Psoriatic arthritis: latest treatments and their place in therapy

Eun Jin Kang and Arthur Kavanaugh

Abstract: Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disease that may affect peripheral and axial joints, entheses, skin and nails, and other organs. Treatment with nonsteroidal anti-inflammatory drugs, steroid and disease-modifying antirheumatic drugs had been the backbone of traditional management of PsA for many years. However, improvement in our understanding of immunopathogenesis of PsA has led to new immunomodulatory therapies. Introduction of novel agents has raised the bar for treatment and helped drive research into additional therapeutic options.

Keywords: disease-modifying antirheumatic drugs, immunomodulatory therapies, psoriatic arthritis

Introduction

Psoriatic arthritis (PsA) is a systemic inflammatory condition that can be associated with joint deformities and destruction in approximately 40–60% of patients. As the prevalence of psoriasis is 2–3% and PsA occurs in about one-third of patients with psoriasis, it is a common condition [Gladman *et al.* 2005]. Although for many years PsA had been considered a milder form of inflammatory arthritis, patients with PsA can have joint destruction, functional impairment, reduced quality of life and psychosocial disability to an extent comparable to that of patients with rheumatoid arthritis (RA) [McHugh *et al.* 2003].

Traditional treatments for PsA included nonsteroidal anti-inflammatory drugs (NSAIDs), steroid and synthetic disease-modifying antirheumatic drugs (DMARDs). The treatment of PsA has changed dramatically since the development and introduction of biologic agents, particularly inhibitors of the proinflammatory cytokine tumor necrosis factor (TNF). With increased understanding of the immunologic processes underlying the pathogenesis of disease, therapy for PsA has evolved. Now, the goals of therapy include inhibition of the progression of structural damage and improved quality of life [Veale, 2013; Olivieri *et al.* 2014; Huynh and Kavanaugh, 2015].

NSAIDs and corticosteroids

NSAIDs are still widely used for PsA treatment and may even be the only therapy for patients with very mild disease. Although NSAIDs can be effective at relieving various musculoskeletal symptoms and signs, they do not have efficacy on skin lesions. In addition, they are often considered “milder” or “less toxic” therapy than DMARDs, and some NSAIDs are available in many countries without a doctor’s prescription.

There are only two randomized controlled trials (RCTs) with NSAIDs in PsA. In a 4-week study with nimesulide (100, 200, or 400 mg/day) or placebo, nimesulide doses of 200 or 400 mg were significantly better than placebo for reducing the number of tender and swollen joints, and improving physician and patient global assessment of efficacy. In a 12-week parallel-group study with celecoxib (200 or 400 mg once daily) or placebo, there were no statistically significant differences in American College of Rheumatology 20% improvement (ACR20) criteria [Sarzi-Puttini *et al.* 2001; Kivitz *et al.* 2007].

NSAIDs can be associated with important adverse effects. These include renal toxicity, gastrointestinal toxicity and risk for cardiovascular events. Therefore, the lowest effective doses and the shortest duration of NSAIDs should be used [Sarzi-Puttini *et al.* 2001; Kivitz *et al.* 2007].

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Local injections of corticosteroids can be considered as adjunctive therapy for some manifestations of PsA, for example, peripheral arthritis and enthesitis. However, systemic steroid use, particularly at high doses, has been reported to cause flares of skin psoriasis. Therefore, systemic steroids should be used with caution, and at the lowest effective dose [Gossec *et al.* 2012; Mrowietz and Domm, 2013].

Conventional DMARDs

Methotrexate

Methotrexate (MTX) has a long history of use in PsA, despite a relative paucity of data establishing its efficacy specifically in this condition. Nevertheless, extrapolated from treatment algorithms in RA, it has been recommended that patients who have active disease despite previous NSAID therapy should receive DMARDs. However, DMARDs including MTX are clearly ineffective for treating axial disease and there is little evidence supporting their role treating other manifestations such as enthesitis. There are no head-to-head comparisons among DMARDs, but MTX is often recommended as the first-choice DMARD in PsA, either as monotherapy or in combination [Ritchlin *et al.* 2009; Gossec *et al.* 2012]. Although the data are limited, there is a suggestion that weekly doses of MTX above 15 mg might have greater clinical efficacy for PsA treatment than lower doses [Ceponis and Kavanaugh, 2010]. In the randomized placebo-controlled trial, the Methotrexate in Psoriatic Arthritis trial (MIPA), MTX was not effective overall for improving synovitis; however, there was significant efficacy in the patient and physician global assessments, and Psoriasis Area and Severity Index (PASI) scores at 6 months, and also efficacy for peripheral arthritis in subsets of patients with more polyarticular disease at enrollment [Kingsley *et al.* 2012]. The MIPA trial had limitations, including high dropout rates, a low percentage (11%) of patients treated with more than 15 mg MTX per week; therefore we are left with uncertainty about the overall value of MTX in PsA [Mease, 2012].

Sulfasalazine

Sulfasalazine has been shown to improve peripheral arthritis and functional outcomes in patients with PsA [Gupta *et al.* 1995; Clegg *et al.* 1999]. However, there is no evidence it can inhibit

the progression of joint damage as assessed by radiographic progression [Rahman *et al.* 1998].

Leflunomide

Leflunomide (LEF) has been shown to improve both joint and skin symptoms in PsA [Kaltwasser, 2007]. In the multinational double-blind, randomized controlled trial, Treatment of PsA Study (TOPAS), LEF showed significant responses in the Psoriatic Arthritis Response Criteria (PsARC), modified ACR20, and PASI after 24 weeks [Nash *et al.* 2006]. In a retrospective study of patients who were refractory to MTX, patients who received a combination of LEF and MTX had improvement in 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism (EULAR) response criteria [Sakellariou *et al.* 2013]. In another prospective, multinational 24-week observational study, patients with active PsA who initiated with LEF achieved a PsARC response and significant improvement in tender, swollen joint counts, pain, fatigue, dactylitis, and skin disease [Behrens *et al.* 2013]. Asiri and colleagues also reported data that LEF led to improvement in almost 50% of patients by 1 year [Asiri *et al.* 2014]. The combination of MTX and LEF can be associated with elevated liver function test abnormalities and therefore requires careful monitoring [Curtis *et al.* 2010].

Cyclosporine and tacrolimus

Cyclosporine (CsA) and tacrolimus are calcineurin inhibitors, thereby inhibiting T-lymphocyte activation. CsA appeared effective for the treatment of peripheral arthritis, axial involvement, and skin lesions in PsA [Salvarani *et al.* 2001]. CsA has also been shown to be effective in combination with MTX and TNF inhibitors (TNFi) [Fraser *et al.* 2005; Karanikolas *et al.* 2011]. Adverse events potentially associated with CsA, such as renal toxicity and hypertension, require monitoring during use of this drug.

TNFi

TNFi improve signs and symptoms of inflammation in both peripheral and axial joints as well as in periarticular tissues such as entheses. TNFi also improve functional status, quality of life, and skin and nail manifestations of PsA. Finally, TNFi have been shown capable of slowing the progression of damage in peripheral joints [D'Angelo *et al.* 2012; Huynh and Chinoy, 2013]. Five TNFi

are approved by the US Food and Drug Administration (FDA) and other health authorities worldwide for PsA treatment: etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol [Mease *et al.* 2000, 2005, 2006, 2009, 2014a; Kavanaugh *et al.* 2007, 2009, 2012; Antoni *et al.* 2008]. The EULAR and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recommend TNFi for various domains of patients with PsA [Ritchlin *et al.* 2009; Gossec *et al.* 2012]. They are often recommended for use in PsA after an inadequate response to at least one synthetic DMARD, although they may also be used as initial therapy.

These agents have all been shown to achieve significantly better responses than placebo in double-blind placebo-controlled randomized clinical trials, with ACR20 improvement criteria 51–59% with TNFi *versus* 9–24.3% with placebo over 12–24 weeks of treatment [D'Angelo *et al.* 2012]. Etanercept, infliximab, and adalimumab have been compared in a single randomized non-blinded study in 100 patients with PsA [Atteno *et al.* 2010]. Clinical and laboratory indices showed similar favorable outcomes for all of these drugs. In other two indirect comparison meta-analyses of adalimumab, etanercept, golimumab, and infliximab, showed no important differences in the effectiveness and safety of these drugs [Thorlund *et al.* 2012; Fenix-Caballero *et al.* 2013].

As is the case in RA, combination therapy with TNFi and MTX is common in PsA. However, in contrast to RA, MTX is not standard-of-care treatment for all patients with PsA. Therefore, clinical trials of TNFi have typically allowed, but not required, concomitant therapy with MTX. All TNFi RCTs for patients with PsA showed no or minor differences in efficacy for peripheral arthritis, as assessed by ACR response [Mease *et al.* 2004, 2005, 2014a; Antoni *et al.* 2005; Mease *et al.* 2005; Gladman *et al.* 2007; Kavanaugh *et al.* 2007, 2009, 2013; Sterry *et al.* 2010]. However, given the study design, namely that patients with PsA needed to have active peripheral arthritis whether or not MTX was being used, it cannot be concluded that MTX and TNFi are not additive or synergistic in their effects. The optimal way to assess this would be in a trial of three arms (TNFi, MTX, TNFi plus MTX) in patients with PsA naïve to both types of treatment. Intriguingly, there is some suggestion that there may be some added benefit. For example, in the GO-REVEAL

trial, while concomitant MTX did not affect peripheral arthritis (ACR20) or skin psoriasis (PASI75) responses, the addition of MTX did appear to reduce radiographic progression [Kavanaugh *et al.* 2014a]. In registry studies also, the combination TNFi plus MTX appears to prolong TNFi drug survival with no effect on safety [Behrens *et al.* 2014]. In other studies of antidrug antibodies (ADAb) with TNFi, 22 patients with PsA who were treated with adalimumab had an ADAb prevalence of 18% and that was associated with a decreased clinical response and low drug level. Zisapel and colleagues' study also showed high levels of ADAb were found in 29% of patients taking adalimumab, 21% taking infliximab, and 0% taking etanercept. ADAb significantly correlated with lower drug level, higher DAS28 scores, and MTX use correlated significantly with a lower prevalence of ADAb [Van Kuijk *et al.* 2010; Zisapel *et al.* 2015].

A relevant clinical question is whether patients with PsA might achieve clinical benefit when switching from one TNFi to another. This is a complex question, as the reasons patients may stop the initial TNFi can vary. Nevertheless, some patients with PsA who switched TNFi did achieve good clinical responses. As has been seen in RA, while switching TNFi can be effective, the response rates tended to diminish with successive TNFi used [Fagerli *et al.* 2013; Glinthorp *et al.* 2013].

In addition to systemic use of TNFi, intra-articular injection of etanercept showed improvement in clinical scores, synovial thickness measured by contrast-enhanced magnetic resonance and ultrasound, as well as reduced levels of synovial tissue and synovial fluid biological markers [Fiocco *et al.* 2013].

Ustekinumab: interleukin-12/interleukin-23 inhibitor

Ustekinumab is a human monoclonal antibody that binds to the shared p40 subunit of interleukin (IL)-12 and IL-23. It has received approval for patients with moderate to severe plaque psoriasis and PsA by the European Medicine Agency and FDA, as well as other regulatory agencies around the world. In the phase III, multicenter, double-blind, placebo-controlled, PSUMMIT 1 trial [McInnes *et al.* 2013], 615 active patients with no exposure to TNFi were studied. More ustekinumab-treated patients [87 of 205 (42.4%) in the 45 mg group and 101 of 204 (49.5%) in the

90 mg group] than placebo-controlled patients [47 of 206 (22.8%)] achieved ACR20 responses at week 24. Responses were maintained through week 52. ACR50 responses were also achieved by 24.9%, 27.9%, and 8.7% of patients in the ustekinumab 45 mg, 90 mg, and placebo groups, respectively ($p < 0.0001$ for both comparisons), and these responses were maintained at week 52. Adverse events were similar in the ustekinumab and placebo group. In PSUMMIT 2, some patients with PsA previously exposed to TNFi were also enrolled [Ritchlin *et al.* 2014]. More ustekinumab-treated patients (43.8% combined) than placebo-treated patients (20.2%) achieved ACR20 at week 24. ACR 50 ($p \leq 0.05$), Health Assessment Questionnaire Disability Index improvement ($p < 0.001$), and PASI75 ($p < 0.01$) also showed significant treatment differences. All benefits were sustained through week 52 and no unexpected adverse events were observed through week 60. Of note, clinical responses tended to be lower among patients previously exposed to TNFi compared with TNFi-naïve patients. Analysis of radiographic data from PSUMMIT 1 and 2 trials indicated that ustekinumab-treated patients (regardless of dose) demonstrated significantly less radiographic progression at week 24 [Kavanaugh *et al.* 2014c].

Small-molecular-weight inhibitors

Small-molecular-weight inhibitors, such as kinase inhibitors, can have several advantages, including oral availability and lower synthesis costs. Two small molecular weight agents have been assessed in later phase studies in patients with PsA [Palfreeman *et al.* 2013].

Apremilast: phosphodiesterase inhibitor

Apremilast is an orally administered, selective inhibitor of phosphodiesterase (PDE4). PDE4 is a member of the major enzyme class responsible for the degradation of cyclic adenosine monophosphate (cAMP). Treatment with apremilast results in elevate intracellular cAMP. This, in turn, leads to downregulation of the inflammatory response, decreasing cytokines such as TNF α , IL-12, IL-23, and increasing production of anti-inflammatory cytokines such as IL-10 [Schafer, 2012]. Approval of apremilast was granted by the FDA in March 2014 for PsA treatment and in September 2014 for skin psoriasis. In a phase II trial, apremilast at a dose of 20 or 40 mg twice daily showed ACR20 responses of 43.5% and 35.8% compared with

11.8% for placebo at week 12 [Schett *et al.* 2012]. Apremilast has been evaluated in four randomized, double-blind, placebo-controlled phase III trials in the PALACE program. The PALACE 1, PALACE 2, and PALACE 3 trials included patients with active PsA, some of whom had been previously treated with DMARDs or biologics [Cutolo *et al.* 2013; Edwards *et al.* 2013; Wells *et al.* 2013; Kavanaugh *et al.* 2014b]. In all four trials, patients were randomized to receive apremilast 20 mg twice daily, 30 mg twice daily, or placebo. The primary outcome was the proportion of patients achieving improvement of ACR20 at week 16. Results of PALACE 1, PALACE 2, PALACE 3, and PALACE 4, showed apremilast to be effective in the treatment of PsA, improving signs and symptoms and physical function (Table 1). Of note, apremilast was generally very well tolerated and no routine laboratory test monitoring was required with its use.

JAK inhibitors

JAKs are intracellular tyrosine kinases that participate in the cytokine signaling pathway (including IL-2, IL-12, IL-6, and many others) by associating with specific cytokine receptors and facilitating activation of signal transducers and activators of transcription (STAT) proteins [Ghoreschi *et al.* 2009]. JAKs consist of four members: tyrosine protein kinase 2 and JAK1, JAK2, and JAK3.

Abnormalities in the expression/activity of different transcription factors involved in the JAK/STAT signaling pathway have been hypothesized to play a role in the pathogenesis of psoriasis. In lesional psoriatic skin, STAT1 expression and activation is increased. In synovial fluid of clinically active joints of patients with PsA, activation of JAK1/STAT3/STAT1 and protein kinase C δ phosphoproteins that may drive the local inflammation is enhanced and T helper 17 (Th17) showed expansion [Eriksen *et al.* 2005; Racz *et al.* 2011; Hald *et al.* 2013; Fiocco *et al.* 2014].

Tofacitinib is an oral inhibitor of JAK3 and JAK1, and to a lesser degree JAK2. It blocks cytokines like IL-2, IL-4, IL-15, and IL-21 by blocking JAK3 and also inhibits signaling of interferon γ , IL-6, and to a lesser extent, IL-12 and IL-23 by blocking JAK1 and JAK2 [Kontzias *et al.* 2012]. Tofacitinib showed efficacy in chronic plaque psoriasis and further studies in PsA are underway [Ports *et al.* 2013].

Table 1. Apremilast phase III clinical trials in psoriatic arthritis.

Trials	Type	Dosage	Number of patients/ duration/extension	ACR 20 (20 mg <i>versus</i> 30 mg <i>versus</i> placebo)
PALACE 1 [Kavanaugh <i>et al.</i> 2014b]	Phase III	20 or 30 mg twice daily	504/16 weeks/1 year	31.3% <i>versus</i> 39.8% <i>versus</i> 19.4%
PALACE 2 [Cutolo <i>et al.</i> 2013]	Phase III	20 or 30 mg twice daily	484/16 weeks/1 year	38.4% <i>versus</i> 34.4% <i>versus</i> 19.5%
PALACE 3 [Edwards <i>et al.</i> 2013]	Phase III	20 or 30 mg twice daily	505/16 weeks/1 year	29.4% <i>versus</i> 42.8% <i>versus</i> 18.9%
PALACE 4 [Wells <i>et al.</i> 2013]	Phase III	20 or 30 mg twice daily	527/16 weeks/1 year	29.2% <i>versus</i> 32.3% <i>versus</i> 16.9%

ACR20, American College of Rheumatology 20% improvement criteria.

Other mechanisms of action

IL-17 inhibitors

IL-17 is a proinflammatory cytokine secreted by Th17 T cells and other cells. There are three IL-17 inhibitors, two monoclonal antibodies specific for the IL-17A isoform, secukinumab and ixekizumab, and one IL-17 monoclonal antibody specific for the IL-17A receptor, brodalumab. These agents all showed significant improvement in skin psoriasis [Leonardi *et al.* 2012; Papp *et al.* 2012, 2013]. In PsA, in a small short, randomized, double-blind, placebo-controlled phase II proof-of-concept trial of secukinumab, the primary end point (the proportion of ACR20 at week 6) was not met. However, clinical responses, acute-phase reactant and quality of life improvement were greater with secukinumab *versus* placebo [McInnes *et al.* 2014]. In the more recent FUTURE 1 and 2 trials, secukinumab reduced the severity of plaque and nail psoriasis, improved joint signs and symptoms, and inhibited radiographic progression [Mease *et al.* 2014c; Gottlieb *et al.* 2014]. Brodalumab significantly improved joint signs and symptoms in a phase II, randomized, double-blind, placebo-controlled study in patients with PsA. The primary end point was ACR20 at week 12 and it was reached by 37% and 39% of patients receiving 140 or 280 mg, brodalumab respectively, compared with 18% of patients in the placebo group ($p < 0.05$) [Mease *et al.* 2014b].

Tocilizumab

Tocilizumab is a humanized monoclonal antibody specific for the IL-6 receptor. Tocilizumab is approved for treatment of refractory RA. In one case report, there was a reduction of C-reactive

protein (CRP) levels but no benefit in skin and joint symptoms [Ogata *et al.* 2012]. In another two case reports, tocilizumab improved clinical symptoms and inflammatory markers [Hughes and Chinoy, 2013; Costa *et al.* 2014].

Abatacept: cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) inhibitor

Abatacept, a fusion protein construct consisting of the extracellular domain of CTLA-4 linked to a modified Fc portion of human immunoglobulin IgG1, inhibits T-cell activation [Veale, 2011]. In a phase II, multicenter, randomized, double-blind, placebo-controlled trial, the percentage of patients achieving ACR20 response was slightly higher for abatacept 10 and 30/10 mg/kg (two initial doses of 30 mg/kg, followed by 10 mg/kg) compared with placebo [Mease *et al.* 2011]. There are anecdotal reports of abatacept in PsA being effective in patients with PsA refractory to DMARDs [Altmeyer *et al.* 2011; Ursini *et al.* 2013]. However, there appears to be minimal effect on skin psoriasis.

Rituximab

Rituximab is a chimeric monoclonal antibody directed against CD20 that targets mature B lymphocytes. According to the Autoimmunity and Rituximab Registry, three of nine patients with PsA showed some response [Wendling *et al.* 2012]. In another open study, five of nine patients (56%) achieved at least a 30% improvement according to PsARC [Jimenez-Boj *et al.* 2012].

Perspectives and place in therapy

PsA is increasingly recognized as an important condition that can cause persistent inflammation,

progressive joint damage, disability, and impaired quality of life. Previously, treatments for PsA included NSAIDs, steroids, and some synthetic DMARDs. The treatment paradigms were largely borrowed from treatment of peripheral arthritis in RA.

The situation changed dramatically with the introduction of biologic agents, particularly TNFi. The notable clinical efficacy of TNFi has resulted in significant advances in the treatment of PsA. Of note, TNFi were effective across the various domains of TNFi. This generated interest in defining outcomes in these varied aspects of PsA, including skin and nail disease, enthesitis, axial arthritis, and dactylitis. In addition, the success of TNFi in improving signs and symptoms of PsA has raised the goals of therapy. Much different than in years past, when any improvement was considered a success, current treatment aims at achieving the lowest level of disease activity possible for each patient in each aspect of disease. In addition to signs and symptoms of disease, optimizing quality of life, preserving functional status and minimizing joint damage are considered goals of treatment.

The success achieved with TNFi has also driven additional research into the immunopathogenesis of PsA, and the development of other new therapeutic agents with distinct mechanisms of action. For example, ustekinumab and apremilast, approved as treatment options for patients with PsA, are now available for patients. Among the agents in development, there is perhaps the greatest interest in IL-17 inhibitors.

What is the place of all these therapeutic options in the treatment of PsA? Given the heterogeneity of PsA, this is a decision that must be made with the individual patient. Consideration of the activity and severity of peripheral arthritis, axial arthritis, skin and nail psoriasis, enthesitis, dactylitis, and other manifestations such as uveitis and gastrointestinal inflammation is relevant for each patient as it affects the choice of therapy. For many patients, NSAIDs are utilized early in the disease course, and sometimes maintained throughout treatment as an adjunct. Traditional DMARDs, especially MTX but also LEF and CsA, remain viable choices for patients with PsA. TNFi have been considered by some to be somewhat of a gold standard in PsA because they can have efficacy across domains. However, there is excitement about newer agents, such as the IL-12/

IL-23 inhibitor ustekinumab, the PDE4 inhibitor apremilast, and the IL-17 inhibitors. As clinicians have had many years of experience with TNFi, it is likely that those agents will remain a therapy of choice for the immediate future. However, for individual patients, the treatment paradigm may be altered and experience may be gained for newer agents. Future developments in disease diagnosis, disease stratification, outcome measures, newer agents, and novel treatment paradigms will no doubt enhance clinicians' ability to optimize outcomes for even more patients with PsA.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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