Psoriatic arthritis (PsA) is the second most common inflammatory arthritis and is one of the seronegative spondyloarthropathies. Although cohorts of PsA patients show less radiographic damage than rheumatoid arthritis (RA) patients with comparable disease durations, PsA has a similar impact on quality of life for these patients.1 Observational studies in PsA have shown that peripheral joint disease activity is a key predictor of future joint damage,2 and this has led to an increasing emphasis on treatment of PsA. Traditionally, treatment has relied on disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine, despite the lack of good-quality evidence of their efficacy. More recently, the treatment of resistant peripheral PsA has been revolutionised by tumour necrosis factor (TNF)-blocking therapies. TNF is a key pro-inflammatory cytokine, and research in PsA has confirmed high levels of TNF in both psoriatic plaques in the skin and synovial fluid taken from active arthritic joints.3 This early research provided a rationale for its use in the treatment of PsA, and clinical trials with this class of drugs have shown excellent clinical benefit. Currently, there are three TNF blockers available in routine clinical practice (etanercept, infliximab and adalimumab), and the evidence from trials of these drugs as well as registry data of their clinical use is discussed in this article. New agents targeting TNF and other key inflammatory mediators are being trialled in psoriasis and PsA, and are also summarised.

These new drugs have had a significant impact on the ability to manage peripheral PsA with evidence-based treatments. However, the vast majority of treatment studies in PsA have concentrated on resistant peripheral polyarticular disease. There has been little research into the typical asymmetrical oligoarticular disease subtype and few studies have concentrated on efficacy in other aspects of psoriatic disease, including dactylitis, enthesitis and spinal involvement. This is due partly to a lack of outcome measures specifically designed and validated for PsA. The majority of treatment studies report outcomes with American College of Rheumatology (ACR) response rates, which have been validated retrospectively for polyarticular peripheral PsA but do not encompass other aspects of the disease. More recently, new outcome measures designed specifically for PsA have been developed, and work is ongoing to develop a composite disease activity measure for PsA. In the future, this should improve the design of trials and provide additional information on the efficacy of treatments for all aspects of the disease.

In the final section of this article, different treatment strategies are discussed. The strategy for the treatment of RA has been revolutionised in recent years, and research in PsA is now investigating the concept of early and aggressive treatment.

### Etanercept

Etanercept was the first anti-TNF therapy to be tested in a randomised trial in patients with PsA. Etanercept is a soluble TNF receptor antagonist usually given by weekly subcutaneous injection. The phase II study of etanercept in active PsA and psoriasis showed an impressive response to treatment with 87% of etanercept-treated patients...
achieving PsA Response Criteria (PsARC) compared with 23% of placebo-treated patients. There was also a significant improvement in patient-reported disability as measured by the Health Assessment Questionnaire (HAQ) following treatment with etanercept, and patients with substantial skin psoriasis also showed a significant improvement in the Psoriasis Area and Severity Index (PASI) scores. The safety profile seemed acceptable, with no significant increase in adverse events. A larger phase III study (n=205) confirmed the articular and cutaneous response to etanercept and, in addition, showed that radiographic disease progression at 12 months was halted by etanercept treatment (mean annualised rate of change in modified Total Sharp Score [mTSS] was -0.03 compared with +1.00 in the placebo group). Infliximab infliximab is a chimeric anti-TNF monoclonal antibody given by intravenous infusion every six to eight weeks. Studies of infliximab in PsA (Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT and IMPACT2)) have shown a significant benefit in peripheral joint disease, physical function, skin psoriasis, enthesis and dactylitis. The larger phase III study also allowed a more thorough assessment of safety. The overall incidence of adverse events was similar in both groups, although increases in liver function tests were seen more commonly in the infliximab group.

Analysis of the phase II trial suggested a halt in radiographic progression with infliximab therapy, but there was no direct comparison against placebo. The analysis of joint damage for the IMPACT2 study was more robust, analysing radiographs at baseline, week 24 (prior to cross-over) and week 54. These showed a significant reduction in radiographic damage in the infliximab group compared with placebo at week 24, despite the fact that nearly half of the placebo-treated patients actually entered an ‘early escape’ arm and had received eight weeks of treatment with infliximab. Repeat radiographs at week 54 showed continued inhibition of joint damage.

Adalimumab Adalimumab is a fully human anti-TNF monoclonal antibody given by subcutaneous injection every two weeks. The Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT) tested adalimumab in patients with active PsA. Interestingly, around 10% of the patients had a positive rheumatoid factor (RF), but all had active skin psoriasis or a documented history of psoriasis. In this study, sub-groups of PsA are reported, showing that 67% had polyarticular disease but 25% of patients did have a typical asymmetrical oligoarthritis. A significant improvement with adalimumab was noted in peripheral joint disease, skin disease, function, health-related quality of life and fatigue. ADEPT also confirmed the inhibition of joint damage seen with anti-TNF treatment, showing a halt in radiographic progression as measured by the mTSS. The safety profile of adalimumab was also similar to that of other anti-TNF therapies, with similar numbers of adverse events in both groups; however, a small increase in liver enzymes was seen with adalimumab-treated patients. Subsequent analyses, after weeks 48 and 144 of the open-label extension study, have showed continued inhibition of disease activity and joint damage as well as sustained improvements in assessments of disability.

Anti-tumour Necrosis Factor Therapy in Clinical Practice The three anti-TNF therapies discussed are now widely used across Europe and the US. Although the majority of the data from large registries have concentrated on RA, observational data from cohorts of patients with PsA are now being published. Registries in Spain and Norway have shown a high persistence with anti-TNF drugs, with 77–88% of patients continuing on the drug at one year. Data from the Swedish registry confirmed good responses to anti-TNF therapy but also highlighted a better persistence with therapy if concomitant methotrexate was used. This seemed to relate to a lower incidence of adverse events. Data from the British Biologics Registry found similar responses at one year but showed a continued decrease in persistence at two and three years. It appeared that persistence with infliximab was lower than with the other anti-TNF agents, predominantly because of infusion reactions with infliximab. Small case series evaluating the use of ‘switching’ anti-TNF therapies in the case of adverse events or non-response have been reported. Overall, 90% of patients achieved a significant response, with 20% of cases switching therapy. Patients who switched drug due to adverse events seemed to have good responses to second- and third-line anti-TNF therapies. However, the response rate was lower in those who switched for inefficacy.

New Anti-tumour Necrosis Factor Therapies in Development Golimumab is a more recent anti-TNF agent that has not been licensed for PsA. It is a human monoclonal antibody that can be given by intravenous infusion or by four-weekly subcutaneous injection. A large study (GO-REVEAL) of PsA patients who were either non-steroidal anti-inflammatory drug (NSAID) or DMARD non-responders showed that a significantly higher proportion achieved the American College of Rheumatology 20% (ACR20) response after just four injections (at weeks zero, four, eight and 12). There was no statistical difference dependent on whether patients were taking methotrexate, and there was no marked difference between the two golimumab doses. In addition to improvement in function and quality of life, there was an improvement in enthesitis, dactylitis and nail psoriasis. Ongoing analysis from this study has shown impressive clinical responses up to week 10, and has confirmed a reduction in radiographic progression in the one-year data for golimumab. Additional analyses have investigated the effect of golimumab treatment in health economic terms, showing benefit even in the short placebo-controlled phase of the GO-REVEAL study.

Certolizumab pegol is a PEGylated Fab’ fragment of a humanised anti-TNF antibody that binds TNF. It has proven efficacy in RA given subcutaneously every fortnight and has already been investigated in plaque psoriasis, where it showed significant improvement in psoriasis compared with placebo. Trials in PsA are planned, but results have not been published.

New Biological Agents with Alternative Modes of Action Although TNF-blocking agents are remarkably effective in PsA, there is a subgroup of patients who seem to be resistant to these drugs or in whom efficacy decreases over time. More recent therapies with different modes of action provide an alternative treatment for patients with resistant disease. However, as newer modes of action become available, research must help clinicians to evaluate which therapies should be used first-line and subsequently. Currently, no head-to-head trials exist comparing biological therapies in PsA, meaning that decisions about which therapies to use in individual cases have a poor evidence base. These therapies are unlicensed for PsA but have shown promise in early trials.
Psoriatic Arthritis

Table 1: Day 169 Results of the Abatacept in Psoriatic Arthritis Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Abatacept</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>3mg/kg</td>
<td>10mg/kg</td>
</tr>
<tr>
<td>All patients (%)</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>Previous TNF (%)</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>Target lesion 50 (%)</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>Target lesion 75 (%)</td>
<td>10</td>
<td>29</td>
</tr>
</tbody>
</table>

ACR = American College of Rheumatology; HAQ = Health Assessment Questionnaire; TNF = tumour necrosis factor.

Table 2: 12-week Results of the Apremilast in Psoriatic Arthritis Trial

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Placebo</th>
<th>Apremilast 20mg BD</th>
<th>Apremilast 40mg OD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 (%)</td>
<td>11.8</td>
<td>43.5</td>
<td>35.8</td>
</tr>
<tr>
<td>ACR50 (%)</td>
<td>2.9</td>
<td>17.4</td>
<td>13.4</td>
</tr>
<tr>
<td>ACR70 (%)</td>
<td>1.5</td>
<td>5.8</td>
<td>7.5</td>
</tr>
</tbody>
</table>

ACR = American College of Rheumatology; BD = twice daily; OD = once daily.

Ustekinumab

Ustekinumab is the first biological drug that is not a TNF blocker to show efficacy in PsA. Ustekinumab is a human monoclonal antibody that binds to the p40 subunit present on both human interleukin (IL)-12 and IL-23. It prevents binding of these interleukins to the IL-12p40 receptor, blocking this signalling pathway. Genetics studies in psoriasis and PsA have confirmed a significant association with alleles of the IL12B and IL23 receptor gene, and this has been confirmed in multiple studies. Studies in patients with skin psoriasis have shown a significant response to ustekinumab, and therefore trials in PsA were conducted.

The phase II trial of ustekinumab in PsA recruited 146 patients to a double-blind, cross-over, randomised trial, where they were randomised into two groups. Patients in group one received four weekly infusions of ustekinumab at weeks zero, one, two and three and were monitored for response. At week 12, patients ‘crossed over’ to the other arm and group one then received placebo infusions. Group two were given four placebo infusions at weeks zero, one, two and three but were then treated with two infusions of ustekinumab given at week 12 and week 16. At week 12, a greater proportion of patients who had received ustekinumab achieved the ACR20, ACR50 and ACR70 response measures (p<0.01). PASI responses reported for those patients with a body surface area (BSA) of at least 3% were also significant for both PASI75 and PASI90. The proportion meeting these response criteria peaked at weeks 12–16 and then showed a very gradual decline to week 36. At week 24, after the cross-over, patients in group two showed similar ACR20 responses following two doses of ustekinumab to those in group one. In addition to these responses, improvement was also seen in patients with enthesitis (bilateral plantar fascia and Achilles tendons) and dactylitis. Significant improvement in function, as measured by the HAQ, was also seen following treatment with ustekinumab.

Ustekinumab also seemed to be well tolerated in this short study. Rates of adverse events and infections were similar in both groups, although it was noteworthy that three patients developed abnormal fasting blood glucose levels during the study. This may be a reflection of the high rate of metabolic syndrome seen in patients with psoriasis and PsA, but it does require further evaluation in larger prospective studies. Phase III trials of ustekinumab are planned to further evaluate optimal dosing regimens and safety in PsA. From this study, it seems possible that ustekinumab may be less effective in treating PsA than the TNF blockers. However, this is a small study and the populations in all of the individual randomised controlled trials differ significantly.

Abatacept

Abatacept (CTLA4 Ig) is a selective T-cell co-stimulation modulator with proven efficacy in RA. A phase II study investigating its use in PsA was presented at the ACR annual meeting in 2009. Patients with PsA and active skin psoriasis were recruited and randomised 1:1:1:1 to placebo, abatacept 3mg/kg, abatacept 10mg/kg or abatacept 30/10mg/kg. The final group received two loading doses of 30mg/kg abatacept followed by subsequent 10mg/kg doses for the rest of the study. The drug was well tolerated, with only 17 discontinuations for inefficacy (n<7) or adverse events (n=10) by six months. At six months, there was a significant difference in the proportion of patients achieving the ACR20 response in the two groups receiving 10mg/kg compared with placebo (see Table 1). A lower response rate was seen in the 3mg/kg group, and this was not significantly higher than the placebo rate. When considering skin responses, both the 3 and 10mg/kg doses improved psoriasis target lesion scores significantly.

This trial has only been presented in abstract form. It is disappointing that the results given in Table 1 only include ACR20 as an arthritis response measure and do not include any results for higher response rates (ACR50 and 70). It appears, like ustekinumab, that the response rates seem lower than expected compared with studies of TNF blockers. In addition, during sub-analysis it was noted that patients who had been exposed to anti-TNF therapy previously had poorer response rates. This is demonstrated clearly in Table 1, where ACR20 responses appear lower for this group. Although this is perhaps not surprising, it is disappointing as it was hoped that drugs with a different mode of action would provide a therapeutic option for TNF-resistant patients. Further data from this study and larger future trials are necessary to characterise the response rate in more detail.

Apremilast

Apremilast is a new phosphodiesterase-4 (PD4) inhibitor that is active orally. The suppression of PD4 causes suppression of multiple inflammatory cytokines, including TNF. Studies in psoriasis showed moderate activity, similar in response rate to ciclosporin. Phase II trials in PsA have been completed. Although the response rates are significantly lower than would be expected in a trial of anti-TNF therapy, it does show efficacy in arthritis (see Table 2). There were significant differences in the proportions of people achieving ACR20 and ACR50 response rates compared with placebo.

Treatment Strategies

In addition to the newer biological therapies available for PsA, the strategy of treatment is now being questioned. Over the last 15 years, multiple studies in RA have shown that aggressive early treatment can improve outcome. A meta-analysis showed that early treatment with DMARDs resulted in a significant 33% reduction in long-term radiographic damage compared with later treatment initiation.
TNF-blocking therapies have also been used in early interventional studies in RA, with remarkable benefit and high rates of remission. In addition to early treatment, the concept of ‘tight control’ has also revolutionised care in RA. This was introduced by the Tight Control for Rheumatoid Arthritis (TICORA) study, comparing standard care and intensive management in RA. Despite only using conventional DMARDs in established disease, the study was able to demonstrate a significant benefit in clinical disease activity and radiographic progression for those treated in the intensive management arm. Since this demonstration of tight control, large numbers of studies in RA have adopted the use of the disease activity score (DAS) within a treatment protocol.

The concept of early aggressive treatment has not been well investigated in PsA. A small unblinded study of 35 patients with recent onset (<12 weeks) psoriatic oligoarthritis compared NSAID treatment with or without methotrexate. At three months, both groups showed a significant improvement compared with baseline but the methotrexate therapy group had a significantly greater improvement in their tender and swollen joint counts (p<0.05). At six months, there was no significant difference between the groups. The authors concluded that methotrexate was only providing partial disease control and recommended treatment combining TNF-blocking therapy and methotrexate. However, the dose of methotrexate given is not specified and the study was only of six months’ duration. The long-term outcome in this small cohort is unknown.

One observational cohort study of early treatment in PsA found a surprisingly high frequency of remission using methotrexate or a combination of methotrexate and ciclosporin if required. From 2003, infliximab and etanercept were also used in the case of non-response to methotrexate or multiple DMARDs. It was found that 24% achieved remission (defined as low visual analogue scores, no active joints, C-reactive protein <0.5mg/dl, no dactylitis/enthesitis/inflammatory spinal pain), but there was no control group for comparison. Although the frequency of remission was higher in those treated with TNF-blocking therapy (79.5 versus 20.4%; p<0.001), there was no significant difference between the groups. The authors concluded that methotrexate was only providing partial disease control and recommended treatment combining TNF-blocking therapy and methotrexate. However, the dose of methotrexate given is not specified and the study was only of six months’ duration. The long-term outcome in this small cohort is unknown.

To date, only one randomised study, the Remicade Study in Psoriatic Arthritis Patients of Methotrexate-Naïve Disease (RESPOND) trial, has investigated the use of early TNF-blocking therapy in PsA. A cohort of 110 DMARD-naïve patients with polyarticular PsA of less than two years’ duration were randomised to receive either methotrexate or a combination of methotrexate and infliximab. There was a significant improvement in all outcomes in favour of infliximab, with an ACR20 response of 86% and an ACR70 response of 50% (see Table 3). This study has also provided evidence for the benefit of methotrexate in early PsA, with an ACR20 response of 66.7%. To date, the concept of tight control has not been investigated in PsA. The obvious limitation in designing such a study is that there was no measure of an acceptable disease state available for PsA that could be utilised instead of the DAS low disease activity state. This may be possible in the future, as an objective target for treatment in PsA has now been developed. As in other inflammatory arthropides, remission is considered the ultimate goal of therapy in PsA. However, it is recognised that remission may be difficult to achieve and maintain and that, in some patients, mild disease activity in one domain may be acceptable. Minimal disease activity (MDA) has been defined by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group as “that state of disease activity deemed a useful target of treatment by both the patient and physician, given current treatment possibilities and limitations”. MDA encompasses both remission and ‘low disease activity’ as acceptable targets for therapy. MDA criteria have now been developed using expert consensus on patient-derived data. The criteria are shown in Table 4.

These new criteria have been tested in both observational cohorts and retrospective analyses of randomised trial data, and achievement of MDA has been shown to predict a better prognosis in terms of clinical and radiographic joint damage. These data suggest a possible role for early intervention with the aim of achieving MDA to improve prognosis in PsA. The use of this new strategy in combination with current therapies and new drugs in development should help clinicians to optimise the treatment of PsA.

**Conclusions**

The advent of new therapies targeting multiple inflammatory mediators in PsA provides new therapeutic options for patients with resistant peripheral joint disease. Therapeutic studies are starting to address other aspects of PsA, including dactylitis and enthesitis, but further research is required to investigate treatments for oligoarticular disease and spinal disease in PsA. Treatment strategies are evolving in line with those in RA to focus on early treatment with effective therapies to improve the long-term outcome in PsA. 

### Table 3: Results of the RESPOND Trial Comparing Methotrexate or Methotrexate with Infliximab in Early Psoriatic Arthritis

<table>
<thead>
<tr>
<th></th>
<th>Infliximab and Methotrexate</th>
<th>Methotrexate Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean TJC</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Mean SJC</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Mean CRP (mg/l)</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>Mean DAS</td>
<td>5.16</td>
<td>5.07</td>
</tr>
<tr>
<td>Mean PASI</td>
<td>8.27</td>
<td>11.62</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR20/50/70 (%)</td>
<td>86/72/50</td>
<td>66.7/39.6/18.8</td>
</tr>
<tr>
<td>Good/moderate EULAR (%)</td>
<td>82.4/15.7</td>
<td>33.3/39.6</td>
</tr>
<tr>
<td>DAS28 response</td>
<td>68.6</td>
<td>29.2</td>
</tr>
<tr>
<td>(reduction of 1.2) (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASI 50/75/90 (%)</td>
<td>100/97/70.6</td>
<td>80/54/28.6</td>
</tr>
</tbody>
</table>

**Table 4: Minimal Disease Activity Criteria for Psoriatic Arthritis**

To achieve minimal disease activity, patients must meet at least five of the following seven cut-points:

- Tender joint count ≤1
- Swollen joint count ≤1
- PASI ≤1 or BSA ≤3
- Patient pain VAS ≤15
- Patient global activity VAS ≤20
- HAQ ≤0.5
- Tender entheseal points ≤1

BSA = body surface area; HAQ = Health Assessment Questionnaire; PASI = Psoriasis Area and Severity Index; VAS = visual analogue scale.
Psoriatic Arthritis


