Psoriatic arthritis: current therapy and future approaches

DoQuyen Huynh1 and Arthur Kavanaugh2

Abstract
PsA is a systemic inflammatory condition that affects 20–30% of patients with psoriasis. It is characterized by potential involvement of diverse tissues, including peripheral and axial joints, enthesitis, dactylitis and skin and nail disease. The degree of involvement in each domain can vary over time in individual patients and can differ substantially between PsA patients. The clinical heterogeneity along with the varying extent of severity and activity can pose significant challenges to treatment. Although some studies had suggested immunopathophysiological similarities between PsA and RA, more recently important distinctions have been defined. Similarly, although some immunomodulatory therapies have proved effective for both PsA and RA, recent data suggest distinct responses to certain targeted therapies. Herein, current DMARDs and biologic agents as well as the potential role of emerging therapeutics will be reviewed.

Key words: psoriatic arthritis, tumour necrosis factor inhibitors, disease-modifying anti-rheumatic drug, treatment, review, ustekinumab, apremilast, IL-17 inhibitor, rituximab, methotrexate.

Clinical features and diagnosis
PsA is a chronic inflammatory arthritis that occurs in patients with psoriasis. Recent studies have suggested that 20–30% of patients with psoriasis may have PsA [1]. Skin manifestations precede the arthritis in >80% of PsA patients, at times by a decade or more. In addition to synovitis, other manifestations common in PsA include enthesitis, dactylitis and anterior uveitis or iritis. Gastrointestinal involvement with a resemblance to IBD is common, although not always clinically apparent. The peak age at onset of PsA is between 30 and 50 years of age. There is equal distribution between men and women with the exception of axial disease, which favours men 3:1. There are significant genetic associations common to psoriasis and PsA, some of which overlap with other autoimmune conditions [2].

The diagnosis of PsA is clinical as there are no pathognomonic, serological, imaging or other diagnostic tests. Some patients may have elevations in acute phase reactants, such as ESR or CRP, however, many patients with active disease will have normal levels. The majority of PsA patients are seronegative, in that serum tests for RF and ACPA are negative; however, there is a greater prevalence of RF/ACPA positivity among PsA patients compared with the general population [3]. The older Moll and Wright criteria to classify PsA have been largely supplanted by the Classification of Psoriatic Arthritis (CASPAR) classification criteria, which have been shown to have high sensitivity and specificity in diverse settings [4].

Treatment guidelines and paradigms
The clinical heterogeneity of PsA poses a challenge to clinicians in selecting the most appropriate treatments. To help address this, international groups such as the Group for Research and Assessment of Psoriasis and Psoriatic arthritis (GRAPPA) and the European League Against Rheumatism (EULAR) have published treatment recommendations [5, 6], as have some individual countries. The GRAPPA recommendations consider five domains of involvement (peripheral arthritis, skin and nail involvement, enthesitis, dactylitis and axial arthritis) and use a grid approach to account for various levels of disease activity and severity. The EULAR recommendations employ an algorithmic approach that focuses mainly on musculoskeletal manifestations, specifically peripheral
arthritides; manifestations such as dactylitis, enthesitis and skin and nail involvement were to be considered separately. With PsA research proceeding apace, inclusion of newer therapies into clinical guidelines requires ongoing modification and updating.

Other therapeutic concepts are also being explored in PsA. Central to any assessment of the efficacy of therapies are the outcome measures used to quantify disease activity across various domains of disease, both in clinical studies and in the clinic. As many of the outcome measures used in PsA are borrowed from other conditions, such as assessment of peripheral synovitis as has long been done for RA, there has been substantial effort in devising and validating PsA-specific outcome measures [7, 8]. A recent review of the various outcomes measures has been performed [9], where there is no single universally accepted measure, in practice, minimal disease activity has become to be considered an acceptable target for treatment.

Newer treatment paradigms, some of which have also been developed in some rheumatic and other diseases, are also being assessed in PsA. Further, there has been growing interest in the concept of treat to target in PsA. In RA, data have shown that regular assessments of disease activity and alteration of therapies aimed at achieving the lowest levels of disease activity possible are associated with optimal benefits in clinical response, joint damage and functional ability. The Tight Control of Psoriatic Arthritis (TICOPA) study addressed this, with PsA patients randomized 1:1 to receive either (i) standard of care with changes in medication and dose escalation to be determined by a physician every 12 weeks or (ii) a 4-week follow-up with dose escalation and medication changes as outlined by a protocol aimed at minimal disease activity [10]. PsA patients under tight control achieved significantly better clinical outcomes in ACR 20%, 50% and 70% responses (ACR20/50/70) of 62%, 51% and 38% at 48 weeks compared with 45%, 25% and 17% in the standard care group [11]. Overall skin improvement as measured by the Psoriasis Area and Severity Index 75 (PASI75) was reached in 59% of the tight control group compared with only 33% in the standard care group. However, there were more adverse effects noted in the tight control group. Further analysis may elucidate the risk/benefit considerations of treat to target in PsA. Lastly, another concept that has received considerable interest in RA and will be also assessed in PsA is whether therapies such as biologic agents might be withdrawn for PsA patients achieving treatment goals, with clinical response being maintained.

**Common conventional treatment agents**

**NSAIDs and corticosteroids**

NSAIDs and corticosteroids are often prescribed as part of the management of inflammatory joint diseases, including PsA. While concerns had been raised about their safety, a recent Cochrane review evaluating the safety of NSAIDs and paracetamol in inflammatory arthritides suggested that overall NSAIDs may be used safely with MTX without an increased risk of toxic adverse events or liver, renal or pulmonary dysfunction [12]. Also, a placebo-controlled study of nimesulide, a selective cyclooxygenase 2 (COX-2) inhibitor, did result in improved signs and symptoms of PsA and, contrary to prior suggestions, NSAID use did not worsen skin disease [13]. Systemic and IA steroids are commonly used for PsA, although again there are limited data confirming their utility specifically in PsA [14, 15]. Nevertheless, it should be noted that between 40% and 50% of patients in clinical trials are or have previously been on oral steroids. One small study compared the use of early IA steroid injection vs conservative management with NSAIDs in early PsA patients presenting with oligoarticular disease. In this study, patients also received SSZ if synovitis persisted or if polyarticular disease occurred. By week 52, 81% of patients on the IA steroid achieved complete response, defined by the absence of synovitis, compared with only 51% in the conservative group. It should be noted that SSZ was started in a greater percentage of the steroid group (45%) as compared with the conservative group (14%) and the study contained a mixture of patients with oligoarticular arthritis, of whom few had an established diagnosis of PsA [16].

**SSZ**

Among DMARDs, SSZ has one of the larger bodies of evidence specifically in PsA. In a placebo-controlled trial of 221 PsA patients there was improvement in peripheral arthritis in 59% of SSZ-treated patients compared with 47% of controls; however, the overall effect size was small [17]. Similarly a smaller double-blind randomized controlled trial (RCT) suggested that the use of SSZ provided improvement in functional outcomes and to a lesser degree skin disease [18]. Unfortunately there is no documented benefit of SSZ with regard to inhibition of joint damage as assessed by radiographic progression [19].

**LEF**

LEF, an inhibitor of pyrimidine synthesis, was studied in a multinational double-blind RCT called the Treatment of PsA Study (TOPAS) [20]. Overall, 58.9% of the LEF-treated patients were clinical responders, compared with 29.7% of placebo controls. LEF was superior to placebo in functional status scores, CRP reduction and 75% improvement in the PASI75. In a small retrospective study of patients who were considered non-responders to MTX, patients who received a combination of LEF and MTX had improvements in their 28-joint DAS (DAS28) and EULAR response criteria compared with those receiving MTX monotherapy [21, 22]. The combination of MTX and LEF can be associated with elevated liver function tests and requires careful monitoring [23].

**CSA and tacrolimus**

CSA and tacrolimus inhibit calcineurin, resulting in the inhibition of T lymphocyte activation. CSA has been shown to be effective in improving both skin and joint...
involvement in a number of clinical studies in psoriasis and PsA [24]. CSA has also been shown to be effective in combination with MTX and TNF inhibitor (TNFi). A double-blind RCT that compared combination CSA + MTX with MTX or placebo in PsA showed significant improvement in CRP, PASI, swollen joint count and US-defined synovitis with combination CSA + MTX [25]. Combinations of CSA with TNFi have also shown positive results in an open label prospective study of 160 patients receiving monotherapy CSA, monotherapy adalimumab (ADA) or combination CSA + ADA. PsA patients on combination CSA + ADA had statistically significant improvements in Psoriatic Arthritis Response Criteria (PsARC), ACR50 and HAQ assessments at 12 months compared with those on monotherapy [26], although there was little difference in PASI outcomes between the groups. The popularity of CSA use has been tempered by the need for close monitoring due to concerns about renal toxicity and hypertension, especially at doses >3 mg/kg/day.

**MTX**

MTX is widely accepted as a cornerstone therapy in PsA, as reflected in both the GRAPPA and EULAR treatment recommendations [27–29]. Despite its popularity there is a paucity of studies assessing MTX use in PsA, and results have been disparate. The MTX in PsA trial randomized 221 PsA patients to placebo or 15 mg of MTX weekly for 6 months [30]. The overall results suggested significant efficacy for MTX only in the physician global assessment and PASI, and the primary outcomes were not achieved. However, a number of factors in study design may have contributed to these results, including a high dropout rate, a relatively low dose of MTX and inclusion of PsA patients with less severe disease. Indeed, when analysis was restricted to polyarticular patients, MTX was effective.

A recent systematic analysis reviewed the five RCTs in the medical literature and about a dozen other observational studies [31]. Although disparate results were reported in the individual studies, in general it appeared that trials using weekly doses of MTX of ≥15 mg achieved clinical benefit, whereas those using smaller doses did not. Further support for the efficacy of MTX comes from the open-label RESPOND [32] study, in which 115 treatment-naive PsA patients were randomized to receive combination MTX + infliximab or MTX monotherapy at a dose of 15 mg. At 16 weeks, 86% of patients received an ACR20 response rate with combination therapy, as did 66% of patients on MTX monotherapy. Overall, despite the paucity of evidence, MTX remains a mainstay of drug therapy in PsA.

**TNF inhibitors**

The introduction of biologic therapies with anti-TNFis has greatly improved the clinician’s ability to treat all of the various manifestations of PsA. The clinical efficacy of TNFis exceeds that of traditional DMARDs and TNFis have been shown to significantly inhibit joint damage as assessed by radiographic progression [33–37]. Currently five TNFis are approved by the US Food and Drug Administration (FDA) for use in PsA: infliximab, etanercept, ADA, golimumab and, most recently, certolizumab pegol (Table 1) [38–48]. Overall, efficacy among the agents appears comparable, although there have not been head-to-head trials. An indirect comparison reviewing data from RCTs of the first four approved TNFis, and focusing on changes in skin, peripheral joint and axial involvement, suggested that there were no significant differences between the TNFis in PsA [49, 50]. Studies of certolizumab pegol, the most recently approved agent, included patients who had previously been treated with other TNFis, and showed efficacy comparable to TNFi-naive patients [46]. This suggests that TNFi switching may be viable in PsA, as has been established in RA. Data supporting this concept also come from registries. In the Norwegian DMARD (NOR-DMARD) registry, the durability of

<table>
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<tr>
<th>Agent/trial</th>
<th>Study size</th>
<th>Patients meeting response criteria, %</th>
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<tr>
<td>Etanercept [38, 39]</td>
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<tr>
<td>Week 12</td>
<td>205</td>
<td>ACR20 = 59, PASI75 = 38</td>
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<td>Week 24</td>
<td>55</td>
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<tr>
<td>Week 48</td>
<td>169</td>
<td>ACR20 = 64, PASI75 = 40</td>
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<td>Infliximab/IMPACT [40, 47, 48]</td>
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<td>Week 14</td>
<td>200</td>
<td>ACR20 = 58, PASI75 = 64</td>
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<td>Week 24</td>
<td>54</td>
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<td>Week 54</td>
<td>173</td>
<td>ACR20 = 59, PASI75 = 50</td>
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<td>104</td>
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<td>ADA/ADEPT [41, 42]</td>
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<td>Week 12</td>
<td>315</td>
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<td>245</td>
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<td>Week 104</td>
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<td>Golimumab/GO-REVEAL [43–45]</td>
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<td>Week 14</td>
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<td>ACR20 = 51, PASI75 = 40</td>
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<td>Week 24</td>
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<td>Week 52</td>
<td>360</td>
<td>ACR20 = 67, PASI75 = 62</td>
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<td>Week 104</td>
<td>335</td>
<td>ACR20 = 67, PASI75 = 86</td>
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<td>Week 104</td>
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TNFis: tumour necrosis factor inhibitors; ADA: adalimumab; ACR20: 20% response to ACR criteria; PASI75: Psoriasis Area and Severity Index 75.
remaining on a second TNFi was less than that for the first TNFi course, but suggested that some patients will respond to TNFi switching [52]. Similarly in DANBIO (a nationwide registry of biologic therapies in Denmark), retention rates on a second or even a third TNFi suggest that switching TNFis can result in clinical improvement [52].

Factors such as cost and patients’ concerns regarding side effects over the long term have raised the question of whether treatments might be tapered or even withdrawn in patients achieving low levels of disease activity. In RA, studies have suggested that such a strategy might be viable for a subset of patients, particularly those with earlier disease who achieve very low levels of disease activity on treatment. In PsA, to date there has been only one prospective case-control study addressing this. Dose reduction of ADA to 40mg every 4 weeks was done in a population that included 76 PsA patients who had obtained clinical remission [53]. At the 28-week follow-up, 88.6% of PsA patients remained in clinical remission; interestingly, only 17.6% of the RA patients in the study remained in remission. Other studies addressing dose reduction and withdrawal are currently under way and may help define the patient characteristics that predict success on lower doses of specific agents.

Newer therapies and agents

Despite advances in therapy, there remain patients who fail to respond to classic DMARDs and TNFis or who have loss of efficacy over time. Driven in part by this unmet clinical need, newer classes and targets of therapy have emerged. This has also been facilitated by studies further advancing our understanding of the immunopathophysiology of disease (Figs. 1 and 2). For example, one study suggested a potentially key role for IL-23 in arthritides characterized by enthesitis, including PsA [54]. Thus, in an animal model of enthesitis, a specific subset T cell residing in the enthesis, distinct from Th17 cells, possessed the ability to respond to IL-23, leading to up-regulation of other inflammatory mediators, including IL-6, IL-17 and IL-22. Of note, this model had a resemblance to human disease, with enthesitis and enthesal new bone formation as well as inflammation in the aortic root and valve.

Ustekinumab: IL-12/IL-23 inhibitor

Ustekinumab is a human mAb directed against the p40 subunit common to IL-12 and IL-23 that has received regulatory approval for psoriasis and PsA. In P-SUMMIT I, 615 PsA patients with no prior TNFi exposure were randomized 1:1:1 to receive placebo vs 45 mg or 90 mg of ustekinumab. ACR20/50/70 and PASI 75 responses were examined at 24 weeks. In the 90 mg ustekinumab group the ACR20/50/70 and PASI75 were 49.5%/27.9%/14.2% and 62.4%, whereas control responses were 22.8%/8.7%/2.4% and 11%, respectively. There were also significant improvements in the enthesitis, dactylitis and function as measured by the HAQ. Responses were maintained up to 108 weeks [55, 56]. In P-SUMMIT II, PsA patients who had previously received treatment with TNFis were included. Of note, the magnitude of clinical response was less than in TNF-naive patients [57]. Analysis of radiographic data from the combined P-SUMMIT I and II databases showed inhibition of radiographic progression [58]. In the studies, ustekinumab was generally safe and well tolerated.

IL-17 inhibitors

IL-17, an inflammatory cytokine secreted by Th17 T cells and other cells, has been identified in psoriatic plaques and inflamed entheses. Currently there are three IL-17 inhibitors in advanced phase clinical trials, including secukinumab, ixekizumab and brodalumab. Secukinumab and ixekizumab are mAbs against IL-17A, while brodalumab is a mAb directed against the IL-17 receptor A (IL-17RA). Data for these agents have shown very robust improvements in skin psoriasis. For example, in a phase Ib RCT of secukinumab at 150 and 75 mg, there was PASI75 improvement of 81% and 57% of the patients, respectively, compared with 9% for placebo at 12 weeks [59]. A dose-finding randomized study of ixekizumab also showed significant PASI improvement in >77% of patients compared with 8% for placebo [60]. These authors also mention a significant reduction in joint pain assessed by a visual analogue scale (VAS) in 12 patients who also carried the diagnosis of PsA. Similar to secukinumab and ixekizumab, a phase II dose-finding trial of brodalumab showed early improvement in PASI75 at 12 weeks compared with placebo (70 mg, 45%; 140 mg, 85.9%; 210 mg, 86.3%; 280 mg, 76%; placebo, 16%) [61].

In PsA, a small (n = 24) double-blind RCT of secukinumab has demonstrated significant improvement in the HAQ disability index (HAQ-DI) and CRP; however, the primary endpoint of ACR20 improvement was not met [62].
Interestingly, in RA, IL-17 inhibitors have also been studied, and clinical responses appeared to be modest compared with therapies with other mechanisms of action. Brodalumab has been studied in PsA as well [63]. Doses of 140 mg and 280 mg given subcutaneously resulted in ACR20 responses at 12 weeks of 36.8% and 39.3%, respectively, compared with 18.2% for placebo. Additional longer-term studies will be necessary to define the effect of IL-17 inhibitors on the various manifestations of PsA.

Apremilast: phosphodiesterase inhibitor

Elevated levels of cyclic adenosine monophosphate (cAMP) down-regulate pro-inflammatory cytokines such as IL-23, TNF-α, and IFN-γ (Fig. 3). Phosphodiesterase enzymes that degrade cAMP, e.g. phosphodiesterase enzyme 4 (PDE4), have become a potential therapeutic target. The PDE4 inhibitor apremilast has been assessed in several studies in PsA patients. In a phase II study, apremilast at a dose of 20 mg or 40 mg twice daily demonstrated significant ACR20 responses of 43.5% and 35.8%, respectively, compared with 11.8% for placebo controls at week 12 [64]. Results from phase III trials, dubbed PALACE 1, 2, 3 and 4, have also recently been reported. In PALACE 1, 504 patients were randomized 1:1:1 to receive placebo, apremilast 20 mg twice a day or apremilast 30 mg twice a day [65]. At 16 weeks, 31% and 40% of apremilast 20 and apremilast 30 mg patients, respectively, achieved ACR20, compared with only 19% on placebo. Long-term follow-up to week 52 in PALACE 4 revealed persistence of benefit, with 58% of patients meeting ACR50 or
70 and benefit to the skin was modest [66]. Overall, apremilast appeared to be well tolerated with minimal effects on any laboratory parameters.

Abatacept: CTLA-4 inhibitor

T cells appear to play an important role in the pathogenesis in PsA. T cell activation is dependent on both specific antigen presentation and co-stimulation. CTLA-4 inhibits CD28 interactions with CD80 and CD86 and thereby down-regulates T cell activation. Abatacept, a fusion protein composed of the extracellular domain of CTLA-4 linked to an IgG1 Fc portion, has proven efficacy in numerous studies in patients with RA [67, 68]. In PsA, the results of a randomized double-blind placebo-controlled trial evaluating varying doses over a 6-month period have been reported [69]. The results suggest abatacept-treated patients, particularly those at a dose of 10 mg/kg, had a significantly higher percentage of ACR20 responses (48%) compared with placebo (19%). Trends toward improvement in erosion, osteitis and synovitis as seen on MRI and general improvement in physical function and quality of life were observed. Unfortunately, the skin response was inconsistent and patients previously exposed to TNFis had a less robust response than TNF-naive patients. Further studies evaluating the potential efficacy of abatacept in PsA are currently ongoing.

Tocilizumab: IL-6 inhibitor

Tocilizumab, a humanized mAb to the IL-6 receptor, has been approved for RA and it is being studied in PsA. Of note, a randomized trial of tocilizumab in AS showed no clinical efficacy despite a decrease in CRP [70]. In a case report of two patients with PsA, there was a reduction in CRP levels but no benefit in skin or joint symptoms, which were alleviated subsequently with the use of anti-TNFis [71]. Currently there is only one documented case report of tocilizumab improving tender joint count, swollen joint count and patient global VAS in an atypical PsA patient that had loss of efficacy on TNFis [72].

Janus kinase (JAK) inhibitors

Another target of drug therapy are the JAK molecules: JAK1, JAK2, JAK3 and TYK2. These intracellular molecules are important in signal transduction of cytokines such as IL-2, IL-12 and IL-6 (Fig. 3). Tofacitinib was FDA approved in late 2012 for the treatment of RA. Of note, it has been shown to be effective in phase II trials of moderate to severe psoriasis at doses of 5 and 15 mg twice daily at 12 weeks of therapy [73]. Further studies in PsA are under way.

Rituximab: CD20 inhibitor

Rituximab (RTX), a chimeric mAb directed against CD20, has been shown to be effective and is approved for use in RA. Recently an open-label trial of RTX in 26 patients who had either AS or PsA showed modest improvement in 11 of 26 patients (47.8%) as measured by the BASDAI [74]. Of note, 23 of the 26 patients had previous exposure to TNFis. Of the 11 patients, 7 had axial disease while the remaining 4 had peripheral disease. Other open-label studies also suggest quite modest improvement in PsA patients treated with RTX, although some improvement may be due to concomitant steroid use [75, 76].

Conclusion

PsA is a chronic inflammatory condition with significant heterogeneity in clinical manifestations, including skin and nail psoriasis, enthesitis, dactylitis, axial arthritis and peripheral arthritis. Among DMARDs, MTX is most commonly used, despite a paucity of high-quality studies supporting its use. LEF, ciclosporin and SSZ are all efficacious for arthritis and psoriasis to varying degrees in some PsA patients. Unarguably, the class of anti-TNFis has established itself as most effective for all the various manifestations of PsA, and in fact could be considered the standard of care, particularly in patients with severe, active disease. There remain unanswered questions concerning established therapies in PsA. Prominent among these is whether TNFi and DMARD combinations, especially with MTX, might be synergistic in PsA as they are in RA. To date, all trials of TNFis in PsA have allowed MTX, but have required active disease as an eligibility criterion. Such a study design obviates the ability to assess the additive or synergistic benefit of TNFi and MTX. As noted, there is great interest in newer treatment approaches, such as treat to target, and possibly tapering or discontinuing therapy in patients achieving treatment goals. Finally, pharmacoeconomic assessments specific to PsA will help establish the value of currently available agents and optimize their use.

Success with established therapies has helped drive interest in newer therapies. Among the newer agents, the greatest amount of data to date are for the IL-12/IL-23 inhibitor ustekinumab. This agent may have its main role in PsA patients in whom skin manifestations are particularly active or severe. On the horizon it appears that apremilast may offer an effective option for PsA, particularly for patients with more moderate disease activity and in whom safety concerns might impact the choice of other treatments. There has been interest in the effects in PsA of therapies already approved for use in RA. Interestingly, some therapies effective in RA, such as RTX, seem not to be very effective in PsA. Abatacept has some efficacy in PsA, but that too appears to be less than its efficacy in RA. This suggests that whereas these disease states both respond to TNFis, differences in their immunopathogenesis may be revealed by distinct responsiveness to other targeted therapies. In that regard, although there are limited data currently available, it might be argued that the efficacy of IL-17 inhibition in the arthritis of PsA seems to be notably less than the response of skin psoriasis. Currently the treatment outlook in PsA appears optimistic, with numerous studies under way. Undoubtedly these studies will allow the introduction of additional agents and novel treatment strategies, and ultimately help optimize the care of patients with this important condition.
**Rheumatology key messages**

- PsA is a chronic inflammatory disease treated by the use of DMARDs and TNF inhibitors.
- Newer agents to treat PsA show promise and clinical trials of agents with different mechanisms of activity are under way.

**Disclosure statement:** A.K. has conducted clinical research activities for AbbVie, Amgen, Janssen, UCB, Pfizer, Roche and Sanofi. The other author has declared no conflicts of interest.

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Psoriatic arthritis: treatment


