Title Page

Current treatments and recommendations

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Abstract

The aims of treatment in psoriatic arthritis (PsA) are to control inflammation, normalise function and impact on patients and prevent complications of disease and its treatment. Over the past decade treatment options for PsA have expanded with the availability of many more novel therapeutic agents. However, the treatment decisions and pathways for the use of these drugs are not always straightforward. There is a need to tailor the choice of medication to the individual patient, taking into account the type of their disease and consideration of other factors such as their co-morbidities. A treat to target approach is recommended with the aim to get the patient into a state of remission or low disease activity (whichever target is chosen). Both European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) have recently published updated guidance in 2018-2019. In this section, we will summarize the evidence for therapies in PsA and review the similarities and differences in these two sets of recommendations.

Key words

Psoriatic arthritis, therapy, treatment guidelines, pharmacological management, non-pharmacological management

Main Text

Introduction

Psoriatic arthritis (PsA), a chronic systemic inflammatory condition, most commonly manifests with peripheral arthritis, spondylitis, dactylitis, enthesitis and psoriasis (skin and nail). Other non-musculoskeletal manifestations include inflammatory bowel disease and uveitis. This condition is also associated with cardiovascular, psychological and metabolic co-morbidities and can pose a significant impact on a patient's ability to function and also their quality of life [1–6].

The management of patients with PsA includes both non-pharmacological and pharmacological interventions. Over the past 10 years the availability of therapeutic agents for PsA have expanded to not only include conventional synthetic DMARDs (csDMARDs), such as methotrexate, but also other targeted biological agents (bDMARDs) aimed at different cytokines, such as TNF, interleukin (IL)-12/23 and IL-17A as well as targeted synthetic DMARDs (tsDMARDs) that inhibit phosphodiesterase-4 (PDE4) or Janus kinases (JAKs) [7–12]. However, the treatment pathways for the use of these drugs are not always straightforward and discrepancies exist in the proposed order of the use of these drugs between published guidelines.

In this report, we review and compare the pharmacological and non-pharmacological treatment recommendations developed by the European League Against Rheumatism (EULAR), a regional organisation, published in 2020 and the American College of Rheumatology (ACR), a national organisation, published in 2018 [13,14]. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), an international organisation, are currently updating their guidelines due to be published in early 2021. In this review, we reference the 2015 GRAPPA recommendations.

Treatment principles

The EULAR guidelines include a detailed table about their overarching principles and assess how this compares to their 2015 version [13]. ACR do not explicitly outline their treatment principles; they are embedded within their treatment recommendations [14]. Nevertheless, the treatment principles of both the EULAR and ACR guidelines are similar and include improving quality of life and function, preventing structural damage and complications, involving the multidisciplinary team in the presence of non-musculoskeletal manifestations, shared decision making between the patient and the rheumatologist, taking into account efficacy, safety and costs and also the importance of identifying and considering other co-morbidities in treatment decisions.

Patient education

Patient education covers a variety of educational activities including therapeutic and health education as well as promoting health [15]. The goal of treatment is to enable patients to manage their life with a chronic condition as well as provide information on disease control and treatments [15]. In patients with rheumatoid arthritis, there is evidence to suggest the beneficial effects of patient education on outcomes such as improved self-management skills, increased self-efficacy and global well-being [16–18]. While not specific to PsA, these studies do highlight the benefits of targeted patient education programmes in patients with chronic inflammatory arthritis. Importantly, due to the differences between RA and PsA, there is a need to develop and appraise targeted

educational interventions specific to PsA and optimum timing for intervention. A recent study investigating educational needs in patients with PsA found that patients with shorter disease duration had a higher educational needs regarding “Managing pain”, “Movement”, “Disease process” and “Self-help measures” suggesting that educational support may be best placed in individuals soon after PsA diagnosis [19].

Non-pharmacological management

Despite the multitude of pharmacological treatment modalities in managing PsA, many patients often continue to experience some level of persistent disease activity with the risk of developing resultant disability. Patients also often report significant problems of physical, emotional and social functioning in established PsA. A comprehensive patient-centred management plan for PsA which is not limited solely to pharmacological approaches and includes patient education; dietary and lifestyle advice including weight loss and smoking cessation; use of rest, exercise, physical and occupational therapy; counselling and pain management is the optimum for providing a range of solutions for patients’ wider and often unmet needs. The key goals in the management of PsA are to control pain and disease activity, prevent any further joint damage, and enhance quality of life and functioning. The various approaches and their relevant evidence in support of these treatment aims will now be explored in further detail.

Non-pharmacological treatment approaches in PsA are not specifically addressed in either the EULAR or GRAPPA guidelines. The ACR/NPF guidelines do however provide support for non-pharmacological treatments in PsA and these will be addressed throughout the following sections [14]. EULAR have published updated cardiovascular disease recommendation and recommendations for physical activity in patients with inflammatory arthritis, both of which apply to PsA [20,21].

Pain Management

PsA carries with it a significant burden of pain. Pain is often the predominant symptom a patient experiences, even after disease control using the various pharmacological approaches available. An analysis of the pain burden in patients with various IA found that patients with PsA had as high or higher self-reported pain levels than those with RA [22]. Pain is a multifaceted and complex experience which can be triggered by pathological processes such as tissue damage and inflammation and can be further propagate by individual factors such as mood, obesity, sleep disturbance, illness beliefs and age [23].

A systematic review conducted by a EULAR multidisciplinary task force on pain management in IA recommended a set of core principles for the clinician approach to managing pain [24]. The task force recommend clinicians follow a patient-centred framework aligned with a biopsychosocial model and specifically to be able to differentiate localised from generalised, non-specific pain [24]. Pain localised to individual joints or body regions is often indicative of a peripheral nociceptive input, such as inflammation or tissue damage. Localised sites of pain are typically more responsive to the pharmacological approaches aimed at controlling levels of inflammation, as outlined previously. Pain is normally considered generalised when it is found to be present bilaterally, above and below the waist and at axial sites. Generalised pain often persists despite tight control of inflammation and requires more comprehensive pain management strategies which incorporate rest and exercise, weight loss and psychosocial support tailored to the individual. The task force also found a lack of

evidence related to pain management approaches specific to PsA and recommend that health professionals use treatment options utilised in RA [24].

Rest, exercise, and physical and occupational therapy

Physical activity (PA) and targeted exercises are important components of the nonpharmacological therapy in PsA. EULAR recommends physical activity as an integral part of standard care in patients with IA. This guideline fails to address PsA or any specific exercise modality [21]. The 2018 ACR/NPF guidelines for treatment of PsA conditionally recommend low impact over high impact exercise.

In the general population, physical activity is known to reduce the risk of cardiovascular disease, obesity, type 2 diabetes and osteoporosis [25,26]. These conditions are all independently associated with increased morbidity and mortality in patients with PsA, either due to the underlying pathogenesis of PsA or the treatments administered [27–29]. In patients with RA and axial spondylarthritis (axial SpA), exercise has been demonstrated to reduce disease activity and improve cardiovascular function [30–32]. The potential mechanisms underlying the beneficial impacts of exercise are multifactorial but likely incorporate some positive impact on circulating inflammatory levels and reduced joint loads from weight loss [33,34].

Two RCTs have examined the impact of exercise regimens on functioning and disease activity in PsA [35,36]. These interventions looked at different exercise modalities; from a resistance training programme to a high-intensity interval training (HIIT) approach. PsA patients randomised to receive a 12-week resistance training programme against controls receiving standard care demonstrated a significantly improved functional capacity, as measured by HAQ-S, and reduced disease activity, measured using the BASDAI [35]. There was found to be no significant difference in disease activity between the intervention and control group for the HIIT programme, however, patients in the intervention group reported less fatigue at 12 weeks [36]. Limitations of these studies include their relatively small sample sizes and the use of non-specific disease activity measures for quantifying post-intervention effects. Further trials looking at larger samples and using targeted PsA-specific disease activity measures such as the minimal disease activity (MDA) criteria or the PsA Disease Activity Score (PASDAS) are warranted [37,38]. The ACR/NPF guidelines have been developed against this backdrop of relatively low quality evidence for exercise in PsA, however, the recommendation for low impact exercise is on the balance low risk [14].

Diet and Nutrition

Dietary interventions aimed at reducing weight and particularly central adiposity have the added benefit of not only reducing mechanical strain on a patient's joints but also reducing cardiovascular disease risk. Patients with PsA have an increased risk of lifetime cardiovascular events against the matched population and any dietary strategy aimed at reducing cardiovascular risk is of benefit in this patient group. Weight loss has been shown to improve disease activity in patients with PsA, both with and without co-occurent obesity [39,40]. The ACR/NPF recommend weight loss over no weight loss for patients who are overweight/obese [14]. The ACR/NPF also strongly recommend smoking cessation advice in current smokers due to the significant association between smoking and cardiovascular disease [14].

Available pharmacological treatments

Treatment of PsA includes a range of traditional and conventional synthetic DMARDs, biologic therapies which modulate specific cytokine pathways and also new targeted oral agents such as PDE4 and JAK inhibitors. The currently available pharmacological treatments for PsA are outlined in Table 1.

Table 1: Summary of the available pharmacological treatments for psoriatic arthritis

Therapeutic class	Examples
Symptomatic therapies	Nonsteroidal anti-inflammatory drugs, glucocorticoids, local glucocorticoid injections
Oral treatments [1,2]	Methotrexate, sulfasalazine, cyclosporine, leflunomide
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
PDE4 inhibitor	Apremilast

[1] Called 'oral small molecules' (OSMs) in the ACR guidelines with the addition of Apremilast.
[2] Methotrexate, sulfasalazine and leflunomide are grouped as csDMARDs in the EULAR recommendations.

The evidence supporting the recommendation of these medications is varied in quality. Data supporting the use of methotrexate in PsA are sparse which is reflected in a recent Cochrane review [41]. However, the recent SEAM-PsA trial revealed that while etanercept was superior to methotrexate monotherapy, methotrexate alone showed good efficacy in this trial in a range of disease activity domains [42]. This trial and open-label data from methotrexate use in the TICOPA trial has reinforced guidance around using methotrexate and other csDMARDs as first-line therapies in the management of PsA [13,43]. The findings from the SEAM-PsA trial are reflected in the recent EULAR guidance but these findings were yet to be published in time for the ACR guidance.

There are significant data for effectiveness for biologic DMARDs in patients with PsA when compared with placebo. RCTs investigating TNF inhibition have consistently demonstrated efficacy and safety with respect to all outcomes in the treatment of PsA. There is also reassuring long-term safety follow-up data available for TNF inhibitors, particularly indicating that risk of malignancy is not increased [44,45].

Ustekinumab; targeting the IL-12/23 signalling pathway and secukinumab and ixekizumab; inhibitors of IL-17A signalling have all been demonstrated to be effective versus placebo in PsA [9,10,46]. These medications are particularly effective in treating psoriasis, with proven superiority over TNF inhibitors [47–51].

The targeted synthetic DMARDs (tsDMARDs), Apremilast and Tofacitinib, have become available for the treatment of PsA. Apremilast is a PDE4 inhibitor with proven, albeit modest efficacy in the treatment of peripheral arthritis, psoriasis, enthesitis, and dactylitis in patients with PsA [52]. Apremilast while not demonstrated the same responses as biologic drugs has been deemed to be very safe with no requirement for regular blood monitoring. Tofacitinib is an oral JAK inhibitor which is licensed for treatment of peripheral arthritis, following a trial demonstrating improvements in arthritis outcomes comparable to that of adalimumab, which was included in the study as an internal control [11].

Assessment of clinical trial data

There are many similarities in the use of available treatments in the EULAR recommendations and ACR guidelines but, differences exist in the treatment algorithms recommended. The differences are in part due to the target healthcare settings (Europe vs North America), differing methods used in the creation of these guidelines and the emphasis that is placed on expert opinion and use of low quality evidence.

Methodology of EULAR recommendations and ACR guidelines

The ACR guidelines used the Grading of Recommendations Assessment, Development and Evaluation (GRADE), which is also used by GRAPPA in a modified version, and EULAR used the Oxford Centre for Evidence-Based Medicine (OCEBM).The composition of the recommendations committee may also influence the differences in the recommendations given. Both EULAR and ACR included patients but there is a greater representation of patients in the ACR committee; they include patients in the expert and voting panels and had a separate patient panel. Moreover, there is a good Rheumatology representation in both committees but both had limited Dermatology representation [13][14] . GRAPPA have greater dermatology involvement in their recommendations including two working groups (on skin and nail disease) with patients involved in each group [53].

Definition of disease severity

The EULAR recommendations and ACR guidelines use different methods for defining severe disease, outlined in Table 2. The EULAR recommendations define disease severity based on the presence of poor prognostic factors whereas, the ACR guidelines provides specific definitions for severe disease in both PsA and skin psoriasis.

Table 2: Definitions of disease severity

EULAR poor prognostic factors	ACR severe psoriatic arthritis	ACR severe psoriasis
• Structural damage • High ESR/ CRP • Presence of dactylitis • Presence of nail changes	• 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

ESR: erythrocyte sedimentation rate, CRP: C reactive protein, PASI: Psoriasis Area and Severity Index, BSA: Body Surface Area

Treatment algorithms

EULAR created a single algorithm for the pharmacological non-topical treatments of PsA, proposing the order in which the treatments should be prescribed. GRAPPA also included their recommendations in flow diagrams, but particularly focussed on the domain of disease involved (for example, peripheral arthritis, axial disease, enthesitis, dactylitis, skin and nails) and outlined the order by which treatments should be prescribed.

In contrast to this, ACR offered several individual figures and tables for each specific situation (for example, treatment naïve active PsA, active PsA despite oral small molecules), but the exact order of treatment selection among the options were not discussed. Instead, reference was made to a specific medication in preference to, or 'over', another specific medication (for example, recommendation for a TNFi biologic over oral small molecule).

The EULAR and ACR recommendations/ guidelines for active PsA patients with predominant peripheral psoriatic arthritis, predominant entheseal psoriatic arthritis and predominant axial psoriatic arthritis are summarised in Figures 1-3. The GRAPPA recommendations were not included in this comparison as their 2015 version is now out of date and the updated version is awaited. Nevertheless, it is important to note that the GRAPPA recommendations include skin and nail disease unlike EULAR and ACR which predominantly focus on joint disease, with minimal reference to this.

A treat to target approach aims to ensure that a set target is objectively monitored at each consultation and that treatments are appropriately adjusted to aid a patient into either a state of remission or low disease activity (decided upon by the physician) [54]. Although both EULAR and ACR recommend using a treat to target approach in patients with active PsA, it is a particular focus in the EULAR recommendations. ACR list circumstances during which one may consider not using a treat to target approach; if there are concerns related to increased adverse events, costs of treatment and the burden that changes to medications associated with tighter control may have on patients [13,14].

In contrast to the EULAR recommendations, the ACR guidelines also provided treatment recommendations for non-pharmacological management and management of active PsA patients with concomitant active IBD, other associated co-morbidities and those requiring vaccinations (killed or live attenuated) when starting treatment with biologics [14]. The EULAR has a separate recommendation for vaccinations in patients with PsA [55].

Practice points

- Management of psoriatic arthritis should include both pharmacological and non-pharmacological approaches to optimise outcome
- An increasing number of evidence-based therapies are available to treat psoriatic arthritis
- Choice of therapy should be individualised for patients depending on which domains of the psoriatic disease are active and whether the patient has any comorbidities

Research agenda

Although our understanding of PsA and the availability of treatments have dramatically increased over the past 10 years, with several ongoing trials, there are still many important unanswered questions and a need for further stronger evidence for the treatment recommendations. EULAR proposed a detailed research agenda for PsA in their recommendations. This included research questions on the following themes: responsibility, diagnosis, prognosis, pathophysiology, phenotypes, biomarkers, treatment strategy, outcomes, csDMARDs, bDMARDs and tsDMARDs, systemic glucocorticoids, switches and comorbidities. Although ACR did not have a specific section on research agenda for PsA in their guidelines, they expressed the need for more comparative data to inform treatment selection and evidence to inform recommendations on the use of biosimilars in PsA [13,14].

Summary

A holistic approach should be taken in the management of patients with PsA and include both non-pharmacological and pharmacological approaches. There are a growing number of evidence-based treatments available to treat PsA and the choice of treatment should be tailored according to which domains of PsA are active and whether the patient has any other co-morbidities. The recent EULAR recommendations and ACR guidelines, and future updates of the GRAPPA recommendations due to be published in 2021, can be used to help support clinicians with these treatment decisions to ensure PsA patients are optimally managed.

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Conflict of interest statement

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