Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis that can involve both the peripheral and axial skeleton [1]. While initially regarded as a relatively rare entity, more recent studies found a prevalence of inflammatory arthritis in psoriasis patients ranging from 11% in the US population [2,10] to 30% in Europe [3,4]. In most patients the skin disease precedes the arthritis by many years [5]. Enthesitis, inflammation at ligamentous and tendon insertion sites to bone and dactylitis, diffuse inflammation in a finger or toe, are cardinal features of PsA [6]. In one study of patients with early PsA [7], radiographic damage was noted at 2 years in the majority of subjects and a report from Scandinavia found that most PsA patients experience a chronic, progressive course [8]. Significant impairment of quality of life is particularly evident in patients with arthritis mutilans, a form of bone destruction that manifests as extensive bone and digit resorption [9]. Moreover, a recent Canadian study reported a significantly increased morbidity and mortality rate in patients with PsA that exceeded that of the general population [10].

The extent of joint involvement and the presence of radiographic damage usually determine the therapeutic approach in PsA [11]. Traditionally, nonsteroidal anti-inflammatory drugs (NSAIDs) combined with physical therapy has been prescribed to treat mild disease, while the use of disease-modifying antirheumatic drugs (DMARDs) has been reserved for patients with more aggressive disease [12]. Methotrexate has been the first choice of many rheumatologists for treatment of PsA despite a lack of evidence from randomized trials to support efficacy. In one trial, efficacy was noted but the high intravenous dose resulted in unacceptable toxicity [13]. In another trial, efficacy was not noted for most measures but the oral dose of methotrexate was quite low by today’s standards and the trial was not adequately powered [14]. A controlled trial that compares methotrexate with placebo in PsA is currently underway in the UK.

Controlled trials with sulphasalazine [15], gold (both oral and intramuscular) [16,17], azathioprine [18] and cyclosporine [19] demonstrated a modest degree of clinical efficacy with benefits limited to the peripheral joints [20,21]. Furthermore, these agents have not been shown to retard the radiographic progression of PsA. Although leflunomide has recently been shown to be moderately efficacious in the treatment of skin and joint manifestation of psoriasis [22], the use of this agent requires close monitoring of liver function. The lack of efficacy of these conventional agents and the marked success of antitumor necrosis factor-α (TNF-α) agents in rheumatoid arthritis (RA) provided the impetus for the development of clinical trials that analyzed the effect of TNF antagonism on the joint and skin manifestations of PsA [23]. Currently, three anti-TNF agents are approved for treatment of psoriatic arthritis in the USA – etanercept, infliximab and adalimumab. This review will outline the rationale for TNF-blockade and summarize the results from randomized clinical trial data regarding the effectiveness and safety of infliximab in PsA.
Role of tumor necrosis factor in PsA

TNF-α, previously also referred to as cachectin, is a member of the TNF superfamily and was first isolated in 1984. TNF is a multifunctional cytokine, produced mostly by activated macrophages and monocytes, that plays a pivotal role in inflammation, growth regulation, cell differentiation and viral replication. TNF has also been implicated in tumorigenesis, allergic responses, autoimmune disease and innate immune reactions to viral, bacterial, fungal and parasitic infections [24]. It promotes joint inflammation by multiple mechanisms, including upregulation of endothelial adhesion molecules, activation of mononuclear cell subsets and release of degradative enzymes. TNF can also potentiate the activity of the receptor activator of nuclear factor κB (RANK/RANKL) signaling pathway. This pathway is required for osteoclastic bone resorption [25]. TNF-α binds to two distinct but structurally similar receptors, p55 and p75, located on the surface of many cells.

Increased understanding of the pathophysiology of PsA has revealed the important role played by T cells and proinflammatory cytokines, such as TNF-α [26], in this disease. Elevated levels of TNF have been identified in the psoriatic serum, synovium and synovial fluid [27–29]. These findings, along with the success of anti-TNF therapy in RA patients, led to initiation of trials to study the effect of anti-TNF agents on PsA involving peripheral joints.

Infliximab

Infliximab (Remicade®, Centocor Inc.), a chimeric human–murine immunoglobulin (Ig)G1-κ monoclonal antibody (mAb) with high affinity and specificity for recombinant and natural human TNF, was first generated in 1993 [30]. To reduce the potential immune response that may have occurred with repeated use of the original murine anti-human mAbs, scientists replaced the murine constant regions with human counterparts and retained the antigen-binding region of the original antibody. The infliximab molecule is approximately 25% murine and 75% human in origin [31].

Chemistry

Infliximab has an approximate molecular weight of 149,100 Da. It specifically binds and efficiently neutralizes human TNF-α but has no effect on the related cytokine TNF-β [30]. It is a mAb that binds both the soluble and the transmembrane forms of TNF-α, thereby inhibiting the binding of TNF-α to its receptors. It mediates both an antibody- and complement-dependent cytotoxicity on a cell line expressing abundant transmembrane TNF-α [32].

Pharmacokinetics

Infliximab has been estimated to have a median half life of 8–9.5 days, for doses of 3–10 mg/kg body weight. A direct, linear relationship is reported between the administered dose and the maximum serum concentration. Age, weight or gender did not seem to affect the clearance of drug, while the effect of hepatic or renal impairment on clearance of drug is not known [33]. Development of antibodies to infliximab increased its clearance.

Drug interactions

While no specific studies have been performed, no drug interactions have been reported between infliximab and other commonly used medications for arthritis [102]. Based on increased frequency of infections, when etanercept and anakinra were combined in one RA trial [33], the use of infliximab with anakinra or with other biologic agents (including TNF antagonists) is not recommended.

Evidence of clinical efficacy

Phase II clinical trial

Antoni and colleagues reported on the results of a Phase II trial of infliximab therapy for skin and joint manifestations of psoriatic arthritis (Infliximab Multinational Psoriatic Arthritis Controlled Trial [IMPACT]) [34]. This was an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled trial. A total of 104 patients with PsA of at least 6 months duration, who had failed at least one DMARD and had five or more swollen and tender joints and an erythrocyte sedimentation rate (ESR) of 28 or greater, or C-reactive protein (CRP) of 15 mg/l or higher and/or morning stiffness of 45 min or more, were randomized to receive infliximab (n = 52) at a dose of 5 mg/kg or placebo (n = 52), at weeks 0, 2, 6 and 14. Patients were allowed concomitant use of DMARDs, steroids (≤10 mg) and NSAIDs at stable doses. In the open-label phase of the study, all subjects were given infliximab at 8-weekly intervals, after an introductory course of infliximab (for patients who had been on placebo) or placebo (for patients who had been on infliximab), at weeks 16, 18 and 22.

The primary end point for the articular manifestations of PsA was the proportion of patients who achieved a 20% improvement in RA in the American College of Rheumatology (ACR) scale.
Infliximab – DRUG EVALUATION

The ACR 20 is defined as a 20% or greater improvement in tender and swollen joint counts and 20% or greater improvement in at least three of the following five measures: pain, patient and physician global assessment, self-assessed physical disability and acute phase reactants [35]. The Psoriasis Area and Severity Index (PASI), the primary efficacy assessment for skin manifestations, was evaluated at weeks 16 and 52. The PASI is calculated based on the extent of psoriasis in the head, trunk, upper and lower extremities graded numerically from 0 to 6 (no involvement to 80–90% involvement, respectively) and the severity of the lesion (degree of erythema, infiltration and desquamation) as assessed on a scale of 0–4. The PASI score ranges 0–72, in steps of 0.1 [36]. Only patients with PASI scores of 2.5 or greater were included in efficacy evaluations. Assessments also made of the number of digits with dactylitis, the Psoriatic Arthritis Response Criteria (PsARC), Disease Activity Score (DAS) 28, presence of enthesitis, the Health Assessment Questionnaire (HAQ) scores, ESR and CRP.

Baseline characteristics were similar in both groups with the exception of the mean CRP, which was higher in the placebo (31.1 mg/l) than in the infliximab group (21.7 mg/l; p = 0.15). Of the 104 patients, 5 discontinued the study, two from the placebo group and three from the infliximab group. Of 52 (65%) patients, 34 achieved an ACR 20 in the infliximab group compared with only five of 52 (10%) in the placebo group (p < 0.001) at week 16. Impressively, 24 patients (46%) achieved an ACR 50 and 15 (29%) reached the ACR 70, while no subjects from the placebo group achieved either of these outcome measures (Table 1). The concomitant use of a DMARD did not appear to influence the proportion of patients achieving an ACR 20 at week 16. The ACR 20 responses were sustained at week 50 in the patients continued on infliximab, while patients initially randomized to placebo exhibited a rapid clinical response after receiving infliximab.

At baseline, 22 patients in the infliximab group and 17 patients in the placebo group had PASI scores of 2.5 or greater. At week 16, a mean improvement of 86% from baseline was noted in the infliximab group compared with a 12% worsening in placebo group (p < 0.0001). A PASI 75, defined as a 75% improvement in disease activity, was seen in 68% of the patients in the infliximab group compared with none in the placebo group (p < 0.001), at week 16. The response to infliximab was sustained at week 50 in the original treatment group, while patients initially randomized to placebo achieved comparable PASI scores at week 50 (Table 1).

A significant improvement was noted for the PsARC and DAS 28, in 75 and 46% of subjects, in the treatment group, compared with 21 and 2.8% in the placebo group, respectively (p < 0.001 for both). Significant improvements were also noted for the HAQ, dactylitis score and the extent of enthesitis (Table 1).

All groups were similar with regard to incidence of adverse events. Severe treatment-related events were reported in two patients in the infliximab group and in one patient in the placebo group.

### Radiographic data

The radiographic analyses of patients from the IMPACT group at 1 year was recently published [37]. The patients enrolled in this trial had x-rays of hands and feet, taken at baseline and week 50. Two radiologists, blinded to treatment arm, scored the images for bone erosion (0–5 in the hands and 0–10 in feet) and joint space narrowing (JSN; 0–4), and calculated total radiographic scores using a PsA-modified van der
Heijde Sharp (vdH-S) scoring method [38]. The total radiographic score ranged from 0 to 528, with higher scores indicating more articular damage.

Of the initial 104 patients enrolled in the trial, 72 were included in the analysis of radiographic data, 35 in the placebo/infliximab group and 37 in the infliximab/infliximab group. At baseline, the number of patients on methotrexate within the placebo/infliximab group (71%) was significantly more than in the infliximab/infliximab group (38%; p = 0.009). The placebo/infliximab group also had less radiographic damage at baseline (p = 0.02). At week 50, no statistically significant differences in the total modified vdH-S score were detected for the hands, feet and the total score for the hands and feet combined, between the placebo/infliximab and the infliximab/infliximab groups. In addition, no significant changes were detected in the erosion scores or the JSN scores except for the JSN scores in the feet, in which the placebo/infliximab group (0.03 ± 0.86) had more radiographic progression than the infliximab/infliximab group (0.35 ± 0.86; p = 0.016) (Table 2).

Interestingly, the majority of patients (n = 59; 84.3%) had no worsening in radiographic progression at 1 year, based on the modified vdH-S score. Furthermore, there was no significant difference in the mean annual progression rate between the treatment groups. The short duration of placebo use, 16 weeks as opposed to 24 weeks in the trials of other anti-TNF agents, may have contributed to the lack of significant change between the two groups. Based on the finding that the mean annual progression rate (estimated at 5.8 modified vdH-S points per year for all patients enrolled in the trial), was reduced to -1.79 vdH-S points with infliximab therapy, the authors concluded that treatment with infliximab inhibited the rate of radiographic progression. Although this interpretation of the data is reasonable, it is important to point out that the vdH-S score has not been validated for use in PsA.

**Phase III clinical trial**

Antoni and colleagues recently reported on the IMPACT 2 study, a Phase III, multicenter, double-blind, randomized, placebo-controlled trial [39]. A total of 200 patients with active disease, defined as the presence of five or more swollen and tender joints, a CRP of 15 mg/l or more or morning stiffness for 45 min or more and a diagnosis of PsA for at least 6 months, were enrolled in this study. Enrollment required a history of inadequate response to a DMARD or NSAID and also the presence of active plaque psoriasis with at least one lesion of greater than 2 cm in size. Concomitant use of methotrexate (up to 25 mg/week) or oral steroids (not ≥10mg of prednisone) at stable doses was allowed. Patients were randomized to infliximab (5 mg/kg body weight) or placebo at weeks 0, 2, 6, 14 and 22. Patients with inadequate responses (<10% improvement in swollen and tender joint counts) at week 16 were eligible to enter early escape and were given infliximab (if they were in the placebo group) or placebo (if they were in the infliximab group), at weeks 16, 18 and 22.

The primary end point was the ACR 20 at week 14. The ACR 20, 50 and 70 as well as other efficacy measurements, including the individual components of ACR and PsARC, were recorded at weeks 14 and 24. The proportion of patients with dactylitis in one or more joints and the number of patients with enthesopathy were also recorded pre- and post-therapy. In patients with greater than 3% psoriasis involvement of body surface area, skin lesions were assessed using the PASI.

Baseline characteristics were similar in the two groups. The primary end point, the ACR 20, was achieved by 58% of those in the infliximab group compared with 11% of those on placebo (p < 0.001), at week 14. Additionally, an ACR 50 and an ACR 70 were achieved by 36 and 15%, respectively, of those in the infliximab group, compared with only 3 and 1% of those in the placebo group. The ACR

<table>
<thead>
<tr>
<th>Joint</th>
<th>Total modified vdH-S score</th>
<th>Erosion score</th>
<th>JSN score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO/IFX</td>
<td>IFX/IFX</td>
<td>PBO/IFX</td>
</tr>
<tr>
<td>Hands</td>
<td>-1.37</td>
<td>-0.87</td>
<td>-0.94</td>
</tr>
<tr>
<td>Feet</td>
<td>-0.53</td>
<td>-0.65</td>
<td>-0.56</td>
</tr>
<tr>
<td>Combined</td>
<td>-1.95</td>
<td>-1.52</td>
<td>-1.48</td>
</tr>
</tbody>
</table>

IFX: Infliximab; JSN: Joint space narrowing; PBO: Placebo; vdH-S-score: Modified van der Heijde Sharp score.
Infliximab – DRUG EVALUATION

quality of life measures

A report by Kavanaugh and colleagues highlighted the effect of infliximab on health-related quality of life (HRQoL) and physical function, based on results from the IMPACT 2 trial [40]. The disability index of the HAQ is a self-administered questionnaire that evaluates the degree of difficulty a person has in accomplishing tasks in eight functional areas [41]. A clinically meaningful change in HAQ has been reported to be 0.3. The short form (SF)-36 is a survey designed for use in clinical practice and research to assess health status and includes one multi-item scale that assesses eight health concepts [42]. Often, two summary measures, the mental component summary (MCS) score and the physical component summary (PCS), are reported.

At week 14, 58.6% of patients in the infliximab group achieved a clinically meaningful improvement in HAQ, compared with 19.4% in the placebo group (p < 0.001) (Table 4). This benefit was maintained at week 24. The IMPACT 2 trial also reported significant improvements in all measures of the SF-36 at week 14 and all but one measure at week 24. The mean improvements in the PCS score for the infliximab and placebo groups were 9.1 and 1.1 at week 14, and 7.7 and 1.3 at week 24, respectively (p < 0.001 at both points). Similarly, the mean improvement in the MCS was 3.8 and 3.9 in the infliximab group compared with -1.2 (p = 0.001) and 0.4 (p > 0.05) in the placebo group, at weeks 14 and 24. The use of concomitant methotrexate did not appear to influence changes in the HAQ or measures of SF-36.

Interestingly greater improvements in the PCS and MCS scores were associated with greater improvements in the ACR and PASI. Patients who

Table 3. Percentage improvement in clinical efficacy parameters in the infliximab and placebo groups at weeks 14 and 24.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 14</th>
<th></th>
<th></th>
<th>Week 24</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (%)</td>
<td>Infliximab (%)</td>
<td>p-value</td>
<td>Placebo (%)</td>
<td>Infliximab (%)</td>
<td>p-value</td>
</tr>
<tr>
<td>ACR 20</td>
<td>11</td>
<td>58</td>
<td>&lt;0.001</td>
<td>16</td>
<td>54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACR 50</td>
<td>3</td>
<td>36</td>
<td>&lt;0.001</td>
<td>4</td>
<td>41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACR 70</td>
<td>1</td>
<td>15</td>
<td>&lt;0.001</td>
<td>2</td>
<td>27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PsARC</td>
<td>27</td>
<td>77</td>
<td>&lt;0.001</td>
<td>32</td>
<td>70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>30</td>
<td>18</td>
<td>0.025</td>
<td>34</td>
<td>12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>34</td>
<td>22</td>
<td>0.016</td>
<td>37</td>
<td>20</td>
<td>0.002</td>
</tr>
<tr>
<td>PASI 50</td>
<td>9</td>
<td>82</td>
<td>&lt;0.001</td>
<td>8</td>
<td>75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PASI 70</td>
<td>2</td>
<td>64</td>
<td>&lt;0.001</td>
<td>1</td>
<td>60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PASI 90</td>
<td>0</td>
<td>41</td>
<td>&lt;0.001</td>
<td>0</td>
<td>39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACR: American College of Rheumatology; PASI: Psoriasis Area and Severity Index.

20, 50 and 70 responses were also significantly higher in the infliximab group compared with the placebo arm, at week 24 (Table 3). The concomitant use of methotrexate did not appear to have any effect on efficacy. Significant improvements were also noted, at weeks 14 and 24, for individual measures of the ACR, the PsARC, as well as dactylitis and enthesitis outcomes (Table 3).

The authors reported 170 patients with psoriasis affecting more than 3% of body surface area. The proportion of patients achieving a PASI 75 score was significantly higher in the infliximab group (64%) than in the placebo (2%) group (p < 0.001) at week 14. Similar findings were recorded at week 24.

Although infliximab was generally well tolerated, the percentage of patients who experienced adverse events and therefore discontinued the study was higher in the infliximab group. Elevated transaminase levels were noted more frequently in patients on infliximab, with markedly elevated levels (alanine transaminase >150 IU/l or ≥100% increase from baseline) recorded in five patients receiving infliximab and none in the placebo group. Only one of these five patients was receiving methotrexate; all five discontinued infliximab and in four of these patients, transaminases reverted to normal. The other patient was lost to follow-up. Antibodies to infliximab were detected in 4.5% of patients, through week 22. Newly positive antinuclear antibodies (ANA) at titers higher than 1:160, was found in 9.9% of patients (three of these patients had anti-double stranded DNA), compared with 2.2% of those on placebo. No cases of lupus-like disease were reported.
achieved an ACR 20 but not a PASI 75 response had greater improvement in the PCS scores but less in the MCS scores, suggesting that articular involvement may have a greater effect on the physical component of the quality of life in PsA patients, while dermatological involvement may have a greater effect on the mental component.

Other clinical trials
Several open-label trials have been reported. While a review of all of these reports are beyond the scope of this article, some of these studies have provided insights into the pathogenesis of psoriatic arthritis and the possible mechanisms of action of anti-TNF-α therapy. Canete and colleagues analyzed the effects of anti-TNF-α therapy on angiogenesis in the synovial tissue of nine patients with PsA [43]. Subjects were treated with infliximab infusions (5 mg/kg body weight) at weeks 0, 2 and 6. Significant decreases were noted in the number of macrophages (CD68+), extent of vascularity (p = 0.04) and in several angiogenesis markers at week 8, compared with baseline. Goedkoop and colleagues also reported similar results in psoriatic skin and synovial tissues [44]. In a trial of 11 patients with active PsA who were administered infliximab (3 mg/kg) the number of CD3+ T cells was decreased at week 4, in both the skin and synovium. The mean number of blood vessels/mm³ was significantly reduced in both the dermis and synovial tissue (p ≤ 0.02 for both). These studies suggest that one of the primary effects of anti-TNF-α therapy may be the deactivation of vascular endothelium, resulting in reduced migration and homing of inflammatory cells into the synovial tissue.

Safety & tolerability
TNF is a pivotal cytokine in the innate immune response to infections. A major concern with the use of anti-TNF therapy, therefore, has been for an increased risk for infections due to TNF suppression. However, no opportunistic infections or tuberculosis were reported in the Phase II or III trials. Upper respiratory tract infections, followed by pharyngitis and sinusitis, were the most common infections. Although no cases of lymphoma were reported, these trials were relatively small and of short duration and were not powered to detect these rare adverse events.

A report from Germany found a relative risk of 3.0 for serious infections in RA patients treated with infliximab [45]. A recent meta-analysis of RA patients treated with infliximab and adalimumab also demonstrated a significant increase in serious infections [46]. The authors calculated a pooled odds ratio (OR) of 3.3 for malignancies in RA patients treated with monoclonal anti-TNF therapy compared with patients on placebo. Furthermore, they estimated that the risk for malignancies was increased with the higher dose of these monoclonal antibodies (OR of 4.3 for high-dose anti-TNF versus placebo compared with an OR of 1.4 for low dose anti-TNF therapy vs placebo). While one cannot directly extrapolate these findings to patients with PsA, it does emphasize the importance of vigilance of patients treated with anti-TNF agents.

Most of the postmarketing surveillance reports have been generated from the studies of infliximab for RA. These reports have suggested an increased risk of serious infections with anti-TNF therapies [47–49]. Severe abnormalities of liver function, including acute liver failure, hepatitis and cholestasis have occurred with some reported fatalities. Rare cases of pancytopenia, optic neuritis, seizure onset or exacerbation of clinical symptoms and demyelinating disorders and CNS manifestations of systemic vasculitis have been reported.

During the controlled segments of various infliximab trials, more cases of malignancies were reported in those receiving TNF blockers compared with controls (0.65/100 vs 0.13/100 patient-years). Analysis of postmarketing surveillance data suggest that the rate of malignancies in the infliximab-treated patients was similar to that expected in the general population, while it was lower in the control patients. Lymphomas were, however, fivefold higher in the clinical trial

<table>
<thead>
<tr>
<th>Measure</th>
<th>Week 14</th>
<th>p-value</th>
<th>Week 24</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Infliximab</td>
<td></td>
<td>Placebo</td>
<td>Infliximab</td>
</tr>
<tr>
<td>HAQ</td>
<td>19.4</td>
<td>58.6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>1.1</td>
<td>9.1</td>
<td>&lt;0.001</td>
<td>1.3</td>
</tr>
<tr>
<td>MCS</td>
<td>-1.2</td>
<td>3.8</td>
<td>0.001</td>
<td>0.4</td>
</tr>
</tbody>
</table>

HAQ: Health assessment questionnaire; MCS: Mental component summary; PCS: Physical component summary.
population receiving infliximab for RA, Crohn’s, PsA, ankylosing spondylitis (AS) and ulcerative colitis than in the general population.

Conclusion
The trials outlined above demonstrate that infliximab is an effective and generally well-tolerated therapy for patients with PA. More than half the patients treated with infliximab experienced a marked improvement in symptoms and signs of arthritis. In addition, approximately two-thirds of patients realized a significant improvement in skin disease. Although no head-to-head to studies are available, the results of the above trials suggest that infliximab demonstrated greater efficacy for psoriasis than etanercept. A reduction in extent of enthesopathy and dactylitis was also demonstrated. Interestingly, unlike in RA, no synergistic response was detected with concomitant use of methotrexate. The side effects between those receiving placebo and infliximab were comparable. Recent reports of an increased rate of malignancies and infections with use of monoclonal anti-TNF agents, however, suggest a need for continued vigilance of patients receiving treatment with these agents.

Future perspective
The TNF antagonists have greatly altered the therapeutic landscape for PA. These agents have been shown to be effective for treatment of the multiple manifestations of PsA, including axial and peripheral joint inflammation and skin disease. Furthermore, only anti-TNF agents have been shown to retard radiographic progression in patients with PsA. In addition, infliximab is currently the only agent with proven efficacy in the treatment of psoriatic enthesitis and dactylitis. Reports of reduced cardiovascular risk in RA patients treated with anti-TNF therapies [50] may be an added benefit, given that PsA patients have a significantly larger body mass index than the RA patients [51] and patients with psoriasis have a higher prevalence of diabetes, obesity and metabolic syndrome compared with healthy controls [52]. The efficacy and safety of anti-TNF therapy in PsA combined with the convenience of a single agent for the treatment of the multiple facets of PsA suggest that infliximab and other anti-TNF agents should be considered early in the treatment of PsA.

The efficacy and convenience of infliximab for the treatment of PsA must be balanced by a careful appraisal of adverse events and economic impact. Although no increase in risk of infections was observed in the randomized trials cited above, postmarketing surveillance and the previously described meta-analysis demonstrated that serious infections have been associated with infliximab and other anti-TNF therapies in RA. To determine the position of infliximab in the treatment scheme of PsA, one should also consider the issue of cost. Indeed, despite limited evidence for efficacy of DMARDs in PsA, cost considerations have strongly influenced the treatment guidelines which mandate a trial of DMARDs for PsA patients with peripheral joint disease prior to anti-TNF therapy. For example, the British Society for Rheumatology PsA Treatment Guidelines state that anti-TNF therapy in patients with peripheral joint disease should only be considered if patients fail to respond to two DMARDs [53]. On the other hand, increased understanding of the economic benefits (quality-adjusted life years) will be important to factor into the therapy equation, since long-term benefits may include the reduced need for joint replacement surgery, lower demand for medical and nursing therapies and improved quality of life with increased life expectancy [53]. Thus, the costs of infliximab therapy must be weighed against the short- and long-term benefits to patients and society [54].

For the treatment of PsA, the recommended starting dose for infliximab is 5mg/kg body weight compared with 3 mg/kg in RA. The use of a higher dose was based on a small study of patients with undifferentiated spondyloarthropathy which showed a superior effect with a dose of 5 mg/kg compared with 3 mg/kg body weight [55]. A recent trial of 22 patients with AS reported that infliximab at a dose of 3 mg/kg body weight may also be effective [56]. Demonstrated efficacy of a lower dose of infliximab would decrease the cost and possibly reduce risk of infection or malignancy.

No added benefit has been demonstrated with the combination of infliximab and MTX compared with infliximab alone for therapy in PsA. Similar findings were noted in PsA trials with etanercept [57] and adalimumab [58]. One cannot make definite conclusions regarding this lack of synergy because the studies cited above were not designed or powered to address this question. Nevertheless, possible explanations for the divergent responses seen in PsA compared with RA include differences in trial design, lack of efficacy for methotrexate in PsA or the fact that patients experienced a high level of efficacy with TNF antagonists that could not be improved with
concomitant methotrexate. A prospective randomized trial will be required to formally address these questions.

Despite the marked efficacy and safety of infliximab and other TNF antagonists in PsA, several other biologic agents are currently in development. Alefacept (a human leukocyte function antigen-3 linked to an IgG1 antibody) and efalizumab (anti-CD11a) are FDA approved for treatment of psoriasis, and a recent trial demonstrated that alefacept in combination with methotrexate may also be effective in the treatment of PsA [59]. Studies with, abatacept (cytotoxic T-lymphocyte-4 IgG), rituximab (anti-CD 20) and anti-interleukin 12 antibody are either in progress or in the planning stages for psoriasis and PsA. Indeed, the treatment paradigm for psoriatic skin and joint disease will continue to evolve as the benefits, safety and tolerability of these new biologic agents are better understood.

**Executive summary**

**Molecule**
- Infliximab is a chimeric monoclonal antibody against tumor necrosis factor.

**Dosage & administration for psoriatic arthritis (PsA)**
- Infliximab is administered by intravenous infusion over 2–3 h.
- The recommended dose is 5 mg/kg body weight.
- The first three doses are given at weeks 0, 2 and 6, followed by infusions every 8 weeks.
- Infliximab can be used with or without methotrexate or other disease-modifying antirheumatic drugs (DMARDs).

**Clinical efficacy**
- The clinical efficacy of infliximab in the treatment of PsA was demonstrated by the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT) 1 (Phase II) and IMPACT 2 (Phase III) trials.
- Improvements were noted in both skin and joint manifestations of psoriasis.
- First antitumor necrosis factor agent to demonstrate efficacy in treatment of enthesopathy and dactylitis in randomized clinical trials.
- Improves function and quality of life measures.
- Retards radiographic progression of PsA.

**Safety**
- Therapy is generally well tolerated.
- Increased risk for infections, tuberculosis and hepatosplenic T-cell lymphomas have led to a black box warning.
- Other side effects include increased risk for malignancies, hepatotoxicity, reactivation of hepatitis B, rare hematological and neurological events.
- Hypersensitivity reactions can occur during infusions.
- Safety for use of infliximab in pregnancy is unclear.

**Bibliography**
Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


• Excellent review on the role of non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) in psoriatic arthritis.


• Treatment guidelines for PsA based on systemic review of available treatments by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).


• First randomized, controlled trial demonstrating efficacy of infliximab in psoriatic arthritis (PsA).


• Phase III clinical trial of infliximab for PsA.


• Provides insights into pathogenesis of PsA and for possible mechanism of action of infliximab.


Websites


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