evidence and thought in the area of PsA management. The five overarching principles and 10 practical recommendations have a high level of face validity and feasibility, and the development of a scientific agenda will guide future research. However, several of the recommendations are strongly based on expert opinion, which in turn is based on clinical practice that has emerged in certain institutions, rather than available evidence. This is due to the paucity of data in the field of PsA. Therefore, the research agenda developed is extensive.

Finally, as has been the case over the past decade, it is to be anticipated that new data on existing or new drugs or therapeutic strategies will emerge over the next few years. Therefore, we will carefully observe the developments in the field and assume that an amendment of these recommendations may be needed in 2–5 years.

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Online supplement – Supplementary Table 1. Categorization of levels of evidence and grades of recommendation [1]

1a	SLR of randomised controlled trials	A: directly derived from level 1 evidence
1b	At least one randomised controlled trial	
2a	At least one controlled study without randomisation	B: derived from 2 or extrapolated from 1
2b	At least one quasi-experimental study	
3	Descriptive studies (comparative, correlation, case-control)	C: derived from 3 or extrapolated from 1 or 2
4	Expert opinion	D: derived from 4 or extrapolated from 1, 2 or 3

Online supplementary text 1- Methods

At the first meeting in January 2010, the expert committee (as defined in the article) prioritised the research questions and defined the appropriate search terms.

With respect to drug therapy, several important questions were addressed through an evidence-based approach, such as: (1) How do the various synthetic DMARDs compare? (2) Which agents improve musculoskeletal symptoms, skin disease, or both? (3) Is combination therapy of additional benefit? (4) Is there a role for switching between biologicals? (5) Are there particular safety aspects or signals of note? (6) Are glucocorticoids beneficial or do they put patients at risk of exacerbation of the skin disease? (7) What are the specific goals of therapy? (8) How should treatment effects be assessed? (9) What research is necessary to fill in current gaps in knowledge regarding PsA therapy?

Subsequently, the 2 fellows (CGV and ZA), with the help of their mentors (HMO, DVDH, LG, OF), performed the respective systematic literature reviews, divided into 2 areas: (a) synthetic DMARDs and non-steroidal anti-inflammatory drugs

(NSAIDs) (CGV); (b) biologic DMARDs and glucocorticoids (intraarticular and systemic) (ZA). Both fellows also addressed the following aspects: combination therapy, therapeutic strategies, effects on extraarticular disease, prognosis and natural history. The literature search was performed in PubMed Medline, Embase and the Cochrane library and also recent congress abstracts, up to January 2010. All meta-analyses, systematic reviews, randomized controlled trials, non-randomised controlled trials and observational studies including data from registries were analysed. If possible, outcome was quantified using effect sizes which are unit-less and therefore allow for the analysis of efficacy irrespective of the measures evaluated in individual clinical trials. The literature review is published separately (please see reference 31 of the article).

Categorizations of evidence and strength of recommendation were determined (Supplementary Table 1).

At the second task force meeting in May 2010, the fellows presented the results of the systematic literature review in an aggregated form. The taskforce was divided into 2 subgroups, which debated and evaluated the evidence presented, and formulated preliminary sets of recommendations. These proposals were reported to the entire committee which discussed the suggestions on the recommendations in detail, amended them as deemed appropriate in the course of the consensus finding and took the final decisions. An ultimate round of refinement of the wording was done via electronic communication, as well as the voting (please see article text).

Subsequently, the explanations of the bullet point were formulated and underwent review by the panel. The final decisions on the detailed manuscript and the graphic representation of the recommendations were made between December 2010 and January 2011.

The recommendations are targeted at the following groups of stakeholders: (a) firstly, physicians; the recommendations are mainly aimed at rheumatologists, but also other physicians dealing with patients with PsA (irrespective of clinical expression), including general practitioners and other specialists. (b) Patients with PsA can use these recommendations for information on current treatment goals, strategies and opportunities. (c) Other stakeholders include officials in governments, social security agencies and reimbursement agencies.

Online supplementary text 2- overarching principles

A. Nature of psoriatic arthritis

Because of the heterogeneity inherent in PsA [2], appropriate assessment of a PsA patient requires a comprehensive approach to all facets of the disease, including not only peripheral arthritis, but also involvement of the skin and nails, spine, and entheses. The diagnosis of PsA in its earliest stage can be extremely challenging [3]. Several criteria developed for classification of PsA are available [4-7]; the CASPAR (Classification Criteria for PsA) criteria [5] work well for both early and late disease and are also frequently used for diagnostic purposes.

B. General treatment principle

Two themes govern the contents of this principle, firstly the term “best care” which the task force felt to be conveyed by the subsequent recommendations, and secondly the phrase “shared decision” with the patient, which refers to the necessity to discuss treatment aims, management plans and reasons for the recommended approaches with the patient. Sharing the decisions within the health care team, including the dermatologist, is also useful.

The optimal management of patients with PsA requires a combination of non-pharmacological and pharmacological treatment modalities; non-pharmacological therapies are important but are not the focus of these recommendations.

C. Rheumatologists as the main specialists and involvement of a dermatologist

This statement stems from indirect evidence that in RA, patients followed by rheumatologists, in comparison with other physicians, are diagnosed earlier, receive DMARD therapy more frequently and have better outcomes [8, 9]. With the advent of modern therapies and strategies, good knowledge of treatment indications and contra-indications as well as recognition and management of adverse events is increasingly important. Therefore, patients with suspected PsA should be referred to a rheumatologist as early as possible. However, the task force intentionally added the

term “primarily” to this statement, since the management of PsA patients should be shared with primary care physicians and other health professionals in a multidisciplinary approach. Multidisciplinary treatment may be useful in all cases, but particularly in patients with severe PsA. Collaboration between rheumatologists, dermatologists and general practitioners may be essential; and occupational therapy, physical therapy, psychological counseling, intervention of a nurse practitioner and cooperation with an orthopedic surgeon may be helpful for some patients. Also, in countries lacking sufficient numbers of rheumatologists, this task may have to be taken over by other physicians with experience in caring for patients with PsA. Furthermore, this statement is related to the musculoskeletal manifestations of PsA; the group felt that significant skin/nail involvement should lead to collaboration with a dermatologist. Indeed, extensive skin disease with little to no joint involvement would be cared for primarily by dermatologists. However, patients with no joint involvement are not the focus of the present recommendations.

D. Objectives of treatment

In RA, attaining a state of remission or low disease activity leads to better structural and functional outcomes than allowing residual disease activity [10, 11]. Thus, remission is the primary therapeutic aim especially in RA [12] and a new definition of remission has been recently elaborated by the American College of Rheumatology and EULAR [13]. In PsA, there exist only few data regarding natural history and even less regarding remission or treatment objectives [14-18]. Since also in PsA inflammation is related to long-term outcomes for joint involvement [19-24], by analogy with RA, this overarching principle states that the abrogation of inflammation is a component of the therapeutic goal, and that remission is in itself an objective. However, the group felt that in the absence of remission, a low or minimal disease activity state [25, 26] is an alternative target, especially for long-standing disease. Nevertheless, the detailed definition of remission in PsA, its predictors and its relationship with long-term outcomes are still a part of the research agenda and more thorough assessment of prognostic markers of severity (related to risk of progressive disease, structural damage and bad functional outcome) must be addressed (Table 2). Prognostic elements may include extent and severity of joint involvement,

dactylitis, baseline structural damage, and baseline inflammatory indices [19-24, 27-29].

This statement also comprises other important aspects, namely aiming at improvement of long-term outcome of PsA by maximising physical functioning and quality of life as well as prevention of structural damage or its progression.

E. Monitoring and treatment adjustment

This is a general statement related to monitoring. Because of the lack of data regarding the best interval for patient monitoring, the statement only concerns 'regular monitoring'. The interval between two consecutive visits may depend on the disease activity, and on the current treatment taken by the patient (e.g., synthetic DMARDs or biologicals). The group recommends the treatment target should preferably be reached within about 4 months after a treatment change [30]. Similarly, treatment should be adjusted 'appropriately': due to the paucity of data, the group did not feel that more detailed recommendations could be formulated at this point, but more data regarding monitoring and treatment strategies (e.g., tight control [31]) are needed.

In clinical trials, widely used outcomes to monitor patients with PsA include joint counts, skin assessment usually by Physician Global Assessment or Psoriasis Area Severity Index (PASI), Dermatology Quality of Life Index (DLQI) and nail assessment by Nail Psoriasis Severity Index (NAPSI) [32] or modified NAPSI (mNAPSI), pain (by visual analog scale) and the Health Assessment Questionnaire (HAQ) [33], specific measures for dactylitis, enthesitis, or axial involvement as well as health-related quality of life. The mainstay for disease activity assessment are composite measures such as American College of Rheumatology response rates [34], PsA Response Criteria (PsARC) [35] and the Disease Activity Score (DAS28) defined for RA [36-38]; further, the Simplified Disease Activity Index and the Clinical Disease Activity Index (SDAI, CDAI), DAREA (Disease Activity index for REactive Arthritis)/DAPSA (Disease Activity index for PSoriatic Arthritis) and the Composite Psoriatic Disease Activity Index (CPDAI) have been recently validated in PsA [39-41].

An OMERACT (Outcome Measures in Rheumatology) consensus recommended assessing peripheral joints, pain, patient global assessment, physical function, quality

of life, fatigue, and acute phase reactants [42]. Fatigue was considered as a measure that still needs more research activities. The current recommendation from this group, in line with RA recommendations and in light of their validity and sensitivity to change, is to use one of the available validated composite scores to assess PsA activity. However, more studies are needed to fully address this issue and define the most pertinent assessment tools.

Online supplementary text 3 – elaboration of the figure

This graphic representation was originally requested by some of the task force members and its depiction elicited a thorough debate. It was felt by some that no such figure should be produced, because a single Figure might not be representative of this complex disease or might not sufficiently capture the diversity of therapeutic approaches. Others, though, indicated that having a figure may facilitate understanding the complexity of PsA and its treatment approaches and the conveyance of the recommendations to various stakeholders. In the course of these discussions, the figure underwent several rounds of amendments and subsequently a vote for agreement. Scores of 1 and 2 were each given once, scores of 6, 7, 8, 9 and 10 given 1, 6, 5, 9 and 8 times, respectively, arriving at a mean level of agreement of 7.9. Thus it appeared that apart from two members of the task force who generally objected to the principle of a figure and thus voted disagreement, the other members were in high agreement.

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