

# Therapies for Peripheral Joint Disease in Psoriatic Arthritis. A Systematic Review

ENRIQUE R. SORIANO and NEIL J. McHUGH

**ABSTRACT.** Traditional drug treatments for psoriatic arthritis (PsA) include nonsteroidal antiinflammatory agents (NSAID) and disease modifying antirheumatic drugs (DMARD), although the evidence base for their effectiveness is not well established. This review was compiled from a comprehensive literature search of electronic bibliographic databases for all English publications that were systematic reviews, meta-analyses, randomized controlled trials, controlled trials, and observational studies. The evidence supports NSAID for symptom relief, although data are lacking for COX-2-specific agents. No evidence exists to support systemic corticosteroids or corticosteroids by intraarticular injection, although the latter are commonly used in clinical practice. Among traditional DMARD, grade 1B evidence supports sulfasalazine, cyclosporine, and leflunomide for symptom relief, with lower-grade evidence for methotrexate. None of them slows radiographic progression. Grade 1B evidence supports improvement in symptoms, physical function, quality of life, and radiographic progression with anti-TNF antagonists (etanercept, infliximab, and adalimumab). The relative lack of evidence poses challenges in developing algorithms for treatment of peripheral arthritis in PsA. (First Release May 15 2006; J Rheumatol 2006;33:1422–30)

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## INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disorder that can affect peripheral joints and the spine and that also can cause widespread destructive joint disease and/or ankylosis in its most severe form. Traditional drug treatments for PsA include nonsteroidal antiinflammatory agents (NSAID) and disease modifying antirheumatic drugs (DMARD), which are used for rheumatoid arthritis (RA). Their effectiveness in PsA, however, is not well established. We review the available evidence for the efficacy and potential toxicity of drug treatments for peripheral joint disease in PsA.

Various patterns of peripheral joint disease have been described for PsA, and these subgroups tend to change over time<sup>1</sup>. In contrast to RA, PsA may involve the distal interphalangeal joints of the hands and the interphalangeal joints of the feet. Peripheral joint involvement may appear less symmetrical than in RA, probably reflecting involvement of fewer joints<sup>2</sup>. There appear to be important differences in peripheral joint synovial histology between PsA and RA. The lining layer of synovial tissue in patients with PsA is not as thick and has greater vascularity<sup>3</sup>.

Peripheral joint disease is often progressive despite use of conventional DMARD<sup>1,4-6</sup>. Erosive and deforming arthritis occurs in 40%–60% of hospital-based patients with PsA and

is progressive from within the first year of diagnosis<sup>1,4,6</sup>. Almost 20% of patients with PsA develop severe, destructive, and deforming arthritis<sup>7</sup>. Moreover, patients with PsA are at greater risk of death compared with the general population<sup>8</sup>. Active and severe disease at presentation is predictive of mortality<sup>9</sup>. Persistently active disease despite drug treatment was found in 72% of a single series, in which 52% of patients in remission had a flare after an average of 2.5 years of remission<sup>9</sup>. Health-related quality of life, as measured by the Medical Outcomes Study Short Form health survey (SF-36) and the Health Assessment Questionnaire (HAQ), is lower in PsA compared to the normal population and is adversely affected to a degree equivalent to RA<sup>10</sup>. Therefore, a review of newer treatments that may prove more effective in slowing disease progression is timely and necessary in shaping guidelines for treatment.

## Search Strategy

The evidence in this review was compiled from a comprehensive literature search of electronic bibliographic databases (Medline, EMBASE, and Ovid) from 1966 to the present, and systematic review databases (Cochrane). Keywords used were psoriatic arthritis therapy and/or treatment, psoriasis/psoriatic, and individual DMARD. The search strategy was supplemented by manually searching references of previous publications; all English publications in the form of systematic reviews, metaanalyses, randomized controlled trials (RCT), controlled trials, and observational studies were included.

In the initial search, 1177 reports were retrieved; from these, 49 were included in the analysis of efficacy, and 51 studies had sufficient information to evaluate toxicity. Reports

*From the Hospital Italiano de Buenos Aires, Buenos Aires, Argentina and the Royal National Hospital for Rheumatic Diseases, Bath, UK.*

*E.R. Soriano, MD, Hospital Italiano de Buenos Aires; N.J. McHugh, MD, Royal National Hospital for Rheumatic Diseases.*

*Address reprint requests to Dr. E.R. Soriano, Hospital Italiano de Buenos Aires, Gascon 450, Capital Federal, Argentina;  
E-mail: enrique.soriano@hospitalitaliano.org.ar*

were excluded if study design was different from that specified in methods, data were already available from RCT, or articles were not published in English.

### Estimation of a Treatment Effect Size

Effect sizes (ES) were calculated based on a simplified Cohen's *d* derived from *t* tests<sup>11</sup>. An ES is the standardized mean difference between a treatment group and a control group for a given outcome variable. Whenever available, the mean changes between baseline and final visit of selected outcome variables were used for ES calculation. In trials where results were reported as percentage of improvement, values were calculated by applying the percentage improvement to basal values and basal standard deviation (SD) used for ES estimation. Unless otherwise stated, the ES was calculated against placebo.

### Outcome Measures

Two primary instruments were used for measuring clinical response in PsA, the Psoriatic Arthritis Response Criteria (PsARC) and the American College of Rheumatology (ACR) improvement criteria (ACR20, ACR50, and ACR70).

The PsARC is adapted from the Veterans Affairs Cooperative Study of sulfasalazine<sup>12</sup>. Response is defined as improvement in 2 measures (one being joint score) with worsening in none of the following 4 measures:

- Patient global assessment (0–5 Likert scale; improvement = decrease by 1 unit; worsening = increase by 1 unit)
- Physician global assessment (0–5 Likert scale)
- Tender joint score (improvement = decrease by 30%, worsening = increase by 30%)
- Swollen joint score (same as tender joint score)

The most widely used method for assessing peripheral joint disease activity in PsA is the ACR joint count, which has been modified for PsA in some studies<sup>13,14</sup>.

Several scoring methods have been proposed to assess structural damage in peripheral joints in PsA, based on existing scoring systems for RA<sup>15</sup>. The most widely used are the modification of the Steinbrocker method by Gladman<sup>15</sup>, and the Sharp method without modification. In more recent clinical trials the Sharp–van der Heijde modified scoring method for PsA has been used<sup>15</sup>.

## RESULTS

### Nonsteroidal Antiinflammatory Drugs

Only one RCT compared an NSAID (nimesulide, NIM) with placebo in patients with PsA<sup>16</sup>. NIM 200 and 400 mg/day significantly reduced pain severity, morning stiffness, patient and investigator assessments of efficacy, tender joint score, and swollen joint score. However, because of adverse drug reactions (many cases of hepatotoxicity, some fatal), NIM is not licensed for use in most developed countries.

Four RCT in PsA compared different NSAID<sup>17–20</sup>. Three studies in a total of 109 patients involved indomethacin: one

(34 patients) compared indomethacin 100 mg with azapropazone 1200 mg<sup>17</sup>; a second (40 patients), indomethacin 150 mg with acemetacin 180 mg<sup>18</sup>; and a third (35 patients), indomethacin 75–150 mg with diclofenac 75–150 mg<sup>19</sup>. All 3 trials showed significant improvement in the assessed clinical outcomes, but no significant differences between indomethacin and any of the comparators. A fourth trial (40 patients) compared etretinate with ibuprofen<sup>20</sup>. Although the articular index improved significantly in both groups, only 1/20 patients on ibuprofen completed 24 weeks of therapy.

No RCT have studied cyclooxygenase-2-specific NSAID in PsA.

Although none of the 5 trials showed any effect on psoriasis, there are reports of exacerbation of psoriasis with ibuprofen<sup>21</sup>, indomethacin<sup>22,23</sup>, phenylbutazone, and oxyphenbutazone<sup>24</sup>.

### Corticosteroids

**Systemic.** No RCT have assessed systemic corticosteroids in PsA. The expert opinion is that systemic corticosteroids are contraindicated in the treatment of psoriasis and are advisable only under special circumstances and not for chronic use<sup>25,26</sup>. Some evidence is available, however, that systemic corticosteroids are used frequently by rheumatologists in PsA. In one multicenter study of 180 patients, 24.4% of patients were taking prednisolone<sup>27</sup>.

**Intraarticular.** No RCT have assessed the effect of intraarticular corticosteroids in PsA. The expert opinion is that intraarticular glucocorticoid injections may be given judiciously to treat persistent mono- or oligoarthritis, often with good clinical results<sup>26</sup>, if care is taken to avoid injection of joints that are surrounded by psoriatic plaques<sup>28</sup>.

### Disease Modifying Antirheumatic Drugs

**Methotrexate (MTX).** Only 2 RCT involving a total 58 patients have compared MTX with placebo<sup>29,30</sup>. In the first study, 3 intravenous MTX pulses (1–3 mg/kg body weight) produced a marked improvement compared with the placebo group<sup>29</sup>. However, one patient died from marrow aplasia and hematemeses, and several other adverse events occurred to produce an unacceptable toxicity profile<sup>26,31,32</sup>.

The second study<sup>30</sup> showed that low-dose oral MTX (7.5–15 mg weekly) reduced the physician's global assessment at 12 weeks compared with placebo. The ES was medium (0.66) on the disease index (summary measure of treatment effect weighting each component of the OMERACT measures included in the trial)<sup>31,32</sup>.

A prospective RCT concluded that MTX was as effective as cyclosporine in treating PsA<sup>33,34</sup>. In 35 patients treated for 1 year, cyclosporine at 3–5 mg/kg/day and MTX at 7.5–15 mg/wk were associated with numerous clinical improvements such as fewer painful or swollen joints, decreased Ritchie index score, shorter duration of morning stiffness, improved grip strength, improvement in the Psoriasis Area and Severity

Index (PASI), and improved patient and physician global assessments.

A recent RCT comparing cyclosporin A (CsA) or placebo in addition to MTX is discussed below<sup>35</sup>.

In a single-center, open-label study, records of 87 patients with PsA treated with intramuscular (IM) gold or MTX during a 24-year period were reviewed<sup>36</sup>. The likelihood of a clinical response after controlling for significant baseline covariates was 8.9 times greater with MTX than IM gold. No major toxicity occurred, and frequency of side effects was similar for both treatments.

Several other uncontrolled studies using low doses of 5–15 mg weekly have shown that MTX therapy was associated with improvement in grip strength, morning stiffness, joint count, and erythrocyte sedimentation rate<sup>37,38</sup>.

Radiographic progression was not prevented in a small case-control study of 38 MTX-treated patients and 38 matched controls with long disease duration<sup>39</sup>. In a randomized controlled trial of MTX plus cyclosporine in patients with active PsA<sup>35</sup>, Larsen scores of radiographic damage increased in both groups.

Liver toxicity is the primary concern in patients taking MTX. MTX, but not cyclosporine, was associated with elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzymes in an RCT<sup>33,34</sup>. A metaanalysis evaluated the risk of liver toxicity from longterm administration of MTX in patients with RA or PsA<sup>40</sup>. The incidence of progression of liver disease (worsening of  $\geq 1$  grade on the histologic classification of Roenigk) was 27.9% among 636 patients (299 with psoriasis or PsA). The rate of progression was associated with the cumulative dose of MTX. Patients had a 6.7% chance of progressing at least one histologic grade for each gram of MTX taken. Patients with psoriasis were more likely than patients with RA to have advanced changes (7.7% vs 2.7%;  $p = 0.003$ ) and histologic progression (33.1% vs 24.3%;  $p = 0.02$ ).

Ninety-eight liver biopsies were performed on 68 patients with psoriasis, and cirrhosis was reported in 1 patient (2%) during 10 years of followup (cumulative dose of 4.1 g)<sup>41</sup>. Of 22 patients receiving sequential liver biopsies, the histologic grade for the specimens remained stable in 77%, improved in 5%, and showed deterioration in 22%, including one (4%) who developed cirrhosis.

In psoriasis, the probability of a normal liver biopsy dropped below 50% at a cumulative MTX dose between 3000 and 5800 mg<sup>42,43</sup>. In contrast to RA, blood biochemistry does not seem to predict histopathologic findings in patients with psoriasis, and significant liver damage can occur without evidence of abnormal liver function tests<sup>40–43</sup>.

The use of dynamic hepatic scintigraphy was investigated in assessing liver damage in patients with MTX-treated psoriasis. It appeared that a portal blood flow contribution of greater than 52% was associated with a 95% chance of normal liver histology<sup>41,44</sup>.

Serial evaluations of amino-terminal propeptide of type III procollagen levels are helpful in ruling out liver fibrogenesis<sup>45</sup>. It is proposed that repeat liver biopsies (after the first normal biopsy specimen at 1.5 g) may be omitted when serial levels of type III procollagen propeptide are normal<sup>41,45</sup>.

In 104 psoriasis and PsA patients treated with MTX and retrospectively evaluated, 165 adverse drug reactions (ADR) were noted in 83 patients<sup>40</sup>. The most common ADR were blood count changes (27%), serum enzyme increase (transaminase increase, 27%), and gastrointestinal side effects, including nausea and vomiting (33%).

*Sulfasalazine.* In a systematic review<sup>31,32</sup>, 6 RCT compared SSZ with placebo<sup>12,46–50</sup>. SSZ had well-demonstrated efficacy in PsA. The calculated ES on some of the outcomes evaluated is summarized in Table 1.

A retrospective analysis of data from RCT on spondyloarthropathies included 221 patients with PsA<sup>51</sup>. Of the peripheral arthritis group, 59% of the SSZ-treated patients and 42.7% of the placebo patients showed a clinical response ( $p = 0.0007$ ).

A more recent 24-week trial compared SSZ (2000 mg/day) with cyclosporine and standard therapy (ST; NSAID, analgesics, and/or prednisone  $\leq 5$  mg/day) in 99 patients with PsA<sup>52</sup>. No significant differences were observed between SSZ and ST-alone groups in pain score, swollen joint count, tender joint count, joint/pain tenderness score, and patient and physician global assessment.

In a case-control study, 20 patients who received SSZ for more than 3 months were compared with 20 control patients<sup>53</sup>. The mean change in the radiographic score at 24 months between the 2 groups was not statistically significant. SSZ does not appear to halt radiographic progression in PsA<sup>53</sup>.

In one study assessing the tolerance of SSZ in a clinical setting, the drug was discontinued in 14 of 36 patients (38%) due to side effects occurring within 3 months of treatment initiation<sup>53</sup>.

A trend has been observed in most of the RCT towards higher withdrawal rates in the SSZ group compared with the placebo group<sup>51</sup>, mostly related to adverse events such as gastrointestinal intolerance, dizziness, and liver toxicity, which have been observed in up to one-third of the patients receiving SSZ<sup>51</sup>.

*Cyclosporine.* While there are no RCT comparing CsA to placebo, 3 published controlled trials have compared CsA to other DMARD<sup>33,35,52</sup>. The first study compared CsA (3–5 mg/kg/day) with MTX in 35 patients, and was effective at 6 and 12 months in terms of joint tenderness and swelling, Ritchie index, duration of morning stiffness, grip strength, physician and patient global assessment, and the PASI<sup>33</sup>.

More recently, the efficacy of CsA in PsA was confirmed by a multicenter 24-week trial comparing CsA (3 mg/kg/day) with SSZ and ST (NSAID, analgesics, and/or prednisone  $\leq 5$  mg/day) in 99 patients with PsA<sup>52</sup>. CsA significantly reduced the pain score compared with ST. A significant decrease in



Table 1. Cohen's d effect size calculated on mean changes between baseline and final visit of selected outcome variables for different disease modifying antirheumatic drugs in various studies. Negative values express an effect favoring placebo.

	SSZ Combe <sup>50</sup> + Gupta <sup>49</sup>	SSZ Clegg <sup>12</sup>	MTX Willkens <sup>30</sup>	CsA Salvarani <sup>52</sup>	LFN Kaltwasser <sup>58</sup>	OG Carette <sup>60</sup>	IMG Palit <sup>61</sup>	AZA Levy <sup>65</sup>	INF Antoni <sup>69*</sup>	INF Antoni <sup>70*</sup>
Patients, n	117;23 <sup>†</sup>	221	37	67	188	188	42	12	104**	200**
Followup, weeks	24+	36	12	24	24	24	24	26	16	16
Tender joint score	0.16	0.12	0.06	0.44	0.22	0.22	0.78	2.68	1.14§	1.14§
Swollen joint score	0.18*	0.02	0.02	0.46#	0.17	0.33	—	—	1.17#	0.81#
Pain (VAS)	0.36	—	—	0.53	—	3.64	-0.23	—	1.74	1.46
HAQ	—	—	—	—	0.29	—	—	—	0.87	1.17

AZA: azathioprine; CsA: cyclosporin A; HAQ: Health Assessment Questionnaire; IMG: intramuscular gold; INF: infliximab; LFN: leflunomide; MTX: methotrexate; OG: oral gold; SSZ: sulfasalazine; VAS: visual analog score. \* Cohen's d effect calculated on final visit outcomes; <sup>†</sup> patients evaluated by Gupta, 1995<sup>49</sup>; \*\* patients on drug and controls; # swollen joint count; § tender joint count.

favor of CsA versus ST was also observed for the swollen joint count (ES: 0.46, medium effect), tender joint count (ES: 0.44, medium effect), joint pain/tenderness score (ES: 0.65, medium effect), patient global assessment by at least 1 point (61% vs 33%), and physical global assessment by at least 1 or 2 points (66% vs 32%, and 24% vs 0%, respectively).

In a recent 12-month randomized, double-blind, placebo-controlled trial, 72 patients with active PsA and an incomplete response to MTX were randomized to receive either CsA (n = 38) or placebo in addition to MTX (n = 34)<sup>35</sup>. In the MTX/CsA group, patients had significant clinical improvements from baseline in swollen joint count and C-reactive protein that were not evident in the MTX/placebo group. The only significant differences between the groups, however, were in synovitis detected by ultrasound and PASI score in favor of the MTX/CsA group.

In a study of 15 patients with active PsA in a 2-year open prospective study on low-dose CsA (starting dose 3 mg/kg/day), radiographs of hands and feet at study entry and at the end of followup were compared<sup>54</sup>. The mean number of eroded joints per patient increased significantly during the study period (p = 0.017). Nine patients had less than 2 new eroded joints (responders), while the remaining 6 patients had 5 or more new eroded joints (non-responders). Thus, there is some evidence from this small study that CsA partially controlled the 2-year progression of radiographic damage in peripheral joints.

In the trial of 99 patients, 21 of the 36 treated with CsA (58%) experienced at least one side effect<sup>52</sup>. The most common adverse event (28%) was mild, reversible kidney dysfunction. Of particular concern, renal damage did not improve following discontinuation of therapy in some cases<sup>26,55</sup>.

In a blinded study of renal toxicity in 30 patients with psoriasis, including 18 patients with PsA, the severity of toxicity increased with length of CsA therapy<sup>56</sup>. After 4 years, all but one patient had arteriolar hyalinosis, with interstitial fibrosis, which was pronounced in 5 and moderate in 6 of 11 patients; at the same time glomerular sclerosis had become significant<sup>56</sup>.

The consensus report on the use of CsA in psoriasis published in 1992 advised to discontinue CsA if the serum creatinine becomes persistently raised 30% above baseline measurements<sup>57</sup>.

**Leflunomide.** In a multinational, double-blind, randomized, placebo-controlled clinical trial on the efficacy and safety of leflunomide in the treatment of active PsA and psoriasis<sup>58</sup>, 190 patients received leflunomide (100 mg/day loading dose for 3 days followed by 20 mg/day orally) or placebo for 24 weeks. Leflunomide was significantly superior to placebo in the primary efficacy endpoint: number of responders by the PsARC (59% vs 30%). Leflunomide was significantly superior to placebo in joint pain/tenderness score (ES: 0.22, small effect); joint swelling score (ES: 0.17, small effect); tender joint count (ES: 0.23, small effect); swollen joint count (ES: 0.19, small effect); HAQ total score (ES: 0.29, small effect); and Dermatology Life Quality Index total score (ES: 0.34, small effect)<sup>58</sup>.

One case report is available of a patient with PsA who had clinical remission and radiographic amelioration after treatment for one year with leflunomide<sup>59</sup>.

Adverse events were reported in 82 of 96 patients in the leflunomide group (85.4%) and 70 of 92 patients in the placebo group (76.1%) in the multinational trial<sup>58</sup>. Serious adverse events occurred in 13.5% of patients in the leflunomide group and in 5.4% of patients in the placebo group. The most frequent adverse events in the leflunomide group were diarrhea (24%), increased ALT level (12.5%), flu-like syndrome (12.5%), and headache (11.5%). No cases of severe liver toxicity were observed.

**Gold salts.** Two RCT of gold salts in PsA have been conducted, one comparing oral gold (auranofin, 3 mg/day) versus placebo<sup>60</sup>, and the other comparing IM gold [sodium thiomalate (GST, 50 mg/week)], oral gold (3 mg BD), and placebo<sup>61</sup>. Both RCT were included in a systematic review, where it appeared that gold salts (oral gold and IM gold) were not statistically better than placebo for the treatment of PsA<sup>31,32</sup>.

Another study compared sodium thiomalate with oral gold

in a multicenter double-blind trial with one-year followup (duration: trial 6 mo, open study 6 mo)<sup>62</sup>. Both gold compounds appeared to be effective in the treatment of PsA. Arthritis was better controlled in the GST group, but the number of improved patients was greater in the auranofin group.

In a case-control study assessing radiographic progression in 18 patients with PsA treated with IM gold and 36 controls<sup>63</sup>, a comparison of the change in radiographic evidence of damage in peripheral joints revealed no statistical difference in disease progression at 24 months<sup>63</sup>.

The effect of gold on lesions of psoriasis does not appear to be positive; there are reports of exacerbation of psoriasis with chrysotherapy<sup>64</sup>.

**Azathioprine.** One RCT with azathioprine<sup>65</sup> was included in a systematic review<sup>31,32</sup>. On comparison of the pooled indices for individual agents, azathioprine was statistically better than placebo. However, only one component variable (Ritchie score) was available for comparison<sup>31,32</sup>. The ES on Ritchie index was 2.68 (huge effect). However, these data are difficult to interpret due to the small number of patients enrolled (n = 12) and the paucity of outcome measures reported.

**Antimalarials.** In a case-control study, 24 patients continued chloroquine for at least 6 months, and 18 (75%) demonstrated > 30% reduction in the actively inflamed joint count<sup>66</sup>. In the control group (24 patients taking no disease-remitting agents and followed during the same period of time), 14 (58%) had > 30% reduction in inflamed joint count. This was not significantly different from the chloroquine-treated group.

Several reports have cited exacerbation of psoriasis with antimalarials<sup>66</sup>. A review of 18 English-language publications revealed that up to 18% of patients with psoriasis developed exacerbation of their disease following antimalarial therapy<sup>34,67</sup>. In contrast to lithium and beta blockers, antimalarials do not induce psoriasis de novo, but only trigger already existing psoriasis<sup>67</sup>.

**Combination therapy of non-biologic DMARD.** An RCT comparing combination of MTX/CsA vs MTX/placebo was described above<sup>36</sup>. In a retrospective study at 3 centers in the UK, 19 patients (15 with PsA) who received combination treatment with MTX and CsA were evaluated<sup>68</sup>. Mean doses of combination therapy were 13.9 mg MTX weekly and 2.6 mg/kg CsA daily. The authors concluded that combination treatment resulted in good control of both skin and joint problems, although they did not provide data on joint assessments<sup>68</sup>.

### Anti-Tumor Necrosis Factor (TNF) Therapy

Table 2 provides a summary of endpoints reached at 24 weeks in recent trials of anti-TNF treatments.

**Etanercept.** US Food and Drug Administration approval of etanercept for PsA was based on 2 controlled randomized trials<sup>34</sup>. A phase 2 randomized, double-blind, placebo-controlled, 12-week study assessed the efficacy and safety of

etanercept (25 mg twice-weekly subcutaneous injections) or placebo in 60 patients with PsA and psoriasis<sup>13</sup>. At 12 weeks, the etanercept group showed significant improvement in all measures of disease activity compared with the placebo group. Disability as assessed by the HAQ was also significantly better in the etanercept group than in the placebo group (83% vs 3%). Twenty-six (87%) etanercept-treated patients met the PsARC compared with 7 (23%) controls.

Results were confirmed by a phase 3, double-blind, placebo-controlled, multicenter trial involving 205 patients with PsA<sup>14</sup>. Patients receiving 25 mg of subcutaneous etanercept twice weekly had significant ACR20 (59% vs 15%) and PsARC responses at 12 weeks compared with placebo patients (23% achieved 75% improvement compared with 3% of placebo patients). This study also demonstrated significant responses in quality of life. Insufficient data were published in either study to estimate ES.

In the study of 205 PsA patients, radiographs of the hands and feet were taken at baseline, after 24 weeks of treatment, at the start of the open-label treatment phase, and after 1 year of open-label treatment<sup>14</sup>. The annualized rate of change in the modified total Sharp score for erosions and joint space narrowing was used<sup>14</sup>. At 12 months, radiographic disease progression was inhibited in the etanercept group (−0.03 unit) compared with worsening of +1.00 unit in the placebo group.

Injection site reactions were the most common adverse event in the etanercept group, and resolved as the study progressed<sup>13,34</sup>. No serious adverse events were associated with etanercept. No patient developed infections that required hospitalization or intravenous antibiotics<sup>13</sup>. In the open-label extension of the trial<sup>14</sup>, the proportion of patients with adverse events and infections was similar between groups, and the safety profile was comparable to that observed in RA patients. One patient in the etanercept group developed multiple sclerosis at the end of the blinded phase of the study.

**Infliximab.** Two randomized, double-blind trials compared infliximab with placebo in PsA patients<sup>69,70</sup>. The first RCT of infliximab (5 mg/kg) or placebo was conducted in 104 patients who had active PsA with 5 or more affected joints<sup>69</sup>. At 16 weeks, an ACR20 response was achieved in 65% of infliximab-treated patients and 10% of placebo patients. The PsARC was achieved by 75% of infliximab-treated patients and 21% of placebo patients (p < 0.0001).

In the second study<sup>69</sup>, 200 patients with active PsA unresponsive to prior therapy were randomized to infusions of infliximab 5 mg/kg or placebo at Weeks 0, 2, 6, 14, and 22. The primary measure of clinical response was ACR20. Other measures included PsARC, PASI, and dactylitis and enthesopathy assessments. At Week 14, 58% of infliximab patients and 11% of placebo patients achieved an ACR20 response, and 77% of infliximab patients and 27% of placebo patients achieved PsARC (both p < 0.001). Insufficient data were published in either study to estimate ES.

Recently, health-related quality of life (using the SF-36)

Table 2. Outcome data at 24 weeks from recent studies in PsA (active vs placebo).

	Leflunomide 2004, n = 188 (58)	Etanercept 2004, n = 205 (14)	Infliximab 2005, n = 200 (64)	Adalimumab 2005, n = 313 (75)
Outcome measure				
PsARC, %*	60 vs 27	70 vs 23	70 vs 32	60 vs 23
ACR 20, %*	36 vs 20	50 vs 13	54 vs 15	57 vs 15
HAQ score (% change)	−0.19 vs −0.05	(54% vs 6%)	−0.2 vs 0.5	−0.4 vs −0.1
PASI 75	17 vs 8	23 vs 3	60 vs 1	42 vs 0

ACR 20: ACR response criteria; PsARC: Psoriatic Arthritis Response Criteria; HAQ: Health Assessment Questionnaire; PASI 75: Psoriasis Area and Severity Index. \* Percentage achieving outcome.

from this trial was reported<sup>71</sup>. At Week 14, increases in physical and mental component summary scores and all 8 scales in the infliximab group were greater than those in the placebo group<sup>71</sup>.

Radiographic data from the IMPACT 1 trial (104 patients) showed no progression in both groups over 50 weeks<sup>72</sup>. Analysis included radiographs of hands and feet that were scored according to the van der Heijde modified Sharp method. Due to the short duration of placebo treatment (14 weeks) with crossover design, no difference in the treatment groups over one year could be shown. The calculated annual progression rate was reduced, however, in both arms.

In a recent open-label study of 8 patients, no significant increase from baseline was observed in Sharp score after 2 years of infliximab treatment [basal global Sharp score (SD): 65.4 (43.5) vs 66 (43.2)]<sup>73</sup>. In 5/8 (63%) patients, there was no increase in Sharp score<sup>73</sup>.

Treatment with infliximab was well tolerated overall<sup>69</sup>. Two infliximab patients in the first trial discontinued the drug because of infection. In the second trial, 13 patients (9%) in the combined group (all infliximab patients plus placebo patients who entered early escape at Week 16 or incorrectly received infliximab) had serious adverse events, compared with 6% of the placebo group; 4% had adverse events leading to withdrawal<sup>70</sup>.

In an open-label 54-week study of 10 patients with PsA, no significant adverse events, severe infections, or infusion reactions occurred<sup>74</sup>.

**Adalimumab.** A double-blind, randomized, placebo-controlled trial compared adalimumab (40 mg) vs placebo subcutaneously every other week for 24 weeks in 313 patients with active PsA with inadequate response to NSAID<sup>75</sup>. About one-half of the patients in both groups were taking MTX at baseline. At Week 24, 57% of the adalimumab-treated patients achieved an ACR20 response compared with 15% of the placebo patients ( $p < 0.001$ ). Among patients receiving adalimumab, the PsARC response rate at Week 24 was 60% compared with 23% of placebo patients<sup>75</sup>. Insufficient data were published to estimate ES.

Disability, as measured by the HAQ Disability Index (DI), also improved significantly among adalimumab patients,

compared with placebo patients (mean  $\pm$  SD change in HAQ DI scores:  $-0.4 \pm 0.5$  in the adalimumab group versus  $-0.1 \pm 0.5$  in the placebo group at Week 12;  $p < 0.001$ ).

In the above trial, adalimumab treatment resulted in significant inhibition of structural changes on radiographs<sup>75</sup>. The mean change in the modified total Sharp score in patients who had both baseline and Week 24 radiographs was  $-0.2$  for adalimumab patients, compared with  $1.0$  for placebo patients ( $p < 0.0001$ ). Significant differences also were observed in erosion and joint space narrowing scores<sup>75</sup>.

No significant progression was observed in the more common PsA features (e.g., gross osteolysis, subluxation, pencil-in-cup deformity).

The incidence of adverse events was similar in both groups<sup>75</sup>. Twelve patients experienced serious adverse events, 7 in the placebo group and 5 in the adalimumab group. Elevations of ALT were seen more frequently among adalimumab patients than among placebo patients, but were transient in most cases.

**Alefacept.** Alefacept is a bioengineered fusion protein of soluble lymphocyte function antigen 3 (LFA-3) with Fc fragments of IgG1. It is marketed in many countries for the treatment of moderate to severe psoriasis<sup>76</sup>. In an open-label, explorative study of 11 patients treated with alefacept 7.5 mg intravenously weekly for 12 weeks, 55% of patients fulfilled the Disease Activity Score (DAS) response criteria<sup>77</sup>.

More recently, alefacept (15 mg/week IM for 12 weeks) in combination with MTX was evaluated in a randomized trial of 185 patients with active PsA; 123 patients received alefacept and 62 received placebo<sup>76,78</sup>. At 6 months, 54% of alefacept-treated patients versus 23% of placebo patients achieved an ACR20 response. Published results of this study are awaited.

### Summary of Guideline Recommendations

1. Indomethacin, diclofenac, azapropazone, acemetacin, and ibuprofen: Evidence grade 1B, recommendation grade A. Sufficient data are lacking to support use of COX-2-specific NSAID.
2. Systemic corticosteroids: No evidence other than expert opinion and case reports (evidence grade 4, recommendation grade D).



3. Intraarticular corticosteroids: No evidence other than expert opinion (evidence grade 4, recommendation grade D).
4. Methotrexate: Parenteral MTX has published efficacy but at an unacceptably high toxic dose. Oral MTX may be beneficial but conclusive proof is lacking. MTX does not prevent radiographic progression (evidence grade 3). Toxicity profile is considered to be low. Overall recommendation: grade B.
5. Sulfasalazine: Evidence grade 1A for efficacy in symptom improvement; evidence grade 3 for prevention of radiographic progression. Toxicity profile is considered low. Overall recommendation: grade A.
6. Cyclosporine: Evidence grade 1B for efficacy in symptom control; evidence grade 3 to control radiographic progression. Toxicity profile is considered high. Overall recommendation: grade B.
7. Leflunomide: Evidence grade 1B for symptom control and improving functional status and quality of life; grade 4 evidence to prevent radiographic progression. Toxicity profile is considered to be low. Overall recommendation: grade A.
8. Gold: ineffective.
9. Etanercept, infliximab, and adalimumab: evidence grade 1B for symptoms, physical function, quality of life, and to control radiographic progression. Toxicity profile is considered to be low. Overall recommendation: grade A.

## CONCLUSION

There is a serious lack of evidence upon which to base strong recommendations for NSAID or DMARD, traditionally used for the treatment of PsA. Some grade A evidence exists that sulfasalazine, cyclosporine, and leflunomide are effective for symptom relief, with lower grade evidence for MTX. All DMARD have problems with toxicity. The evidence that anti-TNF blockade is effective is compelling, although more data are needed concerning longterm efficacy and safety. Head-to-head comparison of a DMARD such as leflunomide versus an anti-TNF agent would provide useful information concerning efficacy, effect size, and toxicity.

The relative lack of evidence poses challenges in developing algorithms for treatment of peripheral arthritis in PsA. Issues remain concerning how early to intervene with DMARD or anti-TNF treatment. More attention may be needed to identify subgroups of patients at risk of poor outcome<sup>79-83</sup>. Such measures such as the number of actively inflamed and swollen joints at presentation<sup>84,85</sup> and/or the presence of dactylitis<sup>86</sup> may need to be considered. Better composite outcome measures that assess a more global perspective of patient well-being are needed. Accurate and reliable information on cost-effectiveness with informative health economic analysis is lacking. Given such constraints, guidelines that should be based on evidence are inevitably shaped by consensus and pragmatism.

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