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# Making the next steps in psoriatic arthritis management: current status and future directions

**Diviya Sritheran and Ying Ying Leung**

***Abstract*:** Psoriatic arthritis (PsA) is a chronic inflammatory condition with articular and extra-articular manifestations: peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail disease. It is associated with cardiovascular comorbidities. It is now recognized as a new entity, different from rheumatoid arthritis and other spondyloarthritis in terms of clinical manifestations, pathogenesis, and response to therapies. Anti-tumor necrosis factors (anti-TNFs) have demonstrated clinical efficacies exceeding that of conventional disease modifying antirheumatic drugs (DMARDs). The current treatment paradigms recommend early diagnosis and treatment, and a strategic and target orientated approach, aiming at a low disease activity status. New understanding in the immunopathogenesis of PsA has led to new treatment targets. This review addresses the evidence of current treatment for each of the domains as an aid to the clinician managing these patients in the clinic. Some new therapeutic targets are presented. We highlight the importance of development and validation in outcome measures, including that of composite scores that capture various disease domains that will facilitate future clinical trials to inform the best treatment.

***Keywords:*** disease modifying antirheumatic drug, psoriatic arthritis, treatment, tumor necrosis factor inhibitors

## Introduction

Psoriatic arthritis (PsA) is increasingly considered a unique disease entity that is different from rheumatoid arthritis (RA) and other spondyloarthritis (SpA) in terms of clinical manifestation, pathogenesis, response to treatment and prognosis. It is a serious condition that leads to joint destruction, disability [Gladman *et al.* 1990] and impaired quality of life [Husted *et al.* 2001; Leung *et al.* 2008] and even increased mortality [Gladman *et al.* 1998]. PsA has a wide spectrum of manifestation and a variable clinical course. Apart from the skin and nails, it affects the joints, synovial sheaths of tendons, entheses, soft tissue of the digits (dactylitis) and the axial skeleton. The increased prevalence of metabolic syndrome, type 2 diabetes mellitus, obesity, hyperlipidemia, hypertension and cardiovascular disease among PsA patients is well described [Mallbris *et al.* 2006; Zhu *et al.* 2012].

Over the past decade, the management of PsA has advanced with earlier diagnosis, validation of outcome measures for different manifestations, development of target of treatment and new modalities of therapeutic agents. In this article, we highlight the progress on PsA diagnosis, outcome measures, and treatment strategies and modalities.

## Classification criteria and outcome measures

Central to the assessment of effectiveness, any modality of treatment are first, whether one could identify PsA as a homogenous entity that is distinct from other conditions, and second, whether there are valid outcome measures used to quantify disease activity in the different manifestations of the disease. The most commonly used classification criteria previously, the Moll and Wright criteria, have been criticized for their ambiguity that has resulted in a wide variation in the proportion of PsA subtypes from different PsA cohorts, inclusion of different proportion of seronegative

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RA and insensitive in classifying patients with early PsA [Helliwell and Taylor, 2005]. In 2006, the CLASsification of Psoriatic ARthritis (CASPAR) criteria were developed from prospective clinical and radiological data in multiple centers [Taylor *et al.* 2006]. The CASPAR criteria are more specific and sensitive, and universally accepted. Studies have established that the CASPAR criteria can identify patients with early disease [Chandran *et al.* 2007; Coates *et al.* 2012; van den Berg *et al.* 2012] and different ethnicities [Leung *et al.* 2010].

There was a general lack of accurate and well validated instruments to measure the clinical outcomes in PsA as most of the instruments were 'borrowed' from other kinds of arthritis [Mease *et al.* 2005a; Wong *et al.* 2012]. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has proposed a core set of six domains of health to be included in randomized clinical trials (RCTs) and observational studies regarding PsA: joints, skin, pain, patient global assessment, physical function, and health-related quality of life. These were endorsed by the Outcome Measures in Rheumatology (OMERACT) [Gladman *et al.* 2007b]. In the last decade, there has been substantial effort in validating PsA-specific outcome measures [Healy and Helliwell, 2008; McKenna *et al.* 2004; Wajed *et al.* 2014; Gossec *et al.* 2014], although there are heterogeneity in reporting outcomes and there is no consensus regarding areas like the number of joints to assess and instruments for dactylitis and enthesitis [Palominos *et al.* 2012]. International collaborative efforts have been put up to develop composite measures that capture all aspects of this complex disease with different domains into a single score that represent 'PsA activity' and also to serve as a responder index [Coates *et al.* 2014]. The concept is similar to the development of Disease Activity Score in 28 joints (DAS28) for RA. While there is no single measure that is universally accepted [Her and Kavanaugh, 2014], the field has generally accepted minimal disease activity (MDA) as a treatment target [Coates *et al.* 2010]. Studies have shown that 96% of subjects who achieved MDA had no radiographic progression of disease in long term [Coates and Helliwell, 2010].

## Current treatment guidelines

A new strategic approach in treatment for PsA has been gaining acceptance within the field. It includes: (1) early diagnosis and treatment; (2) low disease activity state as a treatment target; (3) assessment of all domains for the many clinical manifestations of the disease; and (4) frequent measurement of disease activity and adjusting therapies (treat-to-target). The Group for Research and Assessment of Psoriasis and Psoriatric (GRAPPA) and the European League against Rheumatic Diseases (EULAR) has published recommendations for treatment [Ritchlin *et al.* 2009; Gossec *et al.* 2012]. GRAPPA suggested treatment based on the distinct organ involvement (domain), as per peripheral arthritis, skin and nail involvement, enthesitis, dactylitis and axial arthritis. EULAR used an algorithmic approach that focused mainly on peripheral arthritis and suggested considering other manifestations separately. Both emphasize the use of a strategic and target orientated approach, aiming at a low disease activity status. This approach has been supported by a multicenter open-labelled RCT in early PsA, showing better joints, skin and radiographic outcomes in the protocol-driven tight control group using MDA as a treatment target compared with standard of care at the end of 48 weeks [Coates *et al.* 2013].

## Treatment of PsA

To reiterate the target-orientated approach, we describe the treatment options for each of the following domains: peripheral joint disease, axial disease, dactylitis, enthesitis, skin psoriasis (PsO) and nail dystrophy.

### *Peripheral joint disease*

*Non-steroidal anti-inflammatory drugs (NSAIDs).* NSAIDs are often prescribed as part of the management of PsA. The short term (4 week) improvement in tender and swollen joints was demonstrated in a small RCT [Sarzi-Puttini *et al.* 2001], but was not substantiated in another larger trial at 12 week [Kivitz *et al.* 2007]. A Cochrane systematic review suggested that NSAIDs can be used safely with methotrexate (MTX) without an increased risk of side effects [Colebatch *et al.* 2011].

*Corticosteroids.* Systemic corticosteroids are not typically recommended in the treatment of PsO and PsA, unless in discrete circumstances and not for chronic use. There is a concern of pustular psoriasis after systemic corticosteroid withdrawal, though only a few cases had been reported in the literature [Brenner *et al.* 2009]. The use of intra-articular corticosteroids (IACS) is mainly based on

clinical experience rather than clinical trials. From a prospective observational study in 133 PsA patients with polyarthritis who received at least one IACS, clinical response was achieved in 41% of the injected joints, which were associated with the use of MTX or anti-tumor necrosis factor (anti-TNF) agents at the time of injection. Within 12 months, 25.5% of the joints relapsed [Eder *et al.* 2010].

*Disease-modifying antirheumatic drugs.* Despite the fact that disease antirheumatic drugs (DMARDs) are widely used, the evidence base for their effectiveness is not well established. A Cochrane review in 2000 revealed that only parenteral high-dose MTX and sulfasalazine (SSZ) have demonstrated published efficacy, while the high magnitude of the improvement observed in the placebo group suggested that uncontrolled trials should not be used to guide management decisions [Jones *et al.* 2000]. Subsequently, there were several meta-analysis of use of DAMRDs in PsA [Ravindran *et al.* 2008; Ash *et al.* 2012; Acosta Felquer *et al.* 2014].

Although MTX is the most commonly used DMARD in PsA, results from clinical trials are contradictory. Data from small RCTs have shown the efficacy of MTX in treatment of peripheral arthritis and PsO [Black *et al.* 1964; Scarpa *et al.* 2008; Willkens *et al.* 1984]. Yet in the Methotrexate in Psoriatic Arthritis (MIPA) study, where 221 patients were randomized to MTX (15 mg per week) or placebo for 6 months, there were no differences in the Psoriatic Arthritis Response Criteria (PsARC), American College of Rheumatology (ACR) response criteria or DAS28, active joint counts or erythrocyte sedimentation rate (ESR). There were significant differences only in patient and physician global assessment and mean Psoriasis Area and Severity Index (PASI) score [Kingsley *et al.* 2012]. The study was limited by the high dropout rates and the relatively low dose of MTX used. The use of MTX, however, is supported in a recent meta-analysis that evaluated five RCTs and eight nonrandomized observational studies [Ceponis and Kavanaugh, 2010], showing a beneficial effect of MTX in peripheral arthritis, skin and acute phase reactants. In an open-labelled trial that included 115 treatment-naïve PsA patients, MTX monotherapy was compared with MTX plus infliximab (INF). At week 16, 66.7% and 86.3% of patients receiving MTX monotherapy and MTX plus INF, respectively, achieved an ACR 20% improvement criteria (ACR20) response [Baranauskaite *et al.* 2012], illustrating the efficacy of MTX at least in some PsA patients. Despite the controversies, MTX remains the mainstay of treatment for PsA.

SSZ has a larger evidence base of use in PsA compared with the other DMARDs [Clegg *et al.* 1996]. Studies have shown an improvement in PsARC, peripheral arthritis and functional outcome in those taking SSZ compared with controls but no evidence on improvement of axial symptoms or inhibition of radiographic joint damage [Clegg *et al.* 1999].

The efficacy of leflunomide (LEF), an oral pyrimidine synthesis inhibitor, was evaluated in a multicenter RCT ($n$ = 190). A significantly higher proportion of LEF-treated patients achieved the PsARC response at week 24 compared with placebo (59% *versus* 29.7%) [Kaltwasser *et al.* 2004]. In a large prospective, multinational observational study in patients with active PsA ($n$ = 514) who initiated LEF ($n$ = 514), 86.4% of patients achieved a PsARC response at week 24. Significant improvements were observed in tender and swollen joint counts, dactylitis, skin and nail lesions, fatigue and pain [Behrens *et al.* 2013]. The use of LEF in combination with MTX may be associated with elevation of liver function test that requires cautious monitoring [Curtis *et al.* 2010].

*Anti-TNFs.* Anti-TNFs given either alone or with other DMARDs have revolutionized the treatment paradigm in PsA. The clinical efficacies of anti-TNFs exceed that of conventional DMARDs in improving peripheral arthritis, axial arthritis, enthesitis, dactylitis, skin and nails [Antoni *et al.* 2005; Kavanaugh *et al.* 2006, 2007, 2009, 2012, 2013a; Mease *et al.* 2004, 2005b, 2006, 2009; Gladman *et al.* 2007a], and most importantly in inhibiting joint damage and radiographic progression [Goulabchand *et al.* 2014] (Table 1).

The availability of drugs that can slow down or even prevent joint damage further reinforces the importance of early diagnosis and treatment in PsA. There are five anti-TNFs that are approved by the US Food and Drug Administration (FDA) for PsA including infliximab, etanercept, adalimumab, golimumab and the new certolizumab pegol. Indirect evidence from retrospective review of data from RCTs did not suggest significant differences in efficacies and safety between anti-TNFs [Atteno *et al.* 2010; Thorlund *et al.* 2012; Fénix-Caballero *et al.* 2013], although there has been no head-to-head comparison. The efficacy

**Table 1.** Summary of efficacies of biological DMARDs and apremilast in psoriatic arthritis (PsA).

| Drug/ trial/ dosage | Follow up | Sample size | ACR20 | ACR50 | ACR70 | PsARC | PASI75 | No radiographic progression at 24 months (%): treatment *versus* placebo |
|---|---|---|---|---|---|---|---|---|
| Infliximab/ IMPACT Kavanaugh *et al.* [2006, 2007]; Antoni *et al.* [2005] 5 mg/kg every 8 weeks | Week 14 | 200 | 58 | 36 | 15 | 77 | 64 | 90 *versus* 78 |
| | Week 24 | 200 | 54 | 41 | 27 | 70 | 60 | |
| | Week 54 | 173 | 59 | 37 | 22 | 74 | 50 | |
| | Week 98 | 104 | 62 | 45 | 45 | 52 | 64 | |
| Etanercept Mease *et al.* [2004, 2006] 25 mg twice a week | Week 12 | 205 | 59 | 40 | 15 | 72 | 38 | 90.1 *versus* 68.6 |
| | Week 24 | 205 | 50 | 40 | 14 | 70 | 40 | |
| | Week 48 | 169 | 64 | 44 | 23 | 80 | 40 | |
| Adalimumab/ ADEPT Mease *et al.* [2005b, 2009; Gladman *et al.* [2007a] 40 mg every 15 days | Week 12 | 313 | 58 | 36 | 20 | 62 | 49 | 91.0 *versus* 71.1 |
| | Week 24 | 313 | 57 | 39 | 23 | 60 | 59 | |
| | Week 48 | 281 | 59 | 43 | 28 | 66 | 59 | |
| | Week 104 | 281 | 57 | 45 | 30 | 64 | 58 | |
| Golimumab/ GO-REVEAL Kavanaugh *et al.* [2009, 2012, 2013a] 50 mg every 4 weeks | Week 14 | 405 | 51 | 30 | 15 | 73 | 40 | 78.8 *versus* 62.8 |
| | Week 24 | 405 | 52 | 30 | 18 | 70 | 56 | |
| | Week 52 | 360 | 67 | 49 | 36 | – | 62 | |
| | Week 104 | 335 | 67 | 47 | 29 | – | 86 | |
| Certolizumab / RAPID-PsA Mease *et al.* [2014a] 200 mg every 2 weeks, 400 mg every 4 weeks | Week 12 | 138 | 58 | 36 | 25 | – | 47 | 94 *versus* 80 |
| | Week 24 | 138 | 64 | 44 | 28 | 78 | 62 | |
| | Week 12 | 135 | 52 | 33 | 13 | – | 47 | 90 *versus* 80 |
| | Week 24 | 135 | 56 | 40 | 24 | 77 | 61 | |
| Ustekinumab/ PSUMMIT-1 McInnes *et al.* [2013] 45 mg every 12 weeks combined with 90 mg every 12 weeks | Week 24 | 615 | 39 | 27 | 12 | – | 65 | – |
| | Week 52 | | 62 | 37 | 22 | | 74 | |
| | Week 100 | | 62 | 43 | 23 | | 78 | |
| Ustekinumab/ PSUMMIT-2 Ritchlin *et al.* [2014] 45 mg every 12 weeks combined with 90mg every 12 weeks | Week 24 | 312 | 44 | 20 | NS | – | 51 | – |

*(Continued)*

**Table 1.** (Continued)

| Drug/ trial/ dosage | Follow up | Sample size | ACR20 | ACR50 | ACR70 | PsARC | PASI75 | No radiographic progression at 24 months (%): treatment *versus* placebo |
|---|---|---|---|---|---|---|---|---|
| Apremilast/ PALACE 1 Kavanaugh *et al.* [2014b] 20 mg bid/ 30 mg bid (refractory to DMARDs/ biologics) | Week 16<br>Week 52<br>Week 104 | 504<br>504<br>198 | 30/38<br>63/55<br>61/66 | 16/16<br>25/25<br>30/36 | 6.0/4.2<br>15/14<br>16/20 | –<br>–<br>– | 21/22<br>25/37<br>– | – |
| Apremilast/ PALACE 2 Cutolo *et al.* [2013] 20 mg bid/ 30 mg bid (refractory to DMARDs/ biologics) | Week 16<br>Week 52 | 484 | 37/32<br>53/53 | 15/11<br>27/19 | 3.7/1.2<br>10/6.8 | –<br>– | 19/22<br>27/39 | – |
| Apremilast/ PALACE 3 Edwards *et al.* [2014] 20 mg bid/ 30 mg bid (concurrent skin psoriasis) | Week 16<br>Week 52 | 505 | 28/ 41<br>56/63 | 12/ 15<br>25/ 30 | 4.7/3.6<br>9.2/10.4 | –<br>– | 21/22<br>29/39 | – |
| Apremilast/ PALACE 4 Wells *et al.* [2013] 20 mg bid/ 30mg bid (DMARDs naïve) | Week 16<br>Week 52 | 529 | 28/31<br>53/59 | 11/11<br>27/32 | 4.0/4.0<br>14/18 | –<br>– | – | – |

ACR20, 20% response to American College of Rheumatology criteria; ACR50, 50% response to ACR criteria; ACR70, 70% response to ACR criteria; Adalimumab Effectiveness in Psoriatic Arthritis Trial; ADEPT, GO-REVEAL, Golimumab-A Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis; anti-TNF, tumor necrosis factor inhibitor; bid, twice daily; DMARDs, disease-modifying antirheumatic drugs; IMPACT, Infliximanb Multinational Psoriatic Arthritis Controlled Trial; NS, not significantly different from placebo; PALACE, psoriatic arthritis long-term assessment of clinical efficacy; PsARC, Psoriatric Arthritis Response Criteria; PASI75, Psoriasis Area and Severity Index 75; RAPID-PsA, Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis, 24-week results of a phase III double-blind randomized placebo-controlled study.

of the newly approved certolizumab pegol has been evaluated in the RAPID-PsA study. A significant higher rate of ACR20 response at week 12 was shown in the treatment group than in placebo [Mease *et al.* 2014a] (Table 1). Similarly, there were better ACR50, ACR70, PsARC response rates, enthesitis, dactylitis, nail lesions and physical function in the treatment group.

### *Axial disease*

Axial PsA is distinct from ankylosing spondylitis (AS) in many ways. These includes reduced male predominance, asymmetrical distribution of marginal and paramarginal syndesmophytes, scattered involvement along the axial skeleton (compared with predominant sacroiliitis in AS) and reduced association with the HLA-B27 allele [Scarpa *et al.* 1988; Helliwell *et al.* 1998]. Although axial PsA seem to be less symptomatic [Leung *et al.* 2008; Thumboo *et al.* 1997] and have better preservation of spinal mobility [Leung *et al.* 2011], recent observational data suggest that the limitation in functional capacity and quality of life is similar to AS [Pérez Alamino *et al.* 2011]. The health burden of axial PsA may be higher than peripheral PsA

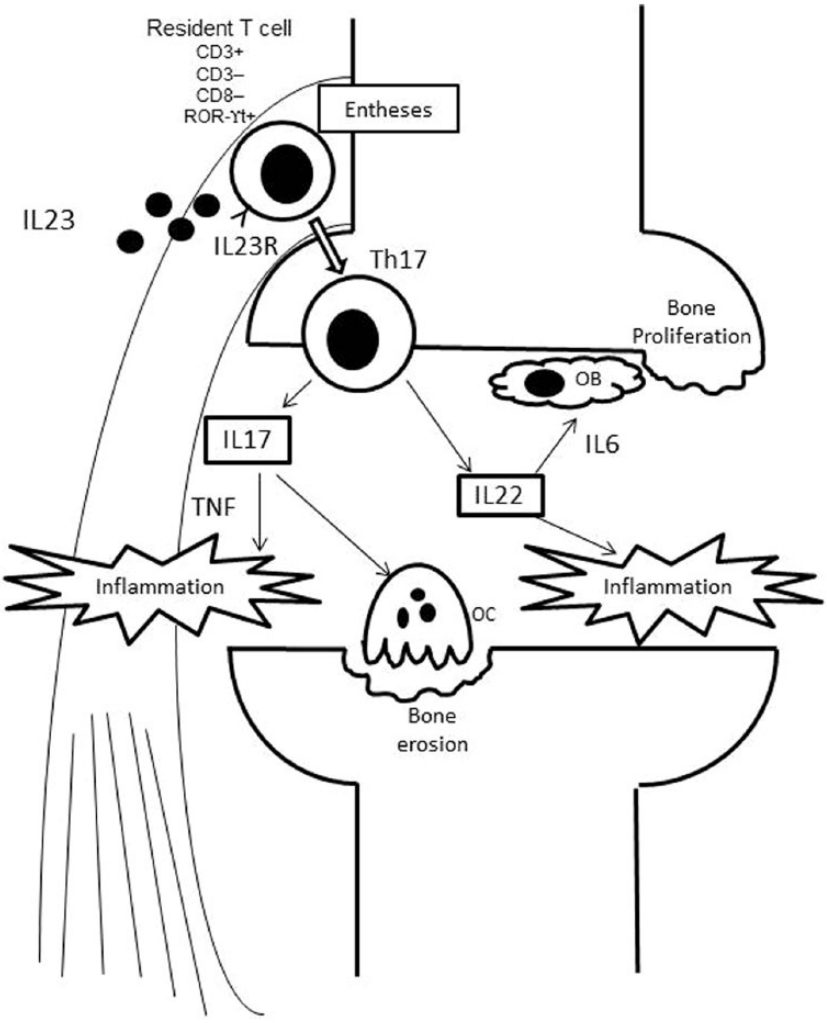


**Figure 1.** Pathogenesis of resident entheseal T cells in psoriatic arthritis.
The resident T cells within the entheses, expressing RORγt receptors can be stimulated by IL23, and further secrete IL17 and IL22. IL22 enhances IL6 causing inflammation; it also activates osteoblasts leading to bone proliferation. IL17 mediates downstream TNF and cytokines, leading to inflammation and bone erosion.
IL, interleukin; IL23R, interleukin 23 receptor; OB, osteoblast; OC, osteoclast; TNF, tumor necrosis factor.

[Zhu *et al.* 2010; Zink *et al.* 2006]. Knowledge gaps exist in the current understanding of axial PsA. There is no formal effect to identify and validate the PsA axial subset, making treatments evaluation specifically for 'axial PsA' difficult to initiate. GRAPPA, by consensus, adopts the Assessment of SpondyloArthritis International Society (ASAS) recommendation guideline for the management of axial spondyloarthritis [van der Heijde *et al.* 2011]. DMARDs are in general not useful for axial PsA and evidence is in support of the use of anti-TNFs [Nash *et al.* 2014].

### *Enthesitis*

Enthesitis is the inflammation at sites where tendons, ligaments and joint capsules attach to bone, and may be the origin of PsA pathogenesis [Benjamin and McGonagle, 2001]. Although local glucocorticoid injection in enthesitis is commonly used, the evidence that support its use is not well established. A systematic review and meta-analysis on controlled studies of local glucocorticoid injections in tendinopathy (not limited to PsA enthesitis) found broadly negative effects on tendon healing, weakened mechanical properties and possible long-term harm to tendon tissue, despite the short-term pain relief in a few studies [Dean *et al.* 2014]. Different clinical trials have used different instrument for enthesitis outcomes. Individual anti-TNF agents have shown effectiveness for enthesitis, with moderate effect sizes for golimumab [Kavanaugh *et al.* 2009] and certolizumab [Mease *et al.* 2014a] and significant

improvement for infliximab [Antoni *et al.* 2005. Based on limited clinical trial data, ustekinumab and apremilast are also effective for enthesitis in PsA [Orbai *et al.* 2014].

### *Dactylitis*

Dactylitis is the hallmark feature of PsA and is counted as an active joint. However, there is a dearth of evidence for treatment. The most commonly used therapies, NSAIDs and local corticosteroid injections, have not been formally assessed. A systematic review included 29 studies that assessed dactylitis as an outcome measure noted again the heterogeneity of outcome measures that ranges from simple count of dactylitis digits to imaging scores. There is also large variability in study design. In general, only biological agents such as ustekinumab, certolizumab and infliximab were likely to be efficacious with effect sizes ranges from 0.29 to 0.50 [Rose *et al.* 2014]. Looking forward, it is important to have quantifiable outcome measures (both clinical and/or imaging indexes) and assessing dactylitis as a primary outcome in trials to determine the most appropriate treatment.

### *PsO*

Most PsA patients have PsO skin lesions. There are numerous guidelines and recommendations for skin management based on multiple clinical trials in patients with PsO [Hsu *et al.* 2012; Langley *et al.* 2012]. From observational study, the severity of PsO was associated with risk of PsA [Wilson *et al.* 2009; Soltani-Arabshahi *et al.* 2010; Haroon *et al.* 2013], PsA patients may have relatively mild skin disease. However, it has been observed that the mean PASI was low among reported PsA cohorts in different parts of the world [Gladman and Chandran, 2011; Leung *et al.* 2014a], as well as patients recruited to RCTs for biologics studies. This limits the direct extrapolation of PsO treatment results to PsA patients with skin PsO. For instance, the milder the skin PsO, the more difficult it is to use the common instruments (e.g. PASI) to detect difference or treatment response. It is also important to note PSAI and many other instruments are not developed on a metric scale, which introduce systematic bias to the studies that included patients with mild skin disease [Leung *et al.* 2014b]. A systematic review by GRAPPA, which included 25 studies, revealed both DMARDs (MTX, LEF, cyclosporine A) and biologics (mainly anti-TNFs) have some efficacy as therapy for skin PsO [Boehncke *et al.* 2014]. Looking forward, it will be important to develop appropriate outcome measures on metric scale to be used in clinical trials.

### *Cardiovascular comorbidities*

Both PsO and PsA patients have increased cardiovascular (CV) comorbidities (type II diabetes mellitus, hyperlipidemia, hypertension, heart failure, ischemic heart disease and cerebrovascular disease), subclinical atherosclerosis, and incident CVS events [Ramonda *et al.* 2011; Jamnitski *et al.* 2013; Zhu *et al.* 2012]. From registry data, PsA has a higher prevalence of all the CVS comorbidities compared with PsO [Husted *et al.* 2011]. The systemic inflammation of PsO or PsA has been postulated to increase insulin resistance, oxidative stress and endothelial cell dysfunction, and thus the development of atherosclerosis.

Annual assessment of CVS risk using national guidelines is recommended for all patients with PsA. Any CVS risk factors identified including smoking habit, systolic blood pressure and lipid (cholesterol and high-density lipoprotein cholesterol levels) and type II diabetes should be managed appropriately. Statins, angiotensin converting enzyme inhibitors and/or angiotensin II blockers are the preferred treatment options due to their potential anti-inflammatory effects. Prescribing cyclooxygenase-2 (COX2) inhibitors and most NSAIDs in patients with a documented CV disease or in the presence of CV risk factors should be cautious. It remains controversial whether treatment of PsA with anti-TNFs may reduce atherosclerosis. In a prospective study in 32 PsA patients, there was significant progression of ultrasonographic carotid intimal thickness (IMT), which is a surrogate for CV disease, despite treatment with anti-TNF for 2 years, although beneficial effects in the arterial remodeling profiles were demonstrated (increase in serum TNF-$\alpha$ levels and reduction in osteoprotegerin) [Ramonda *et al.* 2014]. There are other studies that show treatment with anti-TNFs may reduce carotid IMT in PsA patients compared with those treated with conventional DMARDs [Tam *et al.* 2011; Di Minno *et al.* 2011]. Due to the small absolute number of CV events in studies, there is currently limited evidence to suggest systemic therapies with conventional or biological DMARDs are associated with a decrease in CV risk in PsA. It highlighted the need for larger, prospective, adequately controlled and powered

studies to address the protective effect of treatment [Roubille *et al.* 2015; Ogdie *et al.* 2014]. Based on evidence established mainly in RA, EULAR has developed recommendations for CV risk management in patients with inflammatory arthritis that encompass PsA [Peters *et al.* 2010]. The association between inflammation and atherosclerosis in patients with inflammatory arthritis is recognized and aggressive suppression of disease activity or inflammation is recommended to lower the CV risk.

## New therapeutic targets and therapies

Despite the advances in therapy for PsA with anti-TNFs, there remain many patients who fail to respond and lose efficacy over time. In recent years, there has been new understanding of the importance of the T helper 17 cells (TH17) lineage of T cells and the related cytokines, interleukin (IL) 17 and IL23 that modify the innate immunity and play major roles in immunopathogenesis of SpA. In a landmark study, Sherlock and colleagues identified a new lineage of T cells resident in the enthesis that, in response to IL23, lead to development of entheseal inflammation and local bone erosion and proliferation through a variety of effector mediators, including IL17 and IL22 (Figure 1) [Sherlock *et al.* 2012]. This has led to a new therapeutic target for PsA beyond anti-TNFs.

### *Ustekinumab*

Ustekinumab is a human monoclonal antibody (mAb) directed against the p-40 subunit of IL12 and IL23. It was approved by the FDA in 2013 for use in PsO and PsA based on two phase III multicenter, randomized, double-blind, placebo-controlled trials known as PSUMMIT I and PSUMMIT II (Table 1). In PSUMMIT I, PsA patients with no prior exposure to anti-TNFs received ustekinumab 45 and 90 mg, respectively, and 42% and 50% achieved an ACR20 response at week 24 [McInnes *et al.* 2013] and responses were sustained up to 108 weeks [Kavanaugh *et al.* 2014c]. In PSUMMIT II, which included PsA patients with prior exposure to anti-TNFs, more ustekinumab-treated (43.8% combined) than placebo-treated (20.2%) patients achieved ACR20 at week 24 and clinical responses were sustained at week 52 [Ritchlin *et al.* 2014]. Ustekinumab also improved dactylitis, enthesitis and skin PsO as measured by PASI75. Integrated analysis of combined radiographic data from PSUMMIT-1 and PSUMMIT-2 showed significantly inhibition of radiographic progression of joint damage ustekinumab treated patients [Kavanaugh *et al.* 2014d]. Ustekinumab was safe and well tolerated.

### *IL17 inhibitors*

IL17 is produced by the unique TH17 cells and plays a key role in the pathogenesis of PsO and PsA. There are a number of IL17 inhibitors in phase III clinical trials for PsA. Secukinumab and ixekizumab are mAb against IL17A and brodalumab is a mAb against the IL17 receptor A (IL17RA). They have demonstrated significant improvement in skin PsO [Papp *et al.* 2013]; [Leonardi *et al.* 2012; Papp *et al.* 2012]. However, clinical response in joints is modest. A small RCT of secukinumab has shown significant improvement in physical function and C-reactive protein; however, the primary endpoint of ACR20 improvement was not achieved [McInnes *et al.* 2014].

### *Small molecules*

Apremilast is an oral specific phosphodiesterase-4 (PDE-4) inhibitor that regulates inflammatory mediators. Inhibition of PDE-4 leads to increase in intracellular cyclic adenosine monophosphate (cAMP) which, in turn, reduces the expression of inflammatory cytokines such as IL12, IL23, TNF and interferon gamma (IFN-γ) and increases the expression of anti-inflammatory mediators such as IL10. Apremilast was approved by the FDA in March 2014 for the treatment of PsA based on results from four phase III RCTs, PALACE 1–4. Overall, 1493 adults patients with active PsA, with 76% and 22% who had exposure to conventional or biological DMARDs, were enrolled in PALACE 1–3 trials [Kavanaugh *et al.* 2014a; Cutolo, 2013; Edwards *et al.* 2014]. Apremilast improved signs and symptoms, physical function and skin psoriasis compared to placebo (Table 1). Pooled data from PALACE 1-3 trials demonstrated improvements in enthesitis and dactylitis [Gladman *et al.* 2013]. In the PALACE 4 trial, superiority of apremilast over placebo was demonstrated in DMARD naïve PsA patients, suggest that apremilast may be equally effective as monotherapy as in combination with existing DMARDs [Wells, 2013]. The most common adverse reactions reported in clinical trials were diarrhea (12.2%), nausea (10.1%), and headache (8.0%) [Kavanaugh *et al.* 2014a]. Rates of cardiac events,

serious or opportunistic infections, malignancies or laboratory abnormalities were not increased in the apremilast-treated patients. Apremilast was associated with a small rate of weight decrease, which was not dose-dependent, and without apparent association with gastrointestinal adverse effects and any overt clinical sequelae [Mease *et al.* 2014b].

## Conclusion

PsA is a distinct chronic multisystem inflammatory condition associated with several comorbidities and can lead to significant disability and decreased quality of life. Development and validation of classification criteria and outcome measures have facilitated clinical trials to inform treatment response in DMARDs and anti-TNFs therapies. Current treatment paradigms emphasize early diagnosis, early treatment and a strategic treat-to-target approach for the various domains of the disease. Breakthrough in the understanding of immunopathogenesis has led to novel therapies beyond anti-TNFs. Further development and validation in outcome measures, including that of composite scores that capture various disease domains, will help better define outcomes in clinical trials to inform the best treatment.

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## References

Acosta Felquer, M., Coates, L., Soriano, E., Ranza, R., Espinoza, L., Helliwell, P. *et al.* (2014) Drug therapies for peripheral joint disease in psoriatic arthritis: a systematic review. *J Rheumatol* 41: 2277–2285.

Antoni, C., Krueger, G., de Vlam, K., Birbara, C., Beutler, A., Guzzo, C. *et al.* (2005) Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 64: 1150–1157.

Ash, Z., Gaujoux-Viala, C., Gossec, L., Hensor, E., FitzGerald, O., Winthrop, K. *et al.* (2012) A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis* 71: 319–326.

Atteno, M., Peluso, R., Costa, L., Padula, S., Iervolino, S., Caso, F. *et al.* (2010) Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. *Clin Rheumatol* 29: 399–403.

Baranauskaite, A., Raffayová, H., Kungurov, N., Kubanova, A., Venalis, A., Helmle, L. *et al.* (2012) Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study. *Ann Rheum Dis* 71: 541–548.

Behrens, F., Finkenwirth, C., Pavelka, K., Štolfa, J., Šipek-Dolnicar, A., Thaçi, D. *et al.* (2013) Leflunomide in psoriatic arthritis: results from a large European prospective observational study. *Arthritis Care Res* 65: 464–470.

Benjamin, M. and McGonagle, D. (2001) The anatomical basis for disease localisation in seronegative spondyloarthropathy at entheses and related sites. *J Anat* 199: 503–526.

Black, R., O'Brien, W., Vanscott, E., Auerbach, R., Eisen, A., Bunim, J. *et al.* (1964) Methotrexate therapy in psoriatic arthritis; double-blind study on 21 patients. *JAMA* 189: 743–747.

Boehncke, W., Alvarez Martinez, D., Solomon, J. and Gottlieb, A. (2014) Safety and efficacy of therapies for skin symptoms of psoriasis in patients with psoriatic arthritis: a systematic review. *J Rheumatol* 41: 2301–2305.

Brenner, M., Molin, S., Ruebsam, K., Weisenseel, P., Ruzicka, T., Prinz, J. *et al.* (2009) Generalized pustular psoriasis induced by systemic glucocorticosteroids: four cases and recommendations for treatment. *Br J Dermatol* 161: 964–966.

Ceponis, A. and Kavanaugh, A. (2010) Use of methotrexate in patients with psoriatic arthritis. *Clin Exp Rheumatol* 28(5 Suppl. 61): S132–S137.

Chandran, V., Schentag, C. and Gladman, D. (2007) Sensitivity of the classification of psoriatic arthritis criteria in early psoriatic arthritis. *Arthritis Rheum* 57: 1560–1563.

Clegg, D., Reda, D. and Abdellatif, M. (1999) Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondylarthropathies: a Department of Veterans Affairs cooperative study. *Arthritis Rheum* 42: 2325–2329.

Clegg, D., Reda, D., Mejias, E., Cannon, G., Weisman, M., Taylor, T. *et al.* (1996) Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum* 39: 2013–2020.

Coates, L., Conaghan, P., Emery, P., Green, M., Ibrahim, G., MacIver, H. *et al.* (2012) Sensitivity and specificity of the classification of psoriatic arthritis criteria in early psoriatic arthritis. *Arthritis Rheum* 64: 3150–3155.

Coates, L., FitzGerald, O., Mease, P., Gladman, D., Strand, V., Goel, N. *et al.* (2014) Development of a disease activity and responder index for psoriatic arthritis–report of the Psoriatic Arthritis Module at OMERACT 11. *J Rheumatol* 41: 782–791.

Coates, L., Fransen, J. and Helliwell, P. (2010) Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis* 69: 48–53.

Coates, L. and Helliwell, P. (2010) Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. *Arthritis Care Res* 62: 965–969.

Coates, L., Navarro-Coy, N., Brown, S., Brown, S., McParland, L., Collier, H. *et al.* (2013) The TICOPA protocol (TIght COntrol of Psoriatic Arthritis): a randomised controlled trial to compare intensive management *versus* standard care in early psoriatic arthritis. *BMC Musculoskelet Disord* 14: 101.

Colebatch, A., Marks, J. and Edwards, C. (2011) Safety of non-steroidal anti-inflammatory drugs, including aspirin and paracetamol (acetaminophen) in people receiving methotrexate for inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis). *Cochrane Database System Rev* CD008872.

Curtis, J., Beukelman, T., Onofrei, A., Cassell, S., Greenberg, J., Kavanaugh, A. *et al.* (2010) Elevated liver enzyme tests among patients with rheumatoid arthritis or psoriatic arthritis treated with methotrexate and/or leflunomide. *Ann Rheum Dis* 69: 43–47.

Cutolo, M., Myerson, G., Fleischmann, R., San, U. and Diego, C. (2013) Long term (52 week) results of a phase randomized, controlled trial of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis (PALACE 2). *Arthritis Rheum* 65(Suppl.): abstract 815.

Dean, B., Lostis, E., Oakley, T., Rombach, I., Morrey, M., Carr, A. *et al.* (2014) The risks and benefits of glucocorticoid treatment for tendinopathy: a systematic review of the effects of local glucocorticoid on tendon. *Semin Arthritis Rheum* 43: 570–576.

Di Minno, M., Iervolino, S., Peluso, R., Scarpa, R., Di Minno, G. CaRRDs study group *et al.* (2011) Carotid intima-media thickness in psoriatic arthritis: differences between tumor necrosis factor-α blockers and traditional disease-modifying antirheumatic drugs. *Arterioscler Thromb Vasc Biol* 31: 705–712.

Eder, L., Chandran, V., Ueng, J., Bhella, S., Lee, K., Rahman, P. *et al.* (2010) Predictors of response to intra-articular steroid injection in psoriatic arthritis. *Rheumatology*, 49: 1367–1373.

Edwards, C., Blanco, F., Crowley, J., Hu, C., Stevens, R., Birbara, C. *et al.* (2013) Long-term (52-week) results of a phase 3, randomized, controlled trial of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement (PALACE 3). *Arthritis Rheum* 65: S132

Fénix-Caballero, S., Alegre-del Rey, E., Castaño-Lara, R., Puigventós-Latorre, F., Borrero-Rubio, J. and López-Vallejo, J. (2013) Direct and indirect comparison of the efficacy and safety of adalimumab, etanercept, infliximab and golimumab in psoriatic arthritis. *J Clin Pharm Ther* 38: 286–293.

Gladman, D. and Chandran, V. (2011) Observational cohort studies: lessons learnt from the University of Toronto Psoriatic Arthritis Program. *Rheumatology* 50: 25–31.

Gladman, D., Farewell, V., Wong, K. and Husted, J. (1998) Mortality studies in psoriatic arthritis: results from a single outpatient center. II. Prognostic indicators for death. *Arthritis Rheum* 41: 1103–1110.

Gladman, D., Mease, P., Ritchlin, C., Choy, E., Sharp, J., Ory, P. *et al.* (2007a) Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. *Arthritis Rheum* 56: 476–488.

Gladman, D., Mease, P. and Kavanaugh, A. (2013) Apremilast, an oral phosphodiesterase 4 inhibitor, is associated with long-term (52-week) improvements in enthesitis and dactylitis in patients with psoriatic arthritis: pooled results from three phase 3, randomized controlled trials. *Arthritis Rheum* 65(Suppl. 10): 816.

Gladman, D., Mease, P., Strand, V., Healy, P., Helliwell, P., Fitzgerald, O. *et al.* (2007b) Consensus on a core set of domains for psoriatic arthritis. *J Rheumatol* 34: 1167–1170.

Gladman, D., Stafford-Brady, F., Chang, C., Lewandowski, K. and Russell, M. (1990) Longitudinal study of clinical and radiological progression in psoriatic arthritis. *J Rheumatol* 17: 809–812.

Gossec, L., de Wit, M., Kiltz, U., Braun, J., Kalyoncu, U., Scrivo, R. *et al.* (2014) A patient-derived and patient-reported outcome measure for assessing psoriatic arthritis: elaboration and

preliminary validation of the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire, a 13-country EULAR initiative. *Ann Rheum Dis* 73: 1012–1019.

Gossec, L., Smolen, J., Gaujoux-Viala, C., Ash, Z., Marzo-Ortega, H., van der Heijde, D. *et al.* (2012) European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis* 71: 4–12.

Goulabchand, R., Mouterde, G., Barnetche, T., Lukas, C., Morel, J., Combe, B. *et al.* (2014) Effect of tumour necrosis factor blockers on radiographic progression of psoriatic arthritis: a systematic review and meta-analysis of randomised controlled trials. *Ann Rheum Dis* 73: 414–419.

Haroon, M., Kirby, B. and FitzGerald, O. (2013) High prevalence of psoriatic arthritis in patients with severe psoriasis with suboptimal performance of screening questionnaires. *Ann Rheum Dis* 72: 736–740.

Healy, P. and Helliwell, P. (2008) Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. *Arthritis Rheum* 59: 686–691.

Helliwell, P., Hickling, P. and Wright, V. (1998) Do the radiological changes of classic ankylosing spondylitis differ from the changes found in the spondylitis associated with inflammatory bowel disease, psoriasis and reactive arthritis? *Ann Rheum Dis* 57: 135–140.

Helliwell, P. and Taylor, W. (2005) Classification and diagnostic criteria for psoriatic arthritis. *Ann Rheum Dis* 64(Suppl. 2): ii3–ii8.

Her, M. and Kavanaugh, A. (2014) A review of disease activity measures for psoriatic arthritis: what is the best approach? *Expert Rev Clin Immunol* 10: 1241–1254.

Hsu, S., Papp, K., Lebwohl, M., Bagel, J., Blauvelt, A., Duffin, K. *et al.* (2012) Consensus guidelines for the management of plaque psoriasis. *Arch Dermatol* 148: 95–102.

Husted, J., Gladman, D., Farewell, V. and Cook, R. (2001) Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. *Arthritis Rheum* 45: 151–158.

Husted, J., Thavaneswaran, A., Chandran, V., Eder, L., Rosen, C., Cook, R. *et al.* (2011) Cardiovascular and other comorbidities in patients with psoriatic arthritis: a comparison with patients with psoriasis. *Arthritis Care Res* 63: 1729–1735.

Jamnitski, A., Symmons, D., Peters, M., Sattar, N., McInnes, I., McIinnes, I. *et al.* (2013) Cardiovascular comorbidities in patients with psoriatic arthritis: a systematic review. *Ann Rheum Dis* 72: 211–216.

Jones, G., Crotty, M. and Brooks, P. (2000) Interventions for psoriatic arthritis. *Cochrane Database Syst Rev* CD000212.

Kaltwasser, J., Nash, P., Gladman, D., Rosen, C., Behrens, F., Jones, P. *et al.* (2004) Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum* 50: 1939–1950.

Kavanaugh, A., Antoni, C., Gladman, D., Wassenberg, S., Zhou, B., Beutler, A. *et al.* (2006) The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. *Ann Rheum Dis* 65: 1038–1043.

Kavanaugh, A., Cutolo, M., Mease, P., Gladman, D., Adebajo, A., Gomez-Reino, J. *et al.* (2014a) Apremilast, an oral phosphodiesterase 4 inhibitor, is associated with long-term (52-week) improvement in measures of disease activity in patients with psoriatic arthritis: results from 3 phase 3, randomized, controlled trials. *Arthritis Rheum* 66(Suppl. 11): abstract 548.

Kavanaugh, A., Krueger, G., Beutler, A., Guzzo, C., Zhou, B., Dooley, L. *et al.* (2007) Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. *Ann Rheum Dis* 66: 498–505.

Kavanaugh, A., McInnes, I., Mease, P., Krueger, G., Gladman, D., Gomez-Reino, J. *et al.* (2009) Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 60: 976–986.

Kavanaugh, A., McInnes, I., Mease, P., Krueger, G., Gladman, D., van der Heijde, D. *et al.* (2013a) Clinical efficacy, radiographic and safety findings through 2 years of golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of the randomised, placebo-controlled GO-REVEAL study. *Ann Rheum Dis* 72: 1777–1785.

Kavanaugh, A., Mease, P., Gomez-Reino, J., Adebajo, A., Wollenhaupt, J., Gladman, D. *et al.* (2014b) Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis* 73: 1020–1026.

Kavanaugh, A., Puig, L. and Gottlieb, A. (2013b) Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 2 year results from a phase multicenter, double-blind, placebo-controlled study. In: Proceedings of the Annual Scientific Meeting of the American College of Rheumatology, 25–30 October, San Diego, abstract L10.

Kavanaugh, A., Puig, L., Gottlieb, A., Ritchlin, C., You, Y., Wang, Y. *et al.* (2014c) Efficacy and safety of ustekinumab in psoriatic arthritis patients with spondylitis and peripheral joint involvement: results from a phase 3, multicenter, double-blind, placebo-controlled study. *Arthritis Rheum* 66(Suppl. 11): abstract 39.

Kavanaugh, A., Ritchlin, C., Rahman, P., Puig, L., Gottlieb, A., Li, S. *et al.* (2014d) Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. *Ann Rheum Dis* 73: 1000–1006.

Kavanaugh, A., van der Heijde, D., McInnes, I., Mease, P., Krueger, G., Gladman, D. *et al.* (2012) Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic and safety results from a phase III, randomized, placebo-controlled trial. *Arthritis Rheum* 64: 2504–2517.

Kingsley, G., Kowalczyk, A., Taylor, H., Ibrahim, F., Packham, J., McHugh, N. *et al.* (2012) A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology* 51: 1368–1377.

Kivitz, A., Espinoza, L., Sherrer, Y., Liu-Dumaw, M. and West, C. (2007) A comparison of the efficacy and safety of celecoxib 200 mg and celecoxib 400 mg once daily in treating the signs and symptoms of psoriatic arthritis. *Semin Arthritis Rheum* 37: 164–173.

Langley, R., Saurat, J., Reich, K. and Nail Psoriasis Delphi Expert Panel (2012) Recommendations for the treatment of nail psoriasis in patients with moderate to severe psoriasis: a dermatology expert group consensus. *J Eur Acad Dermatol Venereol* 26: 373–381.

Leonardi, C., Matheson, R., Zachariae, C., Cameron, G., Li, L., Edson-Heredia, E. *et al* (2012) Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med* 366: 1190–1199.

Leung, Y., Ho, K., Li, E., Li, M., Kwok, L., Wong, P. *et al.* (2014a) Predictors of functional deterioration in Chinese patients with psoriatic arthritis: a longitudinal study. *BMC Musculoskelet Disord* 15: 284.

Leung, Y., Ho, K., Tam, L., Zhu, T., Kwok, L., Li, T. *et al.* (2011) Evaluation of spinal mobility measurements in predicting axial psoriatic arthritis. *Clin Rheumatol* 30: 1157–1162.

Leung, Y., Png, M., Conaghan, P. and Tennant, A. (2014b) A systematic literature review on the application of Rasch analysis in musculoskeletal disease – a special interest group report of OMERACT 11. *J Rheumatol* 41: 159–164.

Leung, Y., Tam, L., Ho, K., Lau, W., Li, T., Zhu, T. *et al.* (2010) Evaluation of the CASPAR criteria for psoriatic arthritis in the Chinese population. *Rheumatology* 49: 112–115.

Leung, Y., Tam, L., Kun, E. and Li, E. (2008) Impact of illness and variables associated with functional impairment in Chinese patients with psoriatic arthritis. *Clin Exp Rheumatol* 26: 820–826.

Mallbris, L., Ritchlin, C. and Ståhle, M. (2006) Metabolic disorders in patients with psoriasis and psoriatic arthritis. *Curr Rheumatol Rep* 8: 355–363.

McInnes, I., Kavanaugh, A., Gottlieb, A., Puig, L., Rahman, P., Ritchlin, C. *et al.* (2013) Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 382: 780–789.

McInnes, I., Sieper, J., Braun, J., Emery, P., van der Heijde, D., Isaacs, J. *et al.* (2014) Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. *Ann Rheum Dis* 73: 349–356.

McKenna, S., Doward, L., Whalley, D., Tennant, A., Emery, P., Veale, D. *et al.* (2004) Development of the PsAQoL: a quality of life instrument specific to psoriatic arthritis. *Ann Rheum Dis* 63: 162–169.

Mease, P., Antoni, C., Gladman, D. and Taylor, W. (2005a) Psoriatic arthritis assessment tools in clinical trials. *Ann Rheum Dis* 64(Suppl. 2): ii49–ii54.

Mease, P., Fleischmann, R., Deodhar, A., Wollenhaupt, J., Khraishi, M., Kielar, D. *et al.* (2014a) Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a phase 3 double-blind randomised placebo-controlled study (RAPID-PsA) *Ann Rheum Dis* 73: 48–55.

Mease, P., Gladman, D., Ritchlin, C., Ruderman, E., Steinfeld, S., Choy, E. *et al.* (2005b) Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 52: 3279–3289.

Mease, P., Gladman, D., Kavanugh, A., Adewale, O., Gomez-Reino, J., Wollenhaupt, J. *et al.* (2014b) Change in weight from baseline with apremilast, an oral phosphodiesterase 4 inhibitor: pooled results from 3 phase 3, randomized, controlled trials. *Arthritis Rheum* 66(Suppl. 11): abstract 1579.

Mease, P., Kivitz, A., Burch, F., Siegel, E., Cohen, S., Ory, P. *et al.* (2006) Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. *J Rheumatol* 33: 712–721.

Mease, P., Kivitz, A., Burch, F., Siegel, E., Cohen, S., Ory, P. *et al.* (2004) Etanercept treatment of psoriatic arthritis: safety, efficacy and effect on disease progression. *Arthritis Rheum* 50: 2264–2272.

Mease, P., Ory, P., Sharp, J., Ritchlin, C., Van den Bosch, F., Wellborne, F. *et al.* (2009) Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT) *Ann Rheum Dis* 68: 702–709.

Nash, P., Lubrano, E., Cauli, A., Taylor, W., Olivieri, I., Gladman, D. *et al.* (2014) Updated guidelines for the management of axial disease in psoriatic arthritis. *J Rheumatol* 41: 2286–2289.

Ogdie, A., Schwartzman, S., Eder, L., Maharaj, A., Zisman, D., Raychaudhuri, S. *et al.* (2014) Comprehensive treatment of psoriatic arthritis: managing comorbidities and extraarticular manifestations. *J Rheumatol* 41: 2315–2322.

Orbai, A., Weitz, J., Siegel, E., Siebert, S., Savage, L., Aydin, S. *et al.* (2014) Systematic review of treatment effectiveness and outcome measures for enthesitis in psoriatic arthritis. *J Rheumatol* 41: 2290–2294.

Palominos, P., Gaujoux-Viala, C., Fautrel, B., Dougados, M. and Gossec, L. (2012) Clinical outcomes in psoriatic arthritis: A systematic literature review. *Arthritis Care Res* 64: 397–406.

Papp, K., Langley, R., Sigurgeirsson, B., Abe, M., Baker, D., Konno, P. *et al.* (2013) Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. *Br J Dermatol* 168: 412–421.

Papp, K., Leonardi, C., Menter, A., Ortonne, J., Krueger, J., Kricorian, G. *et al.* (2012) Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med* 366: 1181–1189.

Pérez Alamino, R., Maldonado Cocco, J., Citera, G., Arturi, P., Vazquez-Mellado, J., Sampaio-Barros, P. *et al.* (2011) Differential features between primary ankylosing spondylitis and spondylitis associated with psoriasis and inflammatory bowel disease. *J Rheumatol* 38: 1656–1660.

Peters, M., Symmons, D., McCarey, D., Dijkmans, B., Nicola, P., Kvien, T. *et al.* (2010) EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 69: 325–331.

Ramonda, R., Lo Nigro, A., Modesti, V., Nalotto, L., Musacchio, E., Iaccarino, L. *et al.* (2011) Atherosclerosis in psoriatic arthritis. *Autoimmun Rev* 10: 773–778.

Ramonda, R., Puato, M., Punzi, L., Rattazzi, M., Zanon, M., Balbi, G. *et al.* (2014) Atherosclerosis progression in psoriatic arthritis patients despite the treatment with tumor necrosis factor-alpha blockers: a two-year prospective observational study. *Joint Bone Spine* 81: 421–425.

Ravindran, V., Scott, D. and Choy, E. (2008) A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis. *Ann Rheum Dis* 67: 855–859.

Ritchlin, C., Kavanaugh, A., Gladman, D., Mease, P., Helliwell, P., Boehncke, W. *et al.* (2009) Treatment recommendations for psoriatic arthritis. *Ann Rheum Dis* 68: 1387–1394.

Ritchlin, C., Rahman, P., Kavanaugh, A., McInnes, I., Puig, L., Li, S. *et al.* (2014) Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis* 73: 990–999.

Rose, S., Toloza, S., Bautista-Molano, W., Helliwell, P. and GRAPPA Dactylitis Study Group (2014) Comprehensive treatment of dactylitis in psoriatic arthritis. *J Rheumatol* 41: 2295–2300.

Roubille, C., Richer, V., Starnino, T., McCourt, C., McFarlane, A., Fleming, P. *et al.* (2015) The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis.* DOI:10.1136/annrheumdis-2014-206624.

Sarzi-Puttini, P., Santandrea, S., Boccassini, L., Panni, B. and Caruso, I. (2001) The role of NSAIDs in psoriatic arthritis: evidence from a controlled study with nimesulide. *Clin Exp Rheumatol* 19(1 Suppl. 22): S17–S20.

Scarpa, R., Oriente, P., Pucino, A., Vignone, L., Cosentini, E., Minerva, A. *et al.* (1988) The clinical spectrum of psoriatic spondylitis. *Br J Rheumatol* 27: 133–137.

Scarpa, R., Peluso, R., Atteno, M., Manguso, F., Spanò, A., Iervolino, S. *et al.* (2008) The effectiveness of a traditional therapeutical approach in early psoriatic arthritis: results of a pilot randomised 6-month trial with methotrexate. *Clin Rheumatol* 27: 823–826.

Sherlock, J., Joyce-Shaikh, B., Turner, S., Chao, C., Sathe, M., Grein, J. *et al.* (2012) IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+CD4-CD8- entheseal resident T cells. *Nat Med* 18: 1069–1076.

Soltani-Arabshahi, R., Wong, B., Feng, B., Goldgar, D., Duffin, K., Krueger, G. *et al.* (2010) Obesity in early adulthood as a risk factor for psoriatic arthritis. *Arch Dermatol* 146: 721–726.

Tam, L., Li, E., Shang, Q., Tomlinson, B., Li, M., Leung, Y. *et al.* (2011) Tumour necrosis factor alpha blockade is associated with sustained regression of carotid intima-media thickness for patients with active psoriatic arthritis: a 2-year pilot study. *Ann Rheum Dis* 70: 705–706.

Taylor, W., Gladman, D., Helliwell, P., Marchesoni, A., Mease, P., Mielants, H. *et al.* (2006) Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 54: 2665–2673.

Thorlund, K., Druyts, E., Aviña-Zubieta, J. and Mills, E. (2012) Anti-tumor necrosis factor (TNF) drugs for the treatment of psoriatic arthritis: an indirect comparison meta-analysis. *Biologics Targets Ther* 6: 417–427.

Thumboo, J., Tham, S., Tay, Y., Chee, T., Mow, B., Chia, H. *et al.* (1997) Patterns of psoriatic arthritis in Orientals. *J Rheumatol* 24: 1949–1953.

Van den Berg, R., van Gaalen, F., van der Helm-van Mil, A., Huizinga, T. and van der Heijde, D. (2012) Performance of classification criteria for peripheral spondyloarthritis and psoriatic arthritis in the Leiden Early Arthritis cohort. *Ann Rheum Dis* 71: 1366–1369.

Van der Heijde, D., Sieper, J., Maksymowych, W., Dougados, M., Burgos-Vargas, R., Landewé, R. *et al.* (2011) 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis* 70: 905–908.

Wajed, J., Helliwell, P., Korendowych, E., Gadsby, K., Oliver, S., Parrish, L. *et al.* (2014) Disease assessment in psoriatic spectrum: a modular approach for use in routine clinical practice. *Ann Rheum Dis* 73: 318–319.

Wells, A., Edwards, C., Adebajio, A., San, U. and Diego, C. (2013) Apremilast in the treatment of DMARD-naïve psoriatic arthritis patients: results of a phase 3 randomized, controlled trial (PALACE 4). In: Proceedings of the Annual Scientific Meeting of the American College of Rheumatology, 25–30 October, San Diego, abstract 1543.

Willkens, R., Williams, H., Ward, J., Egger, M., Reading, J., Clements, P. *et al.* (1984) Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. *Arthritis Rheum* 27: 376–381.

Wilson, F., Icen, M., Crowson, C., McEvoy, M., Gabriel, S., Kremers, H. *et al.* (2009) Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. *Arthritis Rheum* 61: 233–239.

Wong, P., Leung, Y., Li, E. and Tam, L. (2012) Measuring disease activity in psoriatic arthritis. *Int J Rheumatol* 2012: 839425.

Zhu, T., Li, E. and Tam, L. (2012) Cardiovascular risk in patients with psoriatic arthritis. *Int J Rheumatol* 2012: 714321.

Zhu, T., Tam, L., Leung, Y., Kwok, L., Wong, K., Yu, T. *et al.* (2010) Socioeconomic burden of psoriatic arthritis in Hong Kong: direct and indirect costs and the influence of disease pattern. *J Rheumatol* 37: 1214–1220.

Zink, A., Thiele, K., Huscher, D., Listing, J., Sieper, J., Krause, A. *et al.* (2006) Healthcare and burden of disease in psoriatic arthritis. A comparison with rheumatoid arthritis and ankylosing spondylitis. *J Rheumatol* 33: 86–90.