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REVIEW

The Role of Biological and Small Molecule Therapy in the Management of Psoriatic Arthritis

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ABSTRACT

The therapy of psoriatic arthritis (PsA) has blossomed in the past decade. Inhibition of tumor necrosis factor (TNF) has been at the fore of this approach and has paved the way for the investigation of many other potential pro-inflammatory and signaling pathways. Most of the initial studies of TNF inhibitors in PsA have been conducted in specific populations, largely focusing on those with established, peripheral joint disease. That said, in excess of 10 years' worth of real world clinical experience has led to increased confidence in the wider use of these agents. We are now faced with an exciting time of discovery of many new molecules; these not only include new, large protein biological agents, but also smaller synthetic chemical molecules, many of which can be administered orally. Those currently under development are discussed within this article. Whilst there is scarce data about their real world efficacy and safety profile, it is evident that the therapeutic armamentarium for treating PsA will greatly increase in the foreseeable future and this is anticipated to improve patient outcomes.

Keywords: Biologics; Disease modifying; Molecule therapy; Psoriatic arthritis; Tumor necrosis factor

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INTRODUCTION

The optimal management of psoriatic arthritis (PsA) entails the adequate suppression of aberrant inflammatory processes that give rise to the clinical PsA phenotype of joint stiffness, pain, tenderness, and swelling. Categorized as one of the seronegative spondyloarthropathies, PsA can manifest as enthesitis, dactylitis, synovitis, arthritis, and/or axial inflammation, either in isolation or in any combination, although animal models and clinical studies

suggest that enthesitis may be the primary lesion [1, 2]. The magnitude and chronicity of psoriatic joint disease and the consequential physical and financial burden, has, in recent years, prioritized PsA on the research agenda [3].

Compared to rheumatoid arthritis (RA), the optimal management of PsA still lags behind considerably. Prior to the advent of biological therapy for RA, disease-modifying anti-rheumatic drugs (DMARDs; methotrexate or sulfasalazine), were most well established option, initially as monotherapy and then in combination as required. The superior efficacy of the biological agents, often anchored to methotrexate therapy, are well established in preventing joint damage and minimizing long-term disability in RA [4–6].

However, for a number of reasons, making progress in the therapeutic field for PsA has been more complicated. Historically, PsA was viewed as a less prevalent or severe disease. In addition, it is considerably more heterogeneous in its evolution and manifestations compared to RA. To date, a reliable serum biomarker, such as the anti-citrullinated protein antibody in RA, does not exist for psoriatic joint disease detection, and this is likely to have negatively impacted on the generation of good-quality, robust clinical trials for PsA. Whilst conventional DMARDs have been employed as the mainstay of PsA therapy for decades, there is a surprising paucity of data to support their clinical efficacy, with clinical experience generally taking precedence over hard evidence. In addition, the majority of trials in PsA have focused on the treatment of peripheral arthritis in polyarticular disease [7], and have largely ignored those patients with primarily axial disease and other subgroups including oligoarthritis.

The current British Society of Rheumatology guidelines for the treatment of PsA were published in 2005, when anti-TNF therapy was not widely available [8]. Only one TNF inhibitor was licensed for active PsA in the UK at the time of publication (etanercept), and only one other anti-TNF therapy demonstrated evidence in PsA (infliximab). There are now four TNF inhibitors with proven efficacy in PsA, established by large, good-quality clinical trials, and a number of novel compounds in development which if prove to be safe, may translate into promising additions to the biological armamentarium against PsA [9–13]. This article assimilates all of the relevant data concerning both old and new biologic molecules, and provides an evidence-based review of the current and emerging therapeutic options for PsA. However, rather than systematically describe and appraise each clinical study in detail, the pertinent commonalities shall be summarized, and relevant differences highlighted. At the current time, patients within the UK must of course fulfill the criteria for biological therapy as stipulated by the National Institute for Health and Clinical Excellence (NICE); that is, they must have failed to improve on or tolerate first-line, disease-modifying agents including methotrexate, leflunomide, and sulfasalazine, either alone or in combination.

ANTI-TNF AGENTS IN PSORIATIC ARTHRITIS

Many pro-inflammatory cytokines have been identified in the pathogenesis of PsA, but amongst these, TNF-alpha exerts a key pro-inflammatory role [14]. Increased levels of TNF-alpha have been observed in skin, synovial fluid, and synovial tissue from patients with PsA [15] and allelic polymorphisms in the promoter region for TNF-alpha have been shown to correlate with certain aspects of the disease [16]. TNF inhibitors have demonstrated

efficacy in both the skin and joint manifestations of psoriatic disease, as well as preventing radiographic damage [9–13, 17]. In the UK, four anti-TNF agents are licensed for the treatment of PsA—infliximab, etanercept, adalimumab, and golimumab. A fifth agent, certolizumab, has also shown promising efficacy in clinical trials [18, 19]. All trials encompass PsA as a single entity, with no primary endpoint data reporting results based on the PsA subtype.

Almost universally, PsA studies have sought to recruit patients with a predominantly peripheral distribution of joint disease. However, it is estimated that up to 40% of patients with PsA will develop some disease within the axial skeleton. Again, no specific data evaluating the effects of TNF inhibitors at this site has been forthcoming, and treatment guidance is based entirely upon data extrapolated from studies into other seronegative spondyloarthropathies, particularly ankylosing spondylitis (AS) [20, 21]. In AS, TNF inhibitors are effective at suppressing the clinical and imaging markers of inflammation [22] and it is this effect that confers the likelihood of benefit in axial PsA—the suppression of associated bone formation (ankylosis) in AS has yet to be determined [23].

The licensed TNF inhibitors each have a distinct structure and target TNF-alpha in slightly different ways, but essentially potentiate the same overall anti-inflammatory effect. Infliximab is a chimeric (mouse/human) monoclonal IgG1 antibody, adalimumab and golimumab are recombinant fully human IgG1 monoclonal antibodies, and etanercept is a 75 kDa IgG1 fusion protein—the former three bind directly to both the circulating and membrane-bound TNF-alpha molecule, whereas etanercept reversibly binds soluble, circulating TNF-alpha [24]. Despite these structural differences, the different TNF inhibitors exhibit comparable efficacy on the joints [25, 26], although no direct head-to-head trials have been conducted. The four licensed agents have demonstrated efficacy at 12–16 weeks for PsA response criteria (PsARC) response, American College of Rheumatology (ACR) 20, 50, and 70 response, and Psoriasis Area Severity Index (PASI) response [9–13, 27–29]. Of note, the onset of clinical benefit of the TNF receptor construct on etanercept has been reported to be of slower onset in those with more extensive skin disease than for the monoclonal antibodies [9], although this was challenged by the outcomes of the more recent PRESTA trial [30]. Again, there are no direct head-to-head comparisons available. This slower onset of action is unlikely to pose a significant problem in the rheumatologic arena, where many PsA cases have a low PASI score (and therefore less cosmetic urgency to respond rapidly) and where current data leads us to believe that no association between PASI score and joint disease exists [31].

In addition to clinical features, subjective improvements in the Health Assessment Questionnaire (HAQ) are reported to be greatest with adalimumab [10, 27] and infliximab [11, 12] at 12 weeks, and with adalimumab [10], etanercept [28], golimumab [13] and infliximab [12] at 24 weeks, when compared to non-TNF-alpha biologic agents, such as ustekinumab (UST) [32] alefacept [33], and placebo. Specifically looking at the TNF-alpha inhibitors, a more recent indirect comparison meta-analysis measured the relative risks for the PsA response criteria (PsARC) and mean differences for improvements from baseline for the HAQ for PsARC responders and non-responders. Etanercept and infliximab yielded the largest mean difference in HAQ score among PsARC responders, while for non-responders,

etanercept, infliximab and golimumab yielded similar mean differences and adalimumab a notably lower mean difference [34].

The key pathogenic importance of enthesitis and dactylitis in PsA has been established [2, 35, 36], and the original studies into TNF inhibitors suggested superiority of some agents (infliximab [11, 12]) over others. In total, seven randomized controlled trials have published data on enthesitis and dactylitis as secondary endpoints [10–13, 27, 32, 37]. In addition to infliximab [11, 12], golimumab [13] (a second generation agent licensed for PsA), has also shown significant benefits. Secondary endpoint data for etanercept (PRESTA trial) demonstrate a significant decrease in enthesitis (−66.0%, week 12; −75.0%, week 24) and dactylitis (−74.3%, week 12; −82.2%, week 24) [37]. However, it is worth noting that the PRESTA trial did not include a placebo arm.

The ADEPT trial reported efficacy of adalimumab on enthesitis and dactylitis as secondary endpoints [10]. Whilst the mean changes were greater in the treatment group over placebo [10] and these responses were maintained throughout 2 years of therapy [38], these changes were not statistically significant at any time point [10, 38].

These seven trials also include data for the anti-IL-12/23 agent ustekinumab [32], although this is only licensed at present for the treatment of psoriasis (PsO). Of these studies, they have all used different outcome measures, with only a proportion of patients having documented baseline dactylitis or enthesitis. However, research aside, it is seemingly evident from clinical experience that enthesitis and dactylitis respond well to TNF inhibitors, irrespective of the agent employed. Early intervention to prevent progressive joint destruction, pain and disability has been widely embraced in the treatment of RA [39, 40], and there is scope to adopt such an approach in early PsA, especially in patients who require a biologic agent for their skin disease.

The efficacy of TNF inhibitors in preventing bone destruction in PsA appears to be independent of the need for combination with DMARDs. This is not true for RA, where anti-TNF monotherapy does not provide the same benefit [40–46]. Often, a DMARD agent is required in addition to a TNF inhibitor if any attempt is to be made at ceasing joint erosion in RA. It is unclear whether the tendency to erosion repair seen in PsA treated with anti-TNF monotherapy is reflective of a distinct disease process that is intrinsically sensitive to the suppression of inflammation, or if it represents a disease-associated/phenotypic process of new bone formation, or both.

Of note, while anti-TNF monotherapy may be efficacious in PsA, patients are still prone to a subsequent reduction in efficacy or frank treatment failure after a period of time [47]. From studies of TNF inhibitors in RA and inflammatory bowel disease (IBD), in addition to improving initial therapeutic efficacy, concurrent administration of methotrexate has additive benefits in that it may lessen the propensity for neutralizing or anti-drug antibody generation [48]. A reduction in such antibodies can retain the efficacy of an agent in the longer term, as a result of fewer side effects that may necessitate withdrawal (e.g. allergic reactions) or loss of effect through neutralization of the monoclonal antibody. Whether this is the case in PsA awaits further investigation: to date, there are no data showing superiority of TNF inhibitors in combination with DMARD versus anti-TNF-alpha monotherapy [10, 12, 17]. Of note, in all of the important trials of TNF inhibitors in PsA, methotrexate was allowed, but not required, and approximately half of these

patients were treated with anti-TNF monotherapy. The data for patients receiving and not receiving concurrent methotrexate was comparable [49].

Of course, based on available evidence, there are certain specific circumstances that may lead the clinician to choose one TNF inhibitor over another. Where a patient has severe PsO, an agent with dual efficacy and availability should be selected. In theory, this should immediately exclude golimumab, which is not, as yet, licensed in the treatment of PsO. However, where it is used primarily for PsA, in our experience, a substantial and meaningful improvement in PASI is repeatedly seen, and it our experience that many rheumatologists are confident in prescribing golimumab where treatment for skin disease is a priority in addition to PsA.

It has repeatedly been shown that infliximab has superior outcomes over etanercept and adalimumab in terms of joint, functional status and rapid skin clearance [50] although for this very reason, it is often not chosen first line and is typically reserved for more recalcitrant and severe PsO (PASI >20). In addition, infliximab is often used second line as a consequence of its less convenient mode of administration (hospital-based infusion). Of adalimumab and etanercept, the data attempting to demonstrate which is superior for skin and joint disease is conflicting, and is rarely statistically significant [50]. As mentioned previously, there are data to suggest that etanercept may be slower to act [9], and thus adalimumab may be the most logical first-line choice of TNF-alpha inhibitor for patients requiring treatment for both PsO and PsA. However, over a prolonged treatment course (as the majority of patients will need), there are no robust data to refute that etanercept will reach equivalence with adalimumab in terms of achieving PASI 75, PASI 90 and ACR 20 [26]; therefore the urgency to achieve these responses should be tailored to the individual.

There is a greater body of evidence to show that etanercept is not efficacious in those with IBD, both in the induction and maintenance of remission [51, 52] and it no longer features in the most current Cochrane Systematic Review (2008), which does support the use of infliximab, adalimumab, and certolizumab [53]. As the latter is not currently licensed for use in PsA, either adalimumab or infliximab are recommended as treatment for patients with both IBD and PsA. From a practicality perspective, adalimumab may be more convenient, being self-administered at home.

WHAT TO DO WHEN TNF-INHIBITION FAILS

The real world use of anti-TNF agents is associated with good drug retention in the short term. Large scale data from the Danish DANBIO registry showed that increased levels of C-reactive protein (CRP) at baseline were associated with both good treatment responses and can serve as a predictor of longer term drug retention [25]. This may be of clinical value in selecting cases with a greater burden of inflammation, which are most likely to benefit from treatment with TNF-alpha inhibitors.

TNF-inhibition irrevocably provides a powerful clinical benefit in terms of the signs and symptoms of PsA and can halt the progression of erosion at a population level in the small joints [54]. However, there is a paucity of evidence to confirm that these agents retard the progressive, structural changes seen in PsA and the subsequent joint fusion that occurs most perceptibly in the axial skeleton; this suggests that pathways involving cytokines

other than TNF are crucial in new bone formation.

Whilst the investigation of many non-anti-TNF molecules often includes patients who have failed TNF-inhibition, it is worth noting that to date, there are no published, completed, randomized controlled trials in PsA that solely include these patients. As such, there is an unmet need to provide conclusive evidence for a clear management strategy for this patient group.

ANTI IL-12/IL-23 IN PSORIATIC ARTHRITIS

Interleukin-23 (IL-23) receptor polymorphisms and IL-12B (p40 IL-12 and IL-23 subunit) polymorphisms have been reported in PsO and PsA [55]. This has been supported by the detection of elevated serum concentrations of IL-23 in spondyloarthropathy patients. A recent publication has shown that, in mice, IL-23 promotes a pathology that resembles spondyloarthritis (including new entheseal bone formation and aortic root inflammation) by acting on a previously unidentified subset of innate-like T cells that reside at the enthesis [1]. Collectively these findings provide robust genetic and molecular evidence for the key role of IL-23 in PsA based, entheseal driven pathology.

Ustekinumab, an anti-IL-12/IL-23 p40 subunit human monoclonal antibody, is licensed for the treatment of PsO, and exhibits impressive reduction in PASI scores in the vast majority of patients. Efficacy in PsA has been investigated in one active crossover, phase II placebo controlled trial of 146 patients, and demonstrated moderate results (42% achieved ACR20 at week 12, compared with 14% of those receiving placebo) [32]. Whilst it should be noted that response outcomes were lower than those reported for TNF inhibitors, it is also worth taking into account that many of these patients had previously failed on the latter. Extrapolating from the more substantial experience of using biologics in RA, prior anti-TNF failures are generally associated with poorer response rates to all forms of treatment, including different biologic agents, and thus negative selection bias may have played a role in this initial trial.

The results from the follow-on phase III (PSUMMIT1) study were reported at the 2012 European League Against Rheumatism (EULAR) Annual Congress, with similar results at a later end point of 24 weeks (Table 1) [56]. Of relevance, significant improvements in enthesitis and dactylitis were reported in the ustekinumab group. This was supported by week 52 data from PSUMMIT1, presented later in the year at the 2012 ACR Annual Conference (Table 1) [57]. Further detail was provided about the effects on enthesitis and dactylitis. At week 24, median changes in enthesitis and dactylitis scores were significantly higher than those patients seen for patients receiving placebo (Table 2; $P < 0.001$ for all comparisons). Improvements in enthesitis and dactylitis scores continue through to week 52 (Table 2).

The results of a second phase III RCT (PSUMMIT II) were also released at ACR 2012 [58]. PSUMMIT II recruited 312 patients, 180 of whom were TNF-alpha experienced. In this subgroup, significantly higher numbers of patients receiving ustekinumab achieved ACR20 responses at the primary endpoint (week 24) compared with placebo (Table 1). For all participants, including those who were biologic naive, significantly greater proportions achieved ACR50 at week 24 compared with placebo, although the improvement failed to reach significance for ACR70 (Table 1).

Table 1 Significant endpoint data from PSUMMIT I and PSUMMIT II

	% reaching ACR20			% reaching ACR50			% reaching ACR70		
	UST 45 mg	UST 90 mg	Placebo	UST 45 mg	UST 90 mg	Placebo	UST 45 mg	UST 90 mg	Placebo
PSUMMIT I									
Primary endpoint (24 weeks)	42.4	49.5	22.8	24.9	27.9	8.7	12.2	14.2	2.3
Secondary endpoint (52 weeks)	55.7	60.3	No placebo	31.4	37.0	No placebo	18.0	21.2	No placebo
PSUMMIT II									
Primary endpoint (24 weeks)	36.7	34.5	14.5	17.5	22.9	6.7	Did not reach significance		

Percentages reaching ACR 20, 50, and 70 after treatment with ustekinumab (UST) 45, 90 mg, or placebo [56–58]
ACR American College of Rheumatology

Table 2 Median percentage change in enthesitis and dactylitis scores after treatment with ustekinumab (UST) 45 or 90 mg for 24 and 52 weeks [56]

PSUMMIT I	Enthesitis (median % change in scores)		Dactylitis (median % change in scores)	
	UST 45 mg	UST 90 mg	UST 45 mg	UST 90 mg
Primary endpoint (24 weeks)	−42.9	−50.0	−75.0	−70.8
Secondary endpoint (52 weeks)	−83.3	−74.2	−100	−100

The positive experience with monoclonal antibody inhibition of the IL-12/IL-23 pathway raised the prospect of using small orally active molecules to attain the same feat. Successful trials with antibodies directed against IL-12/IL-23 in psoriatic disease, and the recent data published into the key role of IL-23 in driving enthesitis has supported the quest to find other molecules that can also inhibit IL-12/IL-23 pathways. Apilimod is an orally administrated small molecule that was developed from a novel triazine derivative identified through high-throughput IL-12 inhibitor screening [59]. It selectively and potently inhibits IL-12 and IL-23 production through the inhibition of transcription of both p35 and p40 genes and has shown clear dose–response reduction in the production/expression of IL-12/IL-23, the number of infiltrating immune cells and the clinical measures of PASI and PGA in phase I PsO studies. However, clinically optimal drug levels were associated with CNS-related adverse events, preventing the molecule from progressing to phase III trials. Similar problems were experienced in the phase-IIa randomized controlled trial of apilimod in patients with RA [60]. Whilst an orally available small molecule would provide superior convenience and cost effectiveness, to date, no apilimod derivatives with improved safety and pharmacokinetics have been forthcoming to the market.

ANTI-IL-17 IN PSORIATIC ARTHRITIS

A novel cytokine target is IL-17, produced by both innate and adaptive immune cells including T_H17 cells, which are induced by IL-23. Currently, there are three monoclonal antibodies that target IL-17 under investigation—ixekizumab (formerly LY2439821), secukinumab (formerly AIN457), and brodalumab (formerly AMG827). Initial

investigation has focused primarily on the dermatological manifestations of psoriatic disease.

Of the many members of the IL-17 cytokine family, both IL-17A and IL-17F are expressed at elevated levels in psoriatic skin [61]. They bind as homodimers or heterodimers to the IL-17 receptor (IL-17R), a heterodimer of IL-17RA and IL-17RC subunits. IL-17RA is highly expressed on keratinocytes and in psoriatic skin—improvements induced by anti-IL-17A therapies further supports the hypothesis that IL-17 is a co-conspirator alongside many other cytokines in the pathogenesis of PsO. Brodalumab is a human IgG2 monoclonal antibody which prevents binding and biological activity of multiple members of the IL-17 cytokine family (IL-17A, IL-17C, IL-17E, IL-17A/F, IL-17F) though high affinity binding and antagonism of the IL-17RA receptor, and in both the phase I and II studies has demonstrated rapid, dose-dependent improvement in PASI scores. Further larger scale studies are required to confirm this effect.

Ixekizumab is a humanized IgG4-type monoclonal antibody that rapidly neutralizes IL-17, leading to improvements both in clinical measures of disease and histopathologic features in lesional skin (i.e. reduced acanthosis, hyperkeratosis and dermal lymphocytic infiltration). These changes are associated with a significant down-modulation of a broad array of genes in the skin from multiple inflammatory pathways. Similar changes were demonstrated in a trial exploring the efficacy of another monoclonal antibody—secukinumab—directed against IL-17, and reductions in PASI score were observed after just one dose [62]. Secukinumab differs structurally from ixekizumab in that it is a fully human monoclonal antibody of IgG1 kappa isotype.

In addition to efficacy in PsO, ixekizumab [63] and secukinumab [62] have demonstrated some worth in the management of RA. Efficacy in inflammatory disorders other than PsO is to be expected, as IL-17 acts as an effector cytokine much like TNF-alpha, and virtually all cell types have been demonstrated to have a biologic response to IL-17. IL-17 can synergize with other pro-inflammatory cytokines to stimulate release of additional pro-inflammatory cytokines and chemokines, nitric oxide, and matrix metalloproteinases. Larger scale clinical trials are required to ascertain the safety and efficacy profile not only in RA but also in many other inflammatory and autoimmune diseases.

To date, only one small proof-of-concept study has investigated IL-17A as a target for the treatment of PsA. McInnes et al. [64] randomized 42 patients to two injections of secukinumab (given at 3-week intervals) or placebo (2:1 randomization). The trial failed to meet the primary endpoint of ACR20 at week 6 (39% active group vs. 23% placebo). At week 28, the ACR20 response rate in the active treatment arm was 43%, suggesting that the week 6 response rate was maintained at 28 weeks. Again, it is worth noting that many of the participants had previously failed TNF-inhibition therapy, which may prejudice the outcome. Coupled with the brief treatment course, no firm conclusions can be made from these data about the true efficacy of secukinumab in PsA. Interestingly, post hoc analysis of data from a more recent phase II study of secukinumab in PsA by the same authors demonstrated a week 6 ACR20 response of 10% in those previously exposed to TNF inhibitors, compared to 62% in those who were biologic naïve [65]. Whilst the numbers in the latter study were small, it will be interesting to see if this observation is repeated in larger cohorts. Overall, the

proportion of patients in these studies demonstrating sustained improvements in clinical scores are encouraging and these support the rationale for larger clinical trials of IL-17A monoclonal antibodies in the spondyloarthropathies.

OTHER BIOLOGIC AGENTS

Leucocyte-Function-Associated Antigen 3 (LFA-3)/CD2 Blocker

Alefacept was the first US Food and Drug Administration (FDA) sanctioned biologic agent for PsO in 2003 [66]. Alefacept is a human fusion protein with a dual mechanism of action—firstly, it inhibits T-cell activation by binding CD2 on T cells and thus inhibiting leukocyte function antigen-3/CD2 interaction with antigen-presenting cells [67]. Secondly, alefacept also bridges between CD2 on target lymphocytes and immunoglobulin Fc receptors on natural killer cells. CD2 expression is higher on memory effector than naive T cells. By binding CD2 on memory T cells and interacting with CD16 receptors on natural killer cells and macrophages, alefacept induces selective apoptosis of CD4 memory effector cells, whilst largely sparing naive T cells [67]. However, the former action necessitates close monitoring of the CD4 count to ensure that it does not drop below 250 cells/mm^3.

Whilst demonstrating efficacy in moderate-to-severe PsO, alefacept was rapidly superseded by the TNF inhibitors. However, as for most biologics, no randomized controlled trials have directly compared the efficacy of alefacept with the other agents. In 2008, Brimhall et al. [68] performed a quantitative meta-analysis of available randomized controlled trials of four biologic agents: alefacept, efalizumab (now withdrawn), etanercept, and infliximab. Across all trials, efficacy was measured by achievement of PASI 75 after 10–14 weeks of treatment—the study showed that all agents were efficacious for improving PsO, though alefacept was the least effective of the agents studied [68]. Pooled relative risk of achieving PASI 75 was 4, 7, 12, and 19 for alefacept, efalizumab, etanercept, and infliximab, respectively, compared with placebo. The corresponding numbers needed to treat were 8, 4, 3, and 2. Alefacept is also slower to act than TNF inhibitors for most PsO patients [68].

Two studies have assessed the role of alefacept in PsA [33, 69]. In the first, 185 patients were randomized 2:1 to receive either 15 mg intramuscular (IM) alefacept with methotrexate (MTX) or placebo and MTX weekly for 12 weeks. ACR20 response at week 24 was 54% for alefacept + MTX versus 23% for placebo + MTX [33]. Response rates did not differ according to the duration of prior treatment with MTX.

In the second study, 185 patients with active PsA despite at least 3 months treatment with MTX were similarly randomized to concurrently receive at least eight once-weekly injections of 15 mg IM alefacept or placebo (double-blinded), followed by a 12-week observational period; 54% achieved ACR20 with alefacept + MTX at week 24, versus 23% of placebo + MTX [69]. All eligible participants (160 in total) were then entered into an extension phase and received open-label treatment with alefacept (15 mg IM weekly) + MTX for 12 weeks. At week 24 of the extension phase, ACR20 reached 55% and 51% for the two initial groups, respectively. Amongst patients who received alefacept plus MTX in both phases of the study, the proportion achieving ACR50 increased with the additional course of alefacept from 17% to 34%, and achieving ACR70 from 7% to 12% [69].

Whilst these trials have demonstrated some efficacy in PsA and a favorable safety profile, the emergence of more efficacious molecules means that alefacept is now unlikely to gain a dominant status in the hierarchical management of PsA.

CD28 Receptor Inhibitors

Full antigen-induced activation of naïve T cells requires two discrete signals from the antigen-presenting cell. Antigen is presented to the T-cell receptor in the context of a major histocompatibility complex molecule, but full activation occurs only when the binding of CD80 or CD86 to the CD28 molecule on the T cell produces a secondary co-stimulatory signal. After activation, the T cell expresses CTLA-4, which competes with CD28 for binding to CD80 or CD86, leading to homeostatic down-modulation of activated T cells.

Abatacept is a recombinant, fully human fusion protein that consists of the extracellular domain of CTLA-4, linked to a modified Fc potion of human IgG1. It selectively binds to the CD80 or CD86 receptor on the antigen-presenting cell, blocking the second signal T-cell activation of the CD28 receptor and thus decreases serum levels of cytokines and proteins implicated in the pathogenesis of psoriatic and other inflammatory diseases [70]. Administered by monthly infusion, abatacept is licensed in Europe and the United States for the treatment of RA in adult patients with an inadequate response to DMARDs or TNF inhibitors. In 2010, it was also approved in Europe for moderate-to-severe juvenile idiopathic arthritis in children aged 6 and over.

A phase I trial has shown good clinical efficacy for abatacept in PsO, with a reduction in intralesional T-cell populations [71]. These observations of abatacept in PsO and other inflammatory arthritides spurred the development of trials in PsA. Initial case reports in PsA of two patients who previously failed TNF inhibitors described significant improvement in clinical signs and symptoms of PsA after regular treatment with abatacept [72, 73]. Formal investigation by Mease et al. [70, 74] confirmed a significant ACR20 response in patients randomized to 10 mg/kg abatacept compared to placebo (48% vs. 19%, $P = 0.006$), but no significant difference in those treated with 3 mg/kg abatacept. Magnetic resonance image assessment of synovitis and psoriatic target lesion scores also improved with abatacept. Unfortunately, TNF failures did not respond as well as others in the trial (ACR20 31% vs. 56%), as seen in many studies of alternative biologics following TNF failure.

Because abatacept was the first therapy targeting the inhibition of co-stimulatory signals to prevent T-cell activation, its use in early disease [75] and in biologic-naïve patients with active RA [76, 77] has generated particular interest and investigation [78–81]. These data may support the investigation of abatacept in biologic-naïve patients with early inflammatory joint disease who have had an inadequate response to MTX. However, it is worth noting that patients included in these studies were exposed to concomitant corticosteroids [76, 77].

SMALL MOLECULES IN PSORIATIC ARTHRITIS

In contrast to biologics, which target soluble extracellular cytokine or cellular receptors, small molecule inhibitors target intracellular enzymes within a signaling pathway, e.g., tyrosine kinases. In essence, this can make it more difficult to anticipate their complete biological effects and may cause potential for unintended side effects, as these molecules will

often interact with the same enzymes but in non-targeted cells involved other biological processes. However, if this can be overcome, small molecule inhibitors have several advantages over biologic agents in that they can be administered orally, and as synthetic compounds, they are comparatively inexpensive to manufacture.

Protein Kinase C Inhibitors

The protein kinase C (PKC) family consists of 10 isoenzymes and each play key roles in cellular signaling, migration, survival and death [82]. Most isoforms are ubiquitously expressed, except PKCγ and PKCθ. PKCγ is exclusively found within the brain, whilst high protein levels of PKCθ are seen mostly in hematopoietic cells and skeletal muscle [83].

PKCθ (along with PKCβ and PKCδ) are functionally important for T and B cell signaling [83, 84]. PKCθ is central to T-cell activation as it is the only isoenzyme that is selectively translocated to the T-cell/antigen-presenting cell contact site immediately after cell-to-cell interaction [85]. Furthermore, PKCθ is essential for IL-2 production, which is required for T-cell proliferation. PKCα in T cells is required for proliferation [86], in addition to IFNγ and IL-17 production. PKCβ is a prerequisite for B cell antigen receptor function, and PKCδ for the induction of tolerance [87]. Identification of specific PKC isoenzymes in T and B cells has promoted their attractiveness as therapeutic targets for inflammatory and autoimmune diseases [88].

To date, only one PKC inhibitor—sotrastaurin (AEB071)—is in the exploratory phase of drug development for autoimmune diseases [89]. Sotrastaurin has a strong inhibitory activity on three PKC isoforms—PKCθ, PKCα and PKCβ, and weaker activity on PKCδ, PKCε, and PKCη, meaning that in addition to T-cell activity, it has inhibitory effects on several other cells [82]. It affects more than 200 kinases, including those important for early T-cell activation such as Lck and ZAP-70. Phase II trial data have shown promising efficacy in PsO and transplant rejection [90]. The proven potent inhibition of IL-17 by sotrastaurin makes this molecule a potential future therapeutic target in PsA [91].

Janus Kinase Inhibitors

Another family of kinases commanding interest in PsO are the Janus kinases (JAK), of which there are four members—JAK1, JAK2, JAK3, and TYK2 [92]. These enzymes, which are expressed primarily in immune and hematopoietic cell lineages, form part of the signaling apparatus used by receptors for various cytokines and growth factors. When such receptors are engaged by their specific ligands, JAKs phosphorylate and thus activate members of the signal transducer and activator of transcription (STAT) family [93]. There are seven STATs (STAT 1, 2, 3, 4, 5a, 5b, and 6), each with a variety of distinct effects on gene transcription in cells of the immune system that are critical in processes such as lymphocyte differentiation, immune regulation and inflammation [94].

Members of the JAK family can combine to form homodimers or heterodimers; these unique pairings give rise to the signaling of specific cytokines. For example, IL-12 and IL-23 have been reported to signal through JAK2–TYK2 heterodimers [92], thus targeting of this pathway would be expected to produce similar therapeutic efficacy to ustekinumab [95]. JAK inhibitors also inhibit signaling from many other cytokines, including IL-17 (which activates multiple JAKs via IL-17R) [96], IL-20

[97], IL-22 (JAK1), and IFNγ (JAK1/2 heterodimers) [92]. JAK3 specifically transduces signals from IL-2, IL-7, IL-15, and IL-21, which are integral to lymphocyte function and survival, and inhibition of their signaling may result in modulation of multiple aspects of the immune response [98]. JAK inhibition therefore has the potential to positively impact on many inflammatory disorders.

Data from phase I and II studies has established that cytokine signaling through the JAK pathway is an important component of the pathogenesis of both PsO and RA, and promising efficacy has been achieved with a compound now known as tofacitinib (CP-690550) in both disorders [99–101]. First described in 2003, it was initially described as a JAK3 inhibitor that could prevent allograft rejection [102]. However, it is now considered to powerfully inhibit both JAK1 and JAK3 (which can function as signaling heterodimers), and to a much lesser extent, JAK2 [103]. The reported success in phase III trials means that it has recently been licensed for treatment of RA in the US [100]. The response to tofacitinib of coincidental PsO in patients with inflammatory RA provides a logical argument for investigation of efficacy in PsA, and is likely that trial data will soon become available in this domain.

Therapeutic inhibition of more selective JAK inhibitors is under investigation. The most extensively studied is ruxolitinib (INCB28050), a selective JAK1/JAK2 inhibitor that has been investigated primarily in myelofibrosis. Latterly, a topical preparation of ruxolitinib has been developed for use in the treatment of PsO, and in a phase-IIb proof-of-concept study of 29 patients, has been reported to improve mean total lesion scores (approximately 53% reduction) and PGA at the 1 and 1.5% concentrations after 28 days of continuous use [93, 104]. However, no firm conclusions can be drawn from this small study, and the high placebo response rate (32% reduction in mean total lesion scores) may simply reflect improved compliance with a topical regimen during the trial.

In terms of inflammatory arthritis, significant efficacy (as assessed by improvements in clinical, histologic, and radiographic signs of disease), has been achieved in the rat adjuvant arthritis model, with doses of ruxolitinib providing partial and/or periodic inhibition of JAK1/JAK2 and no inhibition of JAK3 [105]. Diminution of inflammatory Th1 and Th17 associated cytokine mRNA levels were observed in the draining lymph nodes of treated rats. Ruxolitinib was also effective in multiple murine models of arthritis, with no evidence of suppression of humoral immunity or adverse hematological effects [105]. As a result, clinical evaluation of ruxolitinib for RA is currently underway in humans.

Another orally active small molecule undergoing extensive investigation in a number of inflammatory disorders is ASP015K. This molecule selectively targets JAK1/JAK3 and in a 6-week phase-IIa POC study of patients with PsO, ASP015K was well tolerated and demonstrated dose-dependent improvements in PASI change from baseline [106]. ASP015K is currently being investigated in three phase-IIb studies in patients with RA in the United States, Europe and Japan, with no efficacy data released to date.

A more selective small molecule—CEP33779—which selectively targets only JAK2, has shown efficacy in two mouse models of RA by inhibiting the transduction of signals for several essential pro-inflammatory cytokines, including IL-6, IFNγ, and IL-12

[107]. It has been proposed that use of a selective, rather than pan-JAK inhibitor, avoids the potential complications of immunosuppression, whilst targeting critical signaling pathways involved in autoimmune disease progression. Further safety data are needed on all agents before this conclusion can be definitively drawn.

Phosphodiesterase Inhibitors

Phosphodiesterase-4 plays a key role in degrading cyclic-AMP in cells—inhibition leads to diminished T-cell secretion of pro-inflammatory cytokines, including TNF-alpha, IFN-γ, PDE-4, nitric oxide synthase, IL-2, IL-17, and IL-23 and blocks the degradation of cAMP. Apremilast, a phosphodiesterase-4 inhibitor, is currently in phase III trials in PsO, AS, and PsA. Positive results have been reported in PsO; in one phase-IIb, double-blind, four-arm, randomized controlled study, 352 patients received either 30 mg, 20 mg, or 10 mg oral apremilast twice daily or placebo with 41% of the active treatment group achieving PASI 75 compared to just 6% in the placebo arm [108].

In a similar phase II study of 204 patients with PsA, a modest but significant improvement in ACR20 was achieved at both 20 mg twice daily and 40 mg once daily doses. A significant difference was not seen in ACR70, with very few patients achieving such a marked improvement in disease activity [109]. Preliminary phase III data for apremilast from the PALACE 1 (Psoriatic Arthritis Long-Term Assessment of Clinical Efficacy) study in active PsA was recently presented at the 2012 ACR annual meeting. A primary endpoint of ACR20 at week 16 was achieved in 31.3% ($P = 0.0140$) of patients receiving apremilast 20 mg twice daily and 41.0% ($P < 0.0001$) receiving apremilast 30 mg twice daily compared with 19.4% patients receiving placebo. Adverse events included gastrointestinal upset, headache, and upper respiratory tract infections. Most were mild or moderate in severity and necessitated study discontinuation in up to 7%.

TNF Antagonist Gene Therapy

A recombinant adeno-associated virus (rAAV) serotype 2-based vector containing human TNF-immunoglobulin (IgG1) Fc fusion gene (rAAV-TNFR:Fc) has been developed for clinical use [110]. Once injected into the affected joint(s), the DNA coding for a therapeutic protein is incorporated into native tissue cells by the process of gene transfer. The use of a vector is required to facilitate uptake of the single-stranded DNA by cells within the joint and incorporate it into the genome. Subsequent transcription/translocation should then provide sustained concentrations of the therapeutic protein within the joint [110]. rAAV-TNFR:Fc is based on an adeno-associated virus—a naturally occurring, non-pathogenic, non-integrating and non-replicating virus that depends on a helper virus for replication [111].

To date, one phase I/II study of patients with inflammatory arthritis (including PsA) treated with rAAV-TNFR:Fc has been published [112]—127 patients were randomized to receive intra-articular injections of escalating dose concentrations of the gene, or placebo (3:1 randomization) into a single target joint. Injection site reactions occurred in 20% and were dose-related. Septic arthritis developed in one patient 15 weeks after administration of rAAV-TNFR:Fc, which was deemed 'probably related' to the gene therapy, due to the increased risk of infection caused by expression of TNFR:Fc protein in the

joint. In terms of efficacy, patient reported outcome measures (global visual analogue scores) yielded a greater difference between drug and placebo than clinical examination for the target joint, but this was not statistically significant [112].

Other Molecules in Phase I/II Studies

Several novel agents are in phase I and II trials for a number of inflammatory/immune cell driven disorders, including PsO and RA. Based on experience, for some, it is likely that the natural evolution of investigation for many of these agents will extend to PsA, whilst safety concerns and disappointing efficacy data may halt the progression of others into the clinical domain. Table 3 lists the new compounds currently in early clinical trials in psoriatic disease and other inflammatory arthritides that have not been discussed elsewhere in this paper.

CONCLUSION

The advent of biologic therapies has revolutionized the treatment of PsA and facilitated a real, meaningful, and measurable reduction in both disease progression and symptomatology. With more than a decade of safety data for TNF-alpha inhibitors, confidence in the use of biologics is increasing, and the net is being cast ever wider in the search for new biomarkers, molecular pathways, and therapeutic targets.

The impressive efficacy of TNF inhibitors in inflammatory disease has led to a significantly greater understanding of the inflammatory cascade and allowed for the identification of more direct molecular targets. Numerous agents, both biological and non-biological are in development which can precisely modulate or inhibit key molecules in the pathogenesis of inflammatory arthritis, and are showing promising results in phase II/III trials. The relative efficacy of these agents remains to be established, and, in time, head-to-head trials will be required to determine the best treatment options for patients.

The prospect of preventing radiographic damage in RA and PsA has led to a re-evaluation of how patients with inflammatory arthritides are managed—attempts are being made to identify specific phenotypic subgroups of patients who are more likely to derive benefit from selected treatments. Not only will this hasten the attainment of symptomatic relief, but could potentially reduce the economic burden imposed by 'trial and error' therapeutics and significantly lessen the physical and psychosocial morbidity of chronic disease.

The exciting search for the ultimate inhibitor of musculoskeletal inflammation continues, in terms of superior efficacy, safety, tolerability, mode of administration, and the ability to specifically target aberrant, pathogenic inflammatory pathways in multiple organ systems, without causing damage to healthy structures. Psoriatic disease is an ideal disease model, where aberrations in common inflammatory pathways give rise to the musculoskeletal, cutaneous and/or systemic phenotype, and is anticipated that in future, treatment options may become tailored to an individual's clinical phenotype with the aid of imaging, serological and genetic biomarkers. The key challenge facing rheumatologists will then be how best to integrate all of the new, targeted molecules into daily practice, although the increasing armamentarium at their disposal will allow the provision of a significantly improved quality of life for many more patients.

Table 3 Molecules in development for psoriasis and rheumatoid arthritis

Compound	Disease	Mechanism	Type	Company
AbGn-168	Psoriasis	Biologic	Anti-P-selectin glycoprotein ligand (PSGL)-1	Boehringer Ingelheim
Fezakinumab	Psoriasis	Biologic	Anti-IL-22	Wyeth (Pfizer)
Guselkumab (CNTO 1959)	Psoriasis and RA	Biologic	Anti-IL23 p19	Janssen-Cilag
SCH900222	Psoriasis	Biologic	Anti-IL23 p19	Sanofi Pasteur MSD
ACT-128800	Psoriasis	Small molecule inhibitor	Sphingosine-1-phosphate (S1P) agonist	Actellion
VB-201	Psoriasis	Small molecule inhibitor	Immune modifier	VBL Therapeutics
APG2305	Psoriasis	Small molecule inhibitor	Anti-IL-23R	Allostera Pharma
Erlotinib	Psoriasis	Small molecule inhibitor	Anti-eGFR	OSI Pharmaceuticals
RWJ-445380	Psoriasis	Small molecule inhibitor	Cathepsin S inhibitor	Johnson & Johnson
R3421 (BCX-4208)	Psoriasis	Small molecule inhibitor	Purine nucleoside phosphorylase inhibitor	Roche/BioCryst
CF101	Psoriasis	Small molecule inhibitor	Adenosine receptor agonist	Can-Fite BioPharma
BMS582949	Psoriasis and RA	Small molecule inhibitor	P38 inhibitor	Bristol-Myers Squibb
Fostamatinib	Psoriasis and RA	Small molecule inhibitor	Spleen tyrosine kinase (SYK) inhibitor	Astra-Zeneca/Rigel
Iguratimod (T-614)	RA	Small molecule inhibitor	Inhibitor of Ig and cytokine production	Jiangsu Simcere Pharmaceuticals
GLPG0634	RA	Small molecule inhibitor	JAK-1 inhibitor	Galapagos
CCX354-C	RA	Small molecule inhibitor	Chemokine receptor-1 (CCR1) antagonist	ChemoCentryx
CCX168	RA	Small molecule inhibitor	Complement (C5a) receptor antagonist	ChemoCentryx
VX-509	RA	Small molecule inhibitor	JAK-3 inhibitor	Vertex
Baricitinib (INCB028050)	RA	Small molecule inhibitor	JAK1/2 inhibitor	Eli Lilly/InCyte
LX3305 (LX2931)	RA	Small molecule inhibitor	Sphingosine-1-phosphate (S1P) lyase inhibitor	Lexicon
VX-702	RA	Small molecule inhibitor	P38 MAPK	Vertex
Tasocitinib (CP-690550)	RA	Small molecule inhibitor	JAK-3 inhibitor	Pfizer

Table 3 continued

Compound	Disease	Mechanism	Type	Company
SP930	RA	Small molecule inhibitor	c-Jun-N-terminal kinase (JNK) inhibitor	Celgene
PDA001	RA	Stem cell therapy	Human placental-derived stem cells	Celgene

eGFR estimated glomerular filter rate, *JAK* Janus kinase, *MAPK* mitogen-activated protein kinase, *RA* rheumatoid arthritis

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Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). Arthritis Care Res (Hoboken). 2011;63:S64–85.

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