The future of treatment for psoriatic arthritis

Treatment of psoriatic arthritis has tended to follow evidence-based strategies for achieving remission or minimal disease activity in rheumatoid arthritis. However, distinct immunopathogenic, phenotypic and genetic differences exist between these two inflammatory arthritides, suggesting that application of the evidence base acquired in rheumatoid disease to psoriatic arthritis may lead to suboptimal outcomes in psoriatic disease. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis has been instrumental in addressing this issue, and outcome studies concerning composite measures of disease activity and response, as well as therapeutic strategies, are ongoing. This article reviews some of the key findings the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis have reported with suggestions for future treatment strategies, and a summary of new targeted biologic medications that are undergoing clinical trials in psoriatic arthritis.

KEYWORDS: biologic ▪ biosimilar ▪ composite outcome measures ▪ psoriatic arthritis ▪ treatment ▪ treat-to-target

Barry J Sheane[1,2] & Vinod Chandran*[1,2]

[1]Division of Rheumatology, Department of Medicine, University of Toronto, Toronto, ON, Canada
[2]Center for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, 399 Bathurst Street, Toronto, ON M5T 2S8, Canada
**Author for correspondence:*
Tel.: +1 416 603 5192
Fax: +1 416 603 9387
vchandra@uhnresearch.ca

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease associated with psoriasis, and leads to progressive joint damage and disability. It is estimated that approximately 30% of patients with psoriasis have PsA [1]. PsA is classically described as a seronegative spondyloarthropathy with both peripheral and/or axial arthritis; however, other significant musculoskeletal manifestations include enthesitis and dactylitis, which can also cause marked functional impairment.

Treatment of PsA has advanced significantly in the last two decades, particularly with regard to biologically targeted treatments, such as the TNF inhibitors (TNFi). However, treatment regimens used in PsA have tended to follow those initially applied to rheumatoid arthritis (RA). This may be explained by the fact that peripheral arthritis in PsA has similar clinical characteristics to RA. Furthermore, the incidence and prevalence of RA may be significantly greater than that of PsA, and recruitment for clinical trials is less onerous as a result. While there are commonalities in the immunopathogenesis of both forms of arthritis, there are many genetic, immunologic and phenotypic differences, including gender distribution and extra-articular manifestations. Therefore, the practice of extrapolation and application of results from RA-focused clinical trials to the treatment of patients with PsA is not scientifically robust. To address these deficiencies, an international group of rheumatologists and dermatologists with a special interest in psoriatic disease, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), has been established. GRAPPA has been instrumental in directing the psoriatic disease-specific agenda and its work has influenced much of the content of this piece.

This article examines current knowledge regarding treatment of PsA and has identified how this content can influence future treatment-specific research questions. The authors have also presented a summary of the evidence surrounding the efficacy of many of the newer psoriatic medications, including those that have been recently licensed for clinical use and those undergoing clinical trial.

Current treatment recommendations

GRAPPA published treatment recommendations for PsA in 2009 based on evidence from systematic reviews and consensus of 70 rheumatologists and dermatologists with subspecialty expertise in management of psoriatic disease [2]. The group recommended treatment for all aspects of PsA, including peripheral and axial arthritis, skin and nail disease, enthesitis and dactylitis. NSAIDs were recommended for mild peripheral arthritis and disease-modifying antirheumatic drugs (DMARDs), including sulfasalazine (SSZ), leflunomide, methotrexate (MTX) and cyclosporine, for moderate and severe arthritis. TNFi were recommended as second-line treatment after failure of at least one DMARD, but could be considered as first-line therapy in those with poor prognostic indicators (including polyarticular disease,

Future Medicine part of fsg

elevated erythrocyte sedimentation rate (ESR) and radiographic damage). NSAIDs, physiotherapy and sacroiliac joint injection were recommended for mild-to-moderate spinal disease, with TNFi reserved for moderate-to-severe axial involvement. While NSAIDs, physiotherapy and corticosteroid use were recommended for mild enthesitis and DMARDs for moderate disease, there is little evidence to support their use. However, GRAPPA asserts that there is grade A evidence for use of infliximab or etanercept in severe enthesitis. Similarly with dactylitis, grade A evidence exists for use of infliximab, with weaker evidence for NSAID, steroid or DMARD use.

The European League Against Rheumatism (EULAR) published their recommendations for pharmacotherapeutic management of PsA more recently in 2012 [3]; however, these only focused on the musculoskeletal manifestations of the disease. Recommendations were based on available evidence and consensus, similar to the processes employed by GRAPPA.

The group devised a treatment algorithm based on disease response, drug toxicity, the presence of adverse prognostic factors (≥5 active joints, or high functional impairment or joint damage) and the pattern of arthritis (peripheral joints, axial disease and/or enthesitis). Treatment targets were remission, defined as the absence of signs and symptoms, or at least low disease activity. NSAIDs were considered first line and DMARDs as second line, with MTX favored in patients with significant psoriasis and joint disease. In enthesitis and/or dactylitis, or axial disease that has failed to respond to NSAID treatment, TNFi should be considered. The EULAR group suggested that TNFi use should also be considered despite DMARD naivety in those with poor prognostic indicators (as listed above), but acknowledged that this recommendation is eminence rather than evidence based. Failure of a TNFi merits switching to another TNFi.

The EULAR treatment recommendations also highlight areas for future research, including delineating subpopulations of PsA patients who would benefit from specific DMARD medications, identifying DMARDs that work synergistically in combination, developing a PsA-specific tool to measure disease activity, and the need for treatment targets to be defined. This article will explore many of these issues.

Addressing the paucity of quality trial data on traditional DMARDs

There is a notable lack of randomized controlled trials (RCTs) of quality for DMARD treatment in PsA, either alone or in combination, which contrasts with the abundant evidence for DMARD efficacy in RA [3]. As these medications are established and off-patent, it is unlikely that such trials would be proposed by large pharmaceutical companies, given their sizeable investment in the development of targeted, biological treatments, such as TNFi and newer small-molecule inhibitors. For such trials to be conducted, clinical and scientific investigators will be required to initiate the relevant studies.

In order to plan future studies regarding the role of individual and combinations of DMARD therapy, it is important to understand the findings and limitations of the pre-existing studies of therapeutic strategies in PsA.

Methotrexate

Until recently, randomized placebo-controlled trials with MTX were limited to two studies in 1964 and 1984 with 10 and 16 patients in the MTX group, respectively [4,5].

In the Willkens and colleagues' study, the only significant improvement found was in the physician's assessment of disease activity in the MTX group (n = 16), while tender and swollen joint counts were similar in the placebo group (n = 21) [5]. However, the doses of oral MTX administered were relatively small (between 7.5 and 15 mg per week).

To address the paucity of sufficiently powered and blinded RCTs with MTX, the MIPA study was undertaken, comparing 15-mg oral MTX once weekly with placebo in 109 and 112 patients with a relatively low level of clinically detectable disease activity (at least one active joint was required for inclusion in the study, which contrasts with trials of the TNFi which required at least three active joints for study entry) and psoriasis, respectively, over 6 months [6]. DMARD naivety was not a prerequisite for inclusion. The authors found that there was no statistically significant difference in response to MTX compared with placebo using the PsA Response Criteria (PsARC; see below under the 'Sulfasalazine' section for a description), 20% improvement in disease activity as defined by the ACR20, Disease Activity Score in 28 preselected joints (DAS28), ESR, C reactive protein (CRP), pain score or function (Health Assessment Questionnaire [HAQ]); however, both the patient and physician global response assessment and the extent of psoriasis were significantly improved after 6 months. Despite the poor responses reported,

consideration must be made to the low target dose of MTX used and the low level of disease activity allowing entry to the study.

Further studies examining response to doses of MTX between 20 and 25 mg weekly preferably given subcutaneously, and in more aggressive disease, are necessary. Data from a retrospective analysis of MTX use at the University of Toronto Psoriatic Arthritis Clinic (ON, Canada) suggested that the larger doses of MTX used since the 1990s may slow radiographic progression [7]; however, this needs confirmation in randomized, prospective studies. In addition, the effect of MTX in a DMARD-naive population may provide convincing evidence of a disease-modifying effect.

Sulfasalazine

A number of randomized placebo-controlled studies have been conducted with SSZ; however, these studies have failed to convincingly demonstrate a disease-modifying effect, with only pain scores declining significantly with treatment [8,9]. Validated outcome measures of treatment response were not employed in these studies and inclusion criteria for disease activity differed significantly.

Clegg *et al.* reported on a more significant multicenter RCT with SSZ or placebo given to a large PsA population (n = 221) over 36 weeks that included patients with peripheral and axial disease [10]. Treatment response was defined as improvement in at least two of the following four measures: patient and physician self-assessment, joint pain/tenderness score and joint swelling score, with at least one of the measures including a joint score, and worsening in none (later termed the PsARC). Although a significant decrease in ESR in those taking SSZ was noted ($p < 0.01$) and 57.8% of those in the SSZ arm responded to treatment, 44.6% in the placebo group also responded ($p = 0.05$).

Rahman and colleagues examined the effect of SSZ on radiographic progression at 24 months, and clinical response at 12 months (defined as a 50% reduction in the number of actively inflamed joints from baseline) in a retrospective study of PsA patients attending the University of Toronto Psoriatic Arthritis Clinic [11]. A high proportion discontinued the treatment within 3 months of initiation, and at a later date (39 and 60%, respectively) due to adverse effects. While the remaining study population used to analyze clinical and structural effectiveness was small (n = 20 in each group), SSZ was not found to ameliorate disease activity, either in articular or cutaneous disease, nor slow structural damage.

Collectively, these studies suggest that SSZ has a symptomatic effect only and that tolerability is an issue; however, heterogeneity in entry criteria and response outcome measures in these studies must be acknowledged. A prospective RCT addressing those issues would allow a definitive conclusion regarding its role in PsA to be made. Its role in combination strategies also needs to be ascertained.

Leflunomide

TOPAS was a multinational, double-blind, randomized, placebo-controlled trial examining the safety and efficacy of leflunomide in both psoriasis and PsA across nine different countries in 31 clinical sites over 24 weeks [12]. In total, 59% of 95 patients receiving leflunomide responded according to the PsARC by study end compared with 30% of 91 patients in the placebo arm ($p < 0.0001$). Leflunomide-treated patients had a significantly greater response in each of the four PsARC criteria compared with placebo, as well in CRP, HAQ and the modified ACR20, while a mean percentage improvement of 22.4 ± 51.6% in the Psoriasis Area Severity Index (PASI) for leflunomide-treated patients was significantly greater compared with the 2.2 ± 70.4% deterioration for those on placebo ($p = 0.003$). No assessment on axial disease or peripheral radiographic progression was made; however, the potential of leflunomide as an effective treatment for psoriatic disease was clearly demonstrated in this study.

The OSPAL study assessed the effectiveness of leflunomide in daily practice across 161 centers in Europe [13]. Concomitant DMARD therapy was allowed for the duration of the study, with 22% of patients on a DMARD at the time of enrollment. Data were available for analysis on 440 patients at week 24 from a total of 511 patients at the study start point. The authors reported a PsARC response in 86.4% in 440 patients, with significant improvement in psoriasis, dactylitis and nail lesions on physician assessment, and in fatigue and pain on patient assessment ($p < 0.001$ for all measures). Investigators were not blinded to treatment allocation nor was a placebo arm included in the design, suggesting these finding should be received with caution. Nonetheless, the study does suggest that the findings from the TOPAS study are transferrable to routine rheumatology practice in treatment of PsA.

Leflunomide appears to have a disease-modifying effect on peripheral joint disease and possibly cutaneous disease and dactylitis. Future studies in leflunomide, MTX and SSZ should assess their effect in DMARD combination strategies and whether individually or combined, they can halt or reverse radiographic progression and preserve patient function.

Comparative efficacy of DMARDs

The relative efficacy of DMARDs used in PsA has not been adequately established. However, there are a number of small studies that have partially assessed this.

Spadaro *et al.* compared the efficacy of cyclosporine A (CSA) and MTX over a 12 month period in peripheral PsA [14]. Although the study was randomized and controlled, the total study number was small at 35. Despite this, both treatment arms showed significant improvement at both 6 and 12 months in the number of swollen joints, CRP and the PASI, while ESR was only significantly improved in the group receiving MTX.

The comparative efficacy of cyclosporine (n = 36) and SSZ (n = 32) to symptomatic treatment (ST) with NSAIDs, analgesics and/or prednisone in low dose was examined in an open RCT [15]. While the study reported significant improvements in the swollen joint count in the cyclosporine and SSZ groups compared with the third group, the ACR20 and axial disease response did not reveal a significant improvement between SSZ and ST nor between CSA and SSZ. However, CSA use showed a significant improvement in the ACR50 response only when compared with ST ($p = 0.02$). Both CSA and SSZ significantly improved the PASI when compared with ST, while CSA-treated patients had a greater response in PASI compared with SSZ ($p = 0.01$). Limitations in this study were the short period of follow-up, the small sample size and absence of blinding to treatment allocation.

Future studies will need to establish the comparative efficacy of the traditional DMARDs used in PsA, not only for peripheral joint disease, but also for the other musculoskeletal manifestations of the disease, including spondylitis.

TNFi: using current knowledge to plan future studies

'Head-to-head' studies

While an array of TNFi for treating PsA are available, selecting the one that will result in the best clinical response in an individual patient requires prospective 'head-to-head' blinded studies. In doing so predictors of response for each TNFi may become apparent. These studies have not been conducted, although registries such as the British Society of Rheumatology Biologics Register, the Spanish Biobadaser and the Danish Biologics Registry allow comparative analysis of outcome data retrospectively.

Glintborg *et al.* recently published findings from the Danish Biologics Registry pertaining to clinical response and drug survival in those PsA patients that had switched to a second TNFi [16]. Of over 1400 PsA patients prescribed a TNFi, 39% (n = 548) switched to a second TNFi (during a mean of 2.3 years follow-up). The median overall drug survival of the first TNFi was 2.2 years, 1.3 years for the second TNFi and 1.1 years for the third. Response rates, as per the ACR20, were significantly lower in subsequent treatments after the first TNFi, with 47% of first-time TNFi users having an ACR20 by 3–6 months, 22% using a second TNFi, and 18% on a third ($p < 0.05$). Interestingly, the absence of concomitant MTX use predicted an ACR20 response in those who had switched to a second agent (odds ratio: 14.1; 95% CI: 3.4–59.5; $p = 0.0003$). Results from the Danish Biologics Registry published 2 years prior to this study found that concomitant MTX use (odds ratio: 1.7; 95% CI: 1.1–2.6) was predictive of treatment response and with drug survival [17]. The British Society of Rheumatology Biologics Register reported a trend towards better drug survival with concomitant DMARD prescription, while infliximab had a significantly lower drug survival compared with etanercept (hazard ratio: 3.8; 95% CI: 2.0–7.3) [18]. Heiberg *et al.* reporting on data from Biobadaser, found that concomitant MTX use significantly prolonged TNFi drug survival in both PsA and RA, but not in ankylosing spondylitis [19].

Conflicting evidence from these registries confirms that prospective head-to-head trials of the TNFi licensed for use in PsA would be beneficial in a number of regards, including guiding prescribers in choosing the next TNFi after primary or secondary failure, and on strategies to enhance drug survival of the primary TNFi. Furthermore, a head-to-head comparison should allow comparison of efficacy of each of the TNFi on the different components of psoriatic disease, including peripheral and axial joint disease, enthesitis and psoriasis.

TNFi & DMARD combinations

The TNFi have traditionally been prescribed with MTX, based on the results of trial data in RA demonstrating improved efficacy [20]. In PsA, the open-label RESPOND study reported an ACR20, 50 and 70 response of 86, 72.5 and 49%, respectively, for combination MTX and infliximab (n = 57) at week 16 compared with 67, 40 and 19% in those taking MTX alone (n = 58; $p < 0.05$) [21]. There was also a significantly greater response in skin disease and dactylitis to combination treatment.

A number of open-label studies have examined the efficacy and tolerability of CSA combined with TNFi. A combination of CSA and etanercept, compared with MTX and etanercept, was similar in efficacy in achieving a decrease in DAS28 at 3 and 6 months, while CSA/etanercept was more effective in treating cutaneous disease [22]. A combination of adalimumab and CSA was reported to be superior in improving both peripheral and axial disease, psoriasis, nail disease, enthesitis and dactylitis, compared with CSA or adalimumab alone [23].

While caution must be applied in interpretation of data from unblinded trials, these results do signal that combinations of DMARDs with TNFi, other than the standard MTX–TNFi union, require study in blinded, randomized, placebo-controlled trials. While newer targeted therapies are under development, they will undoubtedly be available at significant financial cost to the purchaser. Therefore, the onus is on investigators to explore the outcomes of less expensive DMARD–TNFi combinations.

Role of biosimilars

The patents on a number of the TNFi will expire in the coming years and the development of biological agents similar to the reference products is ongoing around the world, with the intention of providing treatments of, at least, equal efficacy, safety and quality to the existing TNFi [24]. The availability of such agents, termed 'biosimilars', could create large savings for patients, and for health systems that provide such medications free or at reduced cost to patients. However, concern has been raised that variation in the manufacturing processes of these biosimilars may not yield products with the established efficacy or safety of the reference products [25]. Biosimilars need to be developed under comparative processes used for the reference product while being regulated by authorities, such as the EMA and the US FDA [26]. Pharmacokinetic, pharmacodynamic and immunogenic data need to be acquired on all biosimilars, while RCTs with postmarketing surveillance and the establishment of registries are necessary to ensure equivalent efficacy and safety compared with the original product [25,26]. Rheumatologists treating PsA should expect to have access to these agents in the coming years. If equivalent safety and efficacy can be established, affordable biosimilars could transform care of patients with PsA and may allow use of TNFi as first-line treatment in psoriatic disease.

Treatment targets & strategies

'Treating-to-target' in PsA

As the GRAPPA and EULAR treatment recommendations highlight, the targets of treatment have not been defined, nor is the evidence surrounding putative targets extensive. Evidence analyzed retrospectively from the IMPACT and IMPACT2 trials on infliximab versus placebo demonstrated that attainment of minimal disease activity, as defined by Coates *et al.* (which requires the presence of at least five out of the following seven domains: tender joint count ≤1, swollen joint count ≤1, PASI ≤1 or body surface area ≤3%, tender entheseal points ≤1, HAQ score ≤0.5, patient global disease activity visual analogue scale (VAS) score ≤20 and patient pain VAS ≤15 [27]) is associated with a significant reduction in radiographic progression [28], while evidence from the University of Toronto Psoriatic Arthritis Clinic revealed that sustaining minimal disease activity over 12 months resulted in significantly less clinical joint damage [29]. However, prospective studies examining such outcomes are absent. In that regard, an international group of rheumatologists from Europe and North America convened to provide evidence-based recommendations based on a 'treat-to-target' concept that has been successfully employed in other diseases, including RA [30].

After identifying and reviewing the available evidence pertaining to 'treating-to-target' in PsA, the international group published their definitions of the treatment targets in both PsA and ankylosing spondylitis [31]. Clinical remission of the musculoskeletal components of spondyloarthritis (SpA; arthritis, spondylitis, enthesitis and dactylitis) was identified as the main treatment goal, and defined by the authors as the "absence of clinical and laboratory evidence of significant inflammatory disease activity" followed by attainment of minimal disease activity if remission was not achieved [31]; however, the authors noted that, currently,

there is no definitive evidence that remission leads to a better long-term outcome than maintenance of low disease activity. The 'overarching principles' in the application of treatment for SpA, including PsA, include shared decision-making between the patient and rheumatologist, involvement of other specialists relevant to the extra-articular manifestations of SpA, such as dermatologists and gastroenterologists, and maintenance of quality of life for all patients.

Clearly, the evidence base to support the targets of treatment needs to be expanded, and future treatment of PsA will be dependent on acquisition of this evidence base. Interestingly, the recommendations listed above do not advocate the assessment of PsA patients at the earliest time point in the course of their disease, yet there is evidence to suggest that earlier presentation in the disease course is associated with better clinical and radiographic outcomes [32,33] and the establishment of early arthritis clinics to accommodate early PsA could have a prognostic benefit on the course of PsA.

The TICOPA protocol study will provide important data in that regard. This study, inspired by the TICORA study in RA, is a UK-based, open-label, randomized controlled study examining clinical and radiographic outcome (ACR20, 50 and 70 response, PASI scores, change in enthesitis and dactylitis scores, 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index and change in Sharp/van der Heijde scores) in those randomized to receive either standard care or intensive management in patients with early, treatment-naive PsA [34]. The treatment target in those receiving intensive management will be minimal disease activity, as defined by Coates *et al.* [27].

Treatment of psoriatic disease according to prespecified targets will be the basis of all future therapeutic regimens. The pursuit of disease control, however, will need to account for individual patient needs and the heterogeneity of the PsA population as a whole, including susceptibility to treatment toxicity and adverse events.

Treatment strategies

There have been few studies comparing the efficacy of medication combinations in PsA, unlike, for example, the BeSt trial in RA. The BeSt study is a single-blind, multicenter randomized trial comparing four different treatment strategies in patients (n = 508) with early RA (<2 years disease duration) with a predefined treatment target of a DAS28 score ≤2.4, with clinical evaluation at 3-month intervals [35]. This trial has accumulated prospective data over 7 years and has informed rheumatologists that early and aggressive disease control results in less radiographic damage and functional decline over time, even allowing for DMARD/TNFi discontinuation and drug-free remission [36].

Applying a similar treatment strategy to PsA would be of enormous interest to rheumatologists. Given the lower prevalence of PsA compared with RA; however, international collaboration would be required to attain adequate numbers to sufficiently power the study. In such an instance, GRAPPA may play a central role.

Trials are all on polyarticular PsA: what about other 'forms'?

There are limited data regarding the use of DMARD and TNFi in the treatment of oligoarthritis, enthesitis and dactylitis [3]; however, the initial clinical trials with TNFi showed that infliximab and golimumab have efficacy in treatment of enthesitis, dactylitis and psoriasis [37,38], while golimumab has also been shown to improve nail disease in psoriasis [38].

Treatment recommendations for predominantly axial disease in PsA, however, are based on observational studies in the PsA population and also extrapolated data from ankylosing spondylitis patients with psoriasis [3].

Future studies need to focus on all the musculoskeletal and cutaneous manifestations of psoriatic disease, with predefined criteria for disease activity in each domain, with applicable and validated outcome measures.

Development of PsA-specific composite measures

GRAPPA has suggested that the DAS28, developed for use in RA, is an acceptable outcome measure for assessing disease activity and treatment response in polyarticular peripheral arthritis in PsA [2]. However, the group acknowledges that it has limited applicability outside of clinical trials [39]. The 10th Outcome Measures in Rheumatology Clinical Trials (OMERACT 10) PsA Special Interest Group stated that "outcomes research in PsA has always lagged behind that in RA" and that there exists a need for a composite measure of disease activity and response to treatment that incorporates the multiple aspects of PsA including enthesitis, dactylitis, spine and skin disease [40]. GRAPPA and OMERACT have been working on the development of a PsA-specific composite measure since 2004 (OMERACT 7).

The GRAPPA Composite Exercise (GRACE) project was established to compare existing and emerging composite measures that assess disease activity and response to treatment [41]. In doing so, two new disease activity and responder indices were developed, the Psoriatic Arthritis Disease Activity Score (PASDAS) and the Arithmetic Mean of Desirability [42].

Using multiple linear regression, the PASDAS, was created as a weighted measure comprising eight domains, including a physician and patient global assessment using a VAS, the Short Form 36, swollen and tender joint count, the Leeds Enthesitis Count, a tender dactylitis count and CRP. Notably, the PASDAS did not contain a measure of axial or skin involvement, but is probably captured in the physician and patient global assessments.

The Arithmetic Mean of Desirability was derived empirically using physician-defined cutoffs for disease activity and included tender and swollen joint counts, the HAQ, patient-derived VAS scores for global disease assessment and skin and joint disease, as well as the PASI and PsA Quality-of-Life Questionnaire.

Both the PASDAS and Arithmetic Mean of Desirability were compared with existing composite measures (Composite PsA Disease Activity Index, the Disease Activity for PsA, and the DAS28 for RA) and found to perform well, with the PASDAS being a better discriminator of the extremes of disease activity compared with the other indices. Whether these new composite measures allow detection of deterioration or improvement in a single domain is unclear and GRAPPA suggests reporting the individual component scores of these composite measures. Future work in this area will require application of these new composite measures in clinical trials and in large PsA cohorts to address these issues.

Failure of anti-TNF therapy: what next?

Ustekinumab

Ustekinumab is a fully human monoclonal IgG antibody directed against the common p40 chain of both IL-12 and IL-23 and administered subcutaneously. IL-12 facilitates differentiation of $CD4^+$ T cells into Th-1 T cells, which produce TNF-α while IL-23 stimulates $CD4^+$ cell differentiation into IL-17, IL-22 and TNF-α-producing Th-17 T cells. Both IL-12 and IL-23 are produced by antigen-presenting cells, such as dendritic cells [43]. Monotherapy with ustekinumab in moderate-to-severe psoriasis has been shown to have a sustained benefit over 3 years [43], with over two-thirds of study participants experiencing a 75% decrease in the Psoriasis Area Severity Index (PASI75) compared with 3–4% of those in the placebo arms [44,45].

The PSUMMIT 1 trial (Phase III RCT) examined outcomes of ustekinumab (n = 409) compared with placebo (n = 206) over 1 year of treatment in PsA patients with primary failure of DMARDs [46]. Those taking ustekinumab had significantly better outcomes on all primary and secondary end points, with 42.4% of those taking the 45-mg dose and 49.5% of those receiving 90 mg achieving an ACR20 response at week 24 compared with 22.8% in the placebo arm ($p < 0.0001$). These responses were maintained until week 52. Significant response in axial disease was also found with 49 and 58% of those taking 45 and 90 mg of ustekinumab, respectively, having at least a 20% improvement in the Bath Ankylosing Spondylitis Disease Activity Index, compared with 26% of those taking placebo ($p = 0.01$ and 0.0005, respectively). Response to cutaneous disease was impressive with 59.9% of those taking ustekinumab achieved a PASI75 compared with 11% on placebo ($p < 0.0001$). Adverse event rates were similar in the placebo and treatment arms.

While the ACR20 responses in peripheral arthritis were not as impressive as those reported from the original TNFi trials [37,47,48], the findings are noteworthy. Future studies regarding its use in clinical practice will need to address maintenance of efficacy beyond 52 weeks, its effect on radiographic damage, efficacy in those who have failed TNFi treatment and whether concomitant DMARD prescription enhances response.

Apremilast

Apremilast is an orally administered inhibitor of phosphodiesterase 4 (PDE4), which has downstream effects on inflammatory cytokine expression through increased levels of intracellular cAMP resulting in reduced levels of TNF-α, IL-12 and IL-23 [49].

The efficacy and safety of apremilast in PsA was evaluated in a Phase II multicenter, randomized, double-blind, placebo-controlled trial in patients with active disease despite treatment with DMARD or TNFi [50]. Two doses of apremilast were administered: 20-mg two-times a day (n = 69) and 40-mg once daily (n = 67) with 68 patients in the placebo arm. A significant ACR20 response at week 12 in the

apremilast-treated groups was reported, with 43.5 and 35.8% of patients (taking 20 mg two-times a day and 40 mg, respectively) meeting the primary end point compared with 11.8% receiving placebo (p = 0.002). Treatment response was maintained at 24 weeks. Concomitant MTX use was not associated with a significant augmentation in the ACR20 response in either group, nor was it associated with additional adverse effects. In that regard, the safety profile was encouraging.

Future studies on apremilast will include the Phase III PALACE study which will examine efficacy over 12 months and will separately examine the response in DMARD-naive and DMARD-exposed patients. Once again, its effect on axial disease, psoriasis, dactylitis and enthesitis would be useful to examine, as well as its role with concomitant TNFi therapy.

T-cell activation inhibitors

Abatacept

T cells have a central role in the pathogenesis of PsA [51], and blockade of T-cell activation may be a therapeutic strategy with significant outcomes. Activation of T cells requires costimulatory signals, including that between the MHC and the T-cell receptor, and between either CD80 or CD86 and CD28 on the T cell [52]. Once activated, the T cell attempts to downregulate its activity through production of CTLA-4, which competes with CD28 for either CD80 or CD86.

Abatacept is an intravenously administered fusion protein with the extracellular domain of CTLA-4 linked to the Fc portion of a human IgG1, inhibiting T-cell activation with a decrease in inflammatory cytokine production [52]. A Phase II double-blind RCT assessing its safety and efficacy in PsA over 6 months was conducted in patients with DMARD or TNFi treatment failure [52]. Patients were randomized to placebo (n = 42) and to one of three different dose of abatacept. The ACR20 response was significantly greater in the abatacept 10 mg/kg group and those who received 30 mg/kg on days 1 and 15 followed by 10 mg/kg thereafter compared with placebo (48 and 42% vs 19%, p = 0.006 and 0.022, respectively), while response was greater in the TNFi-naive (56%) compared with those previously treated with TNFi (31%). Abatacept was not found to have a significant effect on psoriasis; however, the study suggests that it has use in treatment of joint disease, particularly in those with a history of DMARD failure.

Anti-IL-17 antibodies

IL-17 is an inflammatory cytokine, found to be elevated in cutaneous psoriatic lesions [53], as well as the synovium of those with PsA [54]. IL-23 has been shown to play a key role in the polarization of $CD4^+$ T cells to become IL-17-producing, or Th-17 cells [55]. IL-17 can also induce the production of other proinflammatory cytokines including IL-6, TNF-α and IL-1β [56]. Based on this evidence, blockade of this cytokine, or its associated receptors, could have therapeutic implications for the treatment of both psoriasis and PsA.

Secukinumab is a fully human anti-IL-17A monoclonal antibody that is currently under trial in moderate-to-severe PsA [57]. In a Phase II proof-of-concept study, 42 patients were randomized to receive either two intravenous doses of secukinumab 21 days apart (n = 28) or placebo (n = 14). Unfortunately, the primary end point, the ACR20 response at 6 weeks, was achieved in only 39% of the secukinumab groups versus 23% for placebo (p = 0.27), while non-significant differences in the ACR20 response at weeks 12 (39 vs 15%; p = 0.13) and 24 (42 vs 18%; p = 0.14) were also found. However, the study size was small and a signal of potential benefit remained. CRP, ESR and HAQ scores all significantly improved compared with placebo. Of note, 62% of the TNFi-naive patients in the secukinumab arm achieved an ACR20 response at week 6, compared with 10% with TNFi exposure. Leukopenia occurred in eight secukinumab-treated patients compared with one in the placebo arm, while infection rates and other adverse events were similar between the two groups.

These findings are of interest and suggest that secukinumab may have a therapeutic role in future treatment of PsA.

Ixekizumab, an anti-IL-17 monoclonal antibody [58] and brodalumab, an anti-IL-17 receptor antibody [59], are currently under trial in moderate-to-severe plaque psoriasis and PsA. The results of both Phase II trials show very encouraging effects in terms of cutaneous manifestations. While improvement in joint disease was not specifically examined, treatment with the highest dose of ixekizumab resulted in significant reductions in joint pain scores at week 12, compared with placebo [58]. An ACR20 response at 12 weeks was reportedly achieved in 37 and 39% of PsA patients assigned 140 and 280 mg of brodalumab, respectively, compared with 18% of those receiving placebo [60]. Peer-reviewed publications regarding both of these treatments in PsA are pending.

Janus kinase inhibitors

Janus kinases (JAKs) are intracellular tyrosine kinases that participate in the cytokine signaling pathway by associating with specific cytokine receptors [61]. Tofacitinib is an oral JAK inhibitor that can suppress IL-23 receptor expression, thereby affecting Th-17 cell differentiation while also interrupting signaling by IL-6 and IFN-γ [62]. A Phase IIb trial in active RA has shown efficacy [63]. A Phase IIb trial in moderate-to-severe plaque psoriasis (n = 197) has recently shown significant results by week 12 compared with placebo; however, analysis examining effect on joint disease was not performed [64]. Infection rates and adverse events were similar in both groups. A trial in PsA is now underway.

With the exponential increase in knowledge of the immunopathology of psoriatic disease, the 'bench-to-bedside' approach in the development of targeted biologic medications is set to continue to provide rheumatologists and patients with therapeutic options. As with the introduction of TNFi into routine practice, new biologic treatments will need to be monitored over time, particularly in regards to long-term safety.

Biomarkers & pharmacogenetics

Treatment response cannot be accurately predicted, nor can an individual's susceptibility to potential treatment-related adverse events. In PsA, treatment is selected empirically, based on the severity of disease, the presence of contraindications, patient preference and cost. As prescribers, we assign the potential for treatment success or failure based on statistics garnered from clinical trial data, yet individuals with disease can never be assured that they will be among the fortunate proportion to attain therapeutic benefit or avoid potentially serious side effects.

Biomarkers are biological factors that can be objectively measured and represent markers of physiological, pathological and/or pharmacological response [65]. To date, a biomarker with the prognostic and diagnostic significance of rheumatoid factor or anticitrullinated protein antibodies used in RA has not been identified in PsA, nor has a biomarker that will predict response to targeted biological treatments, such as TNFi or IL-12/-23 blockade.

Our research group identified four serum biomarkers from a panel of 12 (high-sensitivity CRP, osteoprotegerin, MMP-3 and the ratio of C-propeptide of type II collagen to collagen fragment neoepitopes Col2–3/4$_{\text{long mono}}$ (C2C) that were independently associated with PsA [66]. We have also found that serum MMP-3 levels predict response to therapy with TNFi [67]. However, their role in diagnosis, prognosis and treatment response, as with other putative biomarkers requires study in longitudinal prospective studies.

Data from the GO-REVEAL trial have shown that a panel of serum-based biomarkers may have clinical application in predicting therapeutic response to golimumab (n = 100) [68]. In total, 11 markers (including MMP-3, CRP, VEGF, IL-16 and ICAM-1 from a panel of 92 measured at baseline were shown to be predictive of an ACR20 and/or improvement in DAS28 by week 14, while a smaller group of four proteins was predictive of a PASI75. Models of these predictor biomarkers were constructed to identify the combination that provides the greatest predictive strength, with adiponectin and factor VII appearing in the models for all three clinical end points.

The identification of sensitive and specific biomarkers for PsA in patients with cutaneous manifestations only would allow early identification and treatment of PsA which, as outlined above, could significantly decrease morbidity and disability through preservation of joint function. Villanova *et al.* present an informative review on the role of biomarkers in assessing prognosis and treatment response in psoriatic disease, and describe genetic, blood, tissue and transcriptional biomarkers that have been explored in psoriatic disease [69]. These authors suggest that a 'molecular signature' that incorporates biomarker data from these four sources is more likely to yield diagnostic and prognostic results, than use of a single biomarker, or that from a single source.

The application of pharmacogenetics, or the use of genetic markers to predict efficacy and toxicity [70], will increase prescribers' and patients' certainty that a medication will safely ameliorate the disease process. While pharmacogenetic research in PsA is in its infancy, studies in MTX have shown that genetic polymorphisms in the folate pathway enzymes were associated with treatment response [71]. Similarly, genetic variance in the TNF apparatus has been shown to be predictive of response to TNFi [72–74].

While these findings are of interest to rheumatologists, their confirmation in large, controlled, prospective studies is required, along with the pursuit of other single nucleotide polymorphisms and genetic variants.

Conclusion

Treatment of PsA has progressed significantly in the last two decades. This progress has been facilitated by an expanding knowledge of the immunopathogenesis of psoriatic disease and the application of this to the development of targeted treatments, most notably the TNFi. These new therapies have provided the template for how future licensed cytokine and cell-signaling inhibitors should be monitored for long-term safety and efficacy.

Robust evidence from blinded, randomized trials must be available on all established DMARDs used in the treatment of PsA, initially from placebo-controlled studies and then from comparative efficacy studies. Treatment strategies comparing combinations of DMARDs with and without TNFi in early PsA with remission as the target outcome are essential to best guide rheumatology practice in the future.

Future perspective

With an expanding therapeutic repertoire expected in the coming decade, validated and sensitive composite measures of disease activity and treatment response are required to allow the most rigorous and accurate analysis of disease outcomes. GRAPPA and OMERACT have been instrumental in this regard and future statements will inform the research agenda.

The increased selection of medications available may create a degree of prescribing complexity for rheumatologists. The advent of the 'biosimilars', combined with trials of cheaper combination therapy, may offer the best chance of achieving remission affordably, while simplifying the treatment algorithm. The advent of 'personalized medicine' in PsA will require the identification of patients' individual biomarker 'molecular signature' combined with their pharmacogenetic profile to maximize therapeutic response and disease outcome.

Financial & competing interests disclosure

V Chandran has received honoraria or research grants from Abbott/Abbvie, Amgen, Bristol-Myers Squibb, Celgene, Janssen and Pfizer. V Chandran is supported by a Canadian Institute of Health Research Team in Psoriasis and Psoriatic Arthritis Team grant. The University of Toronto Psoriatic Arthritis Program is supported by the Krembil Foundation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Addressing the paucity of quality trial data on traditional disease-modifying antirheumatic drugs

- Investigator-initiated randomized controlled trials addressing comparative efficacy and disease-modifying antirheumatic drugs combinations are required.
- A trial similar to the BeSt trial assessing different treatment strategies in early psoriatic arthritis should be considered.

TNF inhibitors: role of biosimilars

- Close regulation of emerging 'biosimilar' agents is required to ensure equivalent efficacy and safety to existing TNF inhibitors.
- Licencing these agents should allow patients access to effective and affordable biologic therapy.

Treatment targets & strategies

- Remission, or at least minimal disease activity, should be the target of all treatment strategies in psoriatic arthritis.
- All musculoskeletal and cutaneous manifestations of psoriatic disease need to be considered in treatment targets.
- Sensitive and specific composite measures of disease activity and response to treatment need to be validated in prospective studies.

Failure of anti-TNF therapy: what next?

- Medications targeting IL-12/IL-23 (ustekinumab), phosphodiesterase 4 (apremilast), T-cell activation inhibition (abatacept), IL-17 (secukinumab, ixekizumab and brodalumab) and janus kinases (tofacitinib) are undergoing clinical trials currently and demonstrating promising efficacy data.

Biomarkers & pharmacogenetics

- Identifying biomarkers and genetic variations that can predict disease activity and response to treatment are essential in the pursuit of disease remission in psoriatic arthritis.

Conclusion

- An increased knowledge of the immunopathogenesis of psoriatic disease has stimulated the development of targeted biologic medications.
- Trials examining combinations of disease-modifying antirheumatic drugs, TNF inhibitors, biosimilars and newer targeted treatments are required to guide rheumatologists' prescribing practices in the pursuit of disease remission.

References

Papers of special note have been highlighted as:
▪ of interest

1 Gladman DD. Early psoriatic arthritis. *Rheum. Dis. Clin. North Am.* 38(2), 373–386 (2012).

2 Ritchlin CT, Kavanaugh A, Gladman DD *et al.*; Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Treatment recommendations for psoriatic arthritis. *Ann. Rheum. Dis.* 68(9), 1387–1394 (2009).

▪ **Highlights the recommendations in place for current management of psoriatic arthritis (PsA).**

3 Gossec L, Smolen JS, Gaujoux-Viala C. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann. Rheum. Dis.* 71(1), 4–12 (2012).

▪ **Highlights the recommendations in place for current management of PsA.**

4 Black RL, O'Brien WM, Vanscott EJ, Auerbach R, Eisen AZ, Bunim JJ. Methotrexate therapy in psoriatic arthritis; double-blind study on 21 patients. *JAMA* 189, 743–747 (1964).

5 Willkens RF, Williams HJ, Ward JR *et al.* Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. *Arthritis Rheum.* 27(4), 376–381 (1984).

6 Kingsley GH, Kowalczyk A, Taylor H *et al.* A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology (Oxford)* 51(8), 1368–1377 (2012).

▪ **Largest randomized controlled trial on methotrexate in PsA that demonstrated no statistically significant difference in response to methotrexate compared with placebo.**

7 Chandran V, Schentag CT, Gladman DD. Reappraisal of the effectiveness of methotrexate in psoriatic arthritis: results from a longitudinal observational cohort. *J. Rheumatol.* 35(3), 469–471 (2008).

8 Dougados M, vam der Linden S, Leirisalo-Repo M *et al.* Sulfasalazine in the treatment of spondylarthropathy. A randomized, multicenter, double-blind, placebo-controlled study. *Arthritis Rheum.* 38(5), 618–627 (1995).

9 Combe B, Goupille P, Kuntz JL, Tebib J, Lioté F, Bregeon C. Sulphasalazine in psoriatic arthritis: a randomized, multicentre, placebo-controlled study. *Br. J. Rheumatol.* 35(7), 664–668 (1996).

10 Clegg DO, Reda DJ, Mejias E *et al.* Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative study. *Arthritis Rheum.* 39(12), 2013–2020 (1996).

11 Rahman P, Gladman DD, Cook RJ, Zhou Y, Young G. The use of sulfasalazine in psoriatic arthritis: a clinic experience. *J. Rheumatol.* 25(10), 1957–1961 (1998).

12 Kaltwasser JP, Nash P, Gladman D *et al.*; Treatment of Psoriatic Arthritis Study Group. 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(6), 1939–1950 (2004).

13 Behrens F, Finkenwirth C, Pavelka K *et al.* Leflunomide in psoriatic arthritis: results from a large European prospective observational study. *Arthritis Care Res. (Hoboken)* 65(3), 464–470 (2013).

14 Spadaro A, Riccieri V, Sili-Scavalli A, Sensi F, Taccari E, Zoppini A. Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study. *Clin. Exp. Rheumatol.* 13(5), 589–593 (1995).

15 Salvarani C, Macchioni P, Olivieri I *et al.* A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J. Rheumatol.* 28(10), 2274–2282 (2001).

16 Glintborg B, Østergaard M, Krogh NS *et al.* Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy: results from the Danish Nationwide DANBIO Registry. *Arthritis Rheum.* 65(5), 1213–1223 (2013).

17 Glintborg B, Østergaard M, Dreyer L *et al.* Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor α therapy: results from the nationwide Danish DANBIO registry. *Arthritis Rheum.* 63(2), 382–390 (2011).

18 Saad AA, Ashcroft DM, Watson KD, Hyrich KL, Noyce PR, Symmons DP; British Society for Rheumatology Biologics Register. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. *Arthritis Res. Ther.* 11(2), R52 (2009).

19 Heiberg MS, Koldingsnes W, Mikkelsen K *et al.* The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicentre study. *Arthritis Rheum.* 59(2), 234–240 (2008).

20 Upchurch KS, Kay J. Evolution of treatment for rheumatoid arthritis. *Rheumatology (Oxford)* 51(Suppl. 6), vi28–vi36 (2012).

21 Baranauskaite A, Raffayová H, Kungurov NV *et al.*; RESPOND investigators. 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(4), 541–548 (2012).

22 Atzeni F, Boccassini L, Antivalle M, Salaffi F, Sarzi-Puttini P. Etanercept plus ciclosporin versus etanercept plus methotrexate for maintaining clinical control over psoriatic arthritis: a randomised pilot study. *Ann. Rheum. Dis.* 70(4), 712–714 (2011).

23 Karanikolas GN, Koukli EM, Katsalira A *et al.* Adalimumab or cyclosporine as monotherapy and in combination in severe psoriatic arthritis: results from a prospective 12-month nonrandomized unblended clinical trial. *J. Rheumatol.* 38(11), 2466–2474 (2011).

24 Scheinberg MA, Kay J. The advent of biosimilar therapies in rheumatology – 'O brave new world'. *Nat. Rev. Rheumatol.* 8(7), 430–436 (2012).

▪ **Reports the relevant challenges facing biosimilar development and licensing in each large geographic location of the world.**

25 Lapadula G, Ferraccioli GF. Biosimilars in rheumatology: pharmacological and pharmacoeconomic issues. *Clin. Exp. Rheumatol.* 30(4 Suppl. 73), S102–S106 (2012).

26 Dörner T, Strand V, Castañeda-Hernández G *et al.* The role of biosimilars in the treatment of rheumatic diseases. *Ann. Rheum. Dis.* 72(3), 322–328 (2013).

27 Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann. Rheum. Dis.* 69(1), 48–53 (2010).

28 Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. *Arthritis Care Res.* 62(7), 965–969 (2010).

29 Coates LC, Cook R, Lee KA, Chandran V, Gladman DD. Frequency, predictors, and prognosis of sustained minimal disease activity in an observational psoriatic arthritis cohort. *Arthritis Care Res.* 62(7), 970–976 (2010).

30 Schoels MM, Braun J, Dougados M *et al.* Treating axial and peripheral spondyloarthritis, including psoriatic arthritis, to target: results of a systematic

literature search to support an international treat-to-target recommendation in spondyloarthritis. *Ann. Rheum. Dis.* 73(1), 238–242 (2013).

31 Smolen JS, Braun J, Dougados M *et al.* Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an International Task Force. *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2013-203419 (2013) (Epub ahead of print).

32 Gladman DD, Thavaneswaran A, Chandran V, Cook RJ. Do patients with psoriatic arthritis who present early fare better than those presenting later in the disease? *Ann. Rheum. Dis.* 70(12), 2152–2154 (2011).

33 Theander E, Husmark T, Alenius GM *et al.* Early psoriatic arthritis: short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). *Ann. Rheum. Dis.* 73(2), 407–413 (2013).

34 Coates LC, Navarro-Coy N, Brown SR *et al.* 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 (2013).

35 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF *et al.* Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum.* 52(11), 3381–3390 (2005).

36 van den Broek M, Lems WF, Allaart CF. BeSt practice: the success of early-targeted treatment in rheumatoid arthritis. *Clin. Exp. Rheumatol.* 30(4 Suppl. 73), S35–S38 (2012).

37 Antoni CE, Kavanaugh A, Kirkham B *et al.* Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum.* 52(4), 1227–1236 (2005).

38 Kavanaugh A, McInnes I, Mease P *et al.* 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(4), 976–986 (2009).

39 Leeb BF, Andel I, Sautner J, Fassl C, Nothnagl T, Rintelen B. The disease activity score in 28 joints in rheumatoid arthritis and psoriatic arthritis patients. *Arthritis Rheum.* 57(2), 256–260 (2007).

40 Coates LC, Mumtaz A, Helliwell PS *et al.* Development of a disease severity and responder index for psoriatic arthritis (PsA) – report of the OMERACT 10 PsA special interest group. *J. Rheumatol.* 38(7), 1496–1501 (2011).

41 Helliwell PS, Fitzgerald O, Mease PJ, Gladman DD. GRAPPA Responder Index Project (GRACE): a report from the GRAPPA 2011 annual meeting. *J. Rheumatol.* 39(11), 2196–2197 (2012).

42 Helliwell PS, FitzGerald O, Fransen J *et al.* The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). *Ann. Rheum. Dis.* 72(6), 986–991 (2013).

▪ **Reports a large international study to develop composite disease activity indices for PsA.**

43 Goldminz AM, Gottlieb AB. Ustekinumab for psoriasis and psoriatic arthritis. *J. Rheumatol. Suppl.* 89, 86–89 (2012).

44 Leonardi CL, Kimball AB, Papp KA *et al.*; PHOENIX 1 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 371(9625), 1665–1674 (2008).

45 Papp KA, Langley RG, Lebwohl M *et al.*; PHOENIX 2 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 371(9625), 1675–1684 (2008).

46 McInnes IB, Kavanaugh A, Gottlieb AB *et al.*; on behalf of the PSUMMIT 1 Study Group. 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(9894), 780–789 (2013).

47 Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 356(9227), 385–390 (2000).

48 Mease PJ, Gladman DD, Ritchlin CT *et al.*; Adalimumab Effectiveness in Psoriatic Arthritis Trial Study Group. 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(10), 3279–3289 (2005).

49 Schafer PH, Parton A, Gandhi AK *et al.* Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity *in vitro* and in a model of psoriasis. *Br. J. Pharmacol.* 159(4), 842–855 (2010).

50 Schett G, Wollenhaupt J, Papp K *et al.* Oral apremilast in the treatment of active psoriatic arthritis: results of a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum.* 64(10), 3156–3167 (2012).

51 Chimenti MS, Ballanti E, Perricone C, Cipriani P, Giacomelli R, Perricone R. Immunomodulation in psoriatic arthritis: focus on cellular and molecular pathways. *Autoimmun. Rev.* 12(5), 599–606 (2013).

52 Mease P, Genovese MC, Gladstein G *et al.* Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, Phase II trial. *Arthritis Rheum.* 63(4), 939–948 (2011).

53 Lowes MA, Kikuchi T, Fuentes-Duculan J *et al.* Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *J. Invest. Dermatol.* 128(5), 1207–1211 (2008).

54 Noordenbos T, Yeremenko N, Gofita I *et al.* Interleukin-17-positive mast cells contribute to synovial inflammation in spondylarthritis. *Arthritis Rheum.* 64(1), 99–109 (2012).

55 Wilson NJ, Boniface K, Chan JR *et al.* Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat. Immunol.* 8(9), 950–957 (2007).

56 Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu. Rev. Immunol.* 25, 821–852 (2007).

57 McInnes IB, Sieper J, Braun J *et al.* 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(2), 349–356 (2013).

58 Leonardi C, Matheson R, Zachariae C *et al.* Anti-interleukin-17 monoclonal antibody ixekizumab in chronicplaque psoriasis. *N. Engl. J. Med.* 366(13), 1190–1199 (2012).

59 Papp KA, Leonardi C, Menter A *et al.* Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N. Engl. J. Med.* 366(13), 1181–1189 (2012).

60 Mease PJ, Genovese MC, Greenwald MW *et al.* Efficacy of brodalumab, an anti-IL-17R antibody, in subjects with psoriatic arthritis [abstract]. *Ann. Rheum. Dis.* 72(Suppl. 3), 85 (2013).

61 Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. *Immunol. Rev.* 228(1), 273–287 (2009).

62 Ghoreschi K, Jesson MI, Li X *et al.* Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). *J. Immunol.* 186(7), 4234–4243 (2011).

63 Fleischmann R, Cutolo M, Genovese MC *et al.* Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum.* 64(3), 617–629 (2012).

64 Papp KA, Menter A, Strober B *et al.* Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a Phas00652b randomized placebo-controlled dose-ranging study. *Br. J. Dermatol.* 167(3), 668–677 (2012).

65 Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin. Pharmacol. Ther.* 69(3), 89–95 (2001).

66 Chandran V, Cook RJ, Edwin J *et al.* Soluble biomarkers differentiate patients with psoriatic arthritis from those with psoriasis without arthritis. *Rheumatology (Oxford)* 49(7), 1399–1405 (2010).

67 Chandran V, Shen H, Pollock RA *et al.* Soluble biomarkers associated with response to treatment with tumor necrosis factor inhibitors in psoriatic arthritis. *J. Rheumatol.* 40(6), 866–871 (2013).

68 Wagner CL, Visvanathan S, Elashoff M *et al.* Markers of inflammation and bone remodelling associated with improvement in clinical response measures in psoriatic arthritis patients treated with golimumab. *Ann. Rheum. Dis.* 72(1), 83–88 (2013).

69 Villanova F, Di Meglio P, Nestle FO. Biomarkers in psoriasis and psoriatic arthritis. *Ann. Rheum. Dis.* 72(Suppl. 2), ii104–ii110 (2013).

70 Cronstein BN. Pharmacogenetics in the rheumatic diseases. *Bull NYU Hosp. Jt Dis.* 64(1–2), 16–19 (2006).

71 Chandran V, Siannis F, Rahman P, Pellett FJ, Farewell VT, Gladman DD. Folate pathway enzyme gene polymorphisms and the efficacy and toxicity of methotrexate in psoriatic arthritis. *J. Rheumatol.* 37(7), 1508–1512 (2010).

72 O'Rielly DD, Roslin NM, Beyene J, Pope A, Rahman P. TNF-alpha-308 G/A polymorphism and responsiveness to TNF-alpha blockade therapy in moderate to severe rheumatoid arthritis: a systematic review and meta-analysis. *Pharmacogenomics J.* 9(3), 161–167 (2009).

73 Morales-Lara MJ, Cañete JD, Torres-Moreno D *et al.* Effects of polymorphisms in *TRAILR1* and *TNFR1A* on the response to anti-TNF therapies in patients with rheumatoid and psoriatic arthritis. *Joint Bone Spine* 79(6), 591–596 (2012).

74 Tejasvi T, Stuart PE, Chandran V *et al.* *TNFAIP3* gene polymorphisms are associated with response to TNF blockade in psoriasis. *J. Invest. Dermatol.* 132(3 Pt 1), 593–600 (2012).