# CONVENTIONAL THERAPY OF PSORIATIC ARTHRITIS: EVIDENCE-BASED REVIEW

**N.J. MCHUGH[1], E.R. SORIANO[2]**

*[1]Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath, UK;*
*[2]Hospital Italiano de Buenos Aires, Argentina*

**SUMMARY**

Psoriatic arthritis is a heterogeneous condition, the pattern of which is determined by any combination of pathology affecting peripheral joints, the enthesis and the spine. There is a paucity of evidence for most of the conventional agents used to treat psoriatic arthritis, with many of them being used on the basis of experience in rheumatoid arthritis. Herein, we summarise the evidence compiled relating to effectiveness of treatment for various manifestation of PsA. For those patients with progressive forms of arthritis who may benefit from intervention of newer biological therapies, the continued use of conventional therapy needs ever increasing scrutiny.

***Key words:*** Psoriatic arthritis, psoriasis, therapy

## INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory synovitis and/or enthesitis that affects about 30% of individuals with psoriasis. The prevalence of PsA is likely to be around 0.1-0.3% (1). PsA has been defined as an inflammatory arthritis associated with psoriasis, usually seronegative for rheumatoid factor (2). Historically five subgroups were defined (3), although it is now realised that patients change subgroups over time with disease progression (4). Newer classification criteria have been proposed recently (5).

In its most severe form PsA causes widespread destructive joint disease and/or ankylosis. Conventional drug treatments have included anti-inflammatory agents, corticosteroids and disease-modifying drugs used for rheumatoid arthritis, although the evidence-base for their effectiveness in PsA is not well established. Patients reaching a referral centre for arthritis are likely to have progressive spinal and peripheral joint disease (4, 6-8) despite use of conventional disease modifying antirheumatic drugs (DMARDs). Erosive and deforming arthritis occurs in 40%-60% of hospital-based PsA patients and is progressive from within the first year of diagnosis (4, 6, 8). Therefore, recent international efforts have been made to review the evidence for efficacy and toxicity of available agents for treating PsA, as a prerequisite for developing treatment guidelines (9).

Herein, we summarise some of the evidence that has been compiled using the appropriate methods for literature review, evidence weighting and treatment recommendations. Our summary is confined to conventional treatments for PsA, including peripheral arthritis (10), axial disease (11), enthesopathy (12) and dactylitis (13). More detailed accounts of the outcome methods used and methodology are published elsewhere (9-13).

## NON-STEROIDAL ANTI-INFLAMMATORY AGENTS

Non-steroidal anti-inflammatory drugs (NSAIDs) are usually the first choice of agents in the treatment of PsA and have demonstrated efficacy in relieving symptoms (14-17).

The usual caveats apply in taking caution in patients at risk of gastrointestinal, renal and cardiovascular toxicity.

There is no evidence that NSAIDs slow disease progression, although continued use may slow radiological progression of ankylosing spondylitis

*Corresponding author:*
Neil J McHugh, MD
Royal National Hospital for Rheumatic Diseases
Upper Borough Walls, Bath, BA1 1RL
E-mail: neil.mchugh@rnhrd-tr.swest.nhs.uk

(18). There are occasional reports of NSAIDs causing flare of skin psoriasis (19).

## CORTICOSTEROIDS

There are no RCTs of systemic or intra-articular corticosteroids in PsA. Systemic corticosteroids are occasionally required for severe flares of arthritis. Discontinuation of corticosteroids has been linked to rebound of skin psoriasis. On the other hand, the use of intra-articular corticosteroid injection is widespread and felt to be a valuable form of treatment, especially for persistent mono or oligoarthritis.

## SULPHASALAZINE

Sulphasalzine is often the first disease modifying drug used in PsA. A systematic review (20, 21) found six studies comparing sulphasalazine to placebo for PsA (22-27). Overall there is evidence for efficacy of sulphasalazine in improving clinical symptoms of peripheral joint disease although the effect is no more than modest. Also up to a third of patients may suffer adverse events such as gastrointestinal intolerance, dizziness or liver toxicity. There is no evidence that sulphsalazine prevents radiographic progression. Sulphsalazine appears to be ineffective for the treatment of axial disease (28), and studies are inconclusive for enthesitis and dactylitis.

## METHOTREXATE

Methotrexate is commonly used as a disease modifying drug in PsA and may also be effective for skin psoriasis, although there is a lack of controlled studies in either condition (29, 30). Liver toxicity may be more frequent with methotrexate in PsA than in rheumatoid arthritis (31).
Histopathological findings may not be predicted by liver function tests (32, 33). However, there is some evidence that levels of amino-terminal propeptide of type III procollagen can be used as a guide as to the necessity of a liver biopsy in patients requiring methotrexate longterm (34).

## CYCLOSPORIN

Cyclosporin is an effective agent for skin psoriasis but less often used for PsA.

There have been two studies comparing cyclosporin to other agents used in PsA, suggesting superior efficacy to sulphaslazine (35), similar efficacy to methotrexate (36), but overall greater toxicity. Renal toxicity in particular is a major limitation.

## LEFLUNOMIDE

Leflunomide (Arava - Aventis) is an isoxaol derivative that in its active form inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme essential for the de-novo synthesis of pyrimidines. Since activated lymphocytes require a large pyrimidine pool, leflunomide preferentially inhibits T cell activation and proliferation. As T cells play a pivotal role in the immunopathogenesis of both skin psoriasis and PsA, leflunomide is an obvious candidate agent for use in these conditions. In addition, leflunomide has been shown to be effective in rheumatoid arthritis.
Initial uncontrolled studies suggested that leflunomide was effective in PsA. A further randomised control trial involving 190 patients with active arthritis (at least three tender and three swollen joints) demonstrated efficacy in improving clinical symptoms of arthritis and secondary measures including disability and skin psoriasis (37). Patients were randomised to receive either leflunomide (100mg/day for three days followed by 20mg/day) or placebo with outcomes measured at 4 weeks. Leflunomide was significantly superior to placebo in the number of patients to respond as measured by the PsARC (Psoriatic arthritis response criteria)(59% (95% CI 48-70) versus 30% (95% CI 21-40)) and in each individual component of the PsARC. Leflunomide was also significantly better than placebo in improving disability and quality of life as measured by the HAQ (Health Assessment Questionaire) and the DQLI (Dermatology Quality of Life Index). Improvement in skin psoriasis as measured by a PASI (Psoriasis Area and Severity Index) score was also significantly better with leflunomide. Compared to the placebo group, a greater proportion of patients in the leflunomide group experienced a ?50% reduction in PASI scores (PASI 50; 18.9% vs 30.4%; p=0.050) and ?75% reduction in PASI scores (PASI 75; 7.8% vs 17.4%; p = 0.048) from baseline.
In the above study serious adverse events were more common in the leflunomide-treated group (13.5%) than in the placebo-treated group (5.4%). The most frequent adverse events with leflunomide

were diarrhoea (24%), increased liver enzymes (12.5%), flu-like syndrome (12.5%) and headache (11.5%). Three leflunomide treated patients and 1 placebo treated patient were withdrawn from the study because of elevated transaminase levels, which returned to normal during follow up. No cases of severe liver toxicity were observed. The level of unwanted effects appears to be similar to that experienced in rheumatoid arthritis patients treated with leflunomide.

## MYCOPHENOLATE

Mycophenolate mofetil (MMF) inhibits inosine monophosphate and the subsequent *de novo* guanine synthesis necessary for DNA replication in lymphocytes but not neutrophils. MMF is most commonly used to prevent organ graft rejection and is gaining more widespread use for maintaining disease remission in a range of autoimmune disorders. Small studies in PsA have been promising (38). MMF is rapidly converted to its active metabolite mycophenolic acid, that may have less gastrointestinal side effects than MMF.

## OTHER DISEASE MODIFYING AGENTS

Most of the disease modifying drugs used for rheumatoid arthritis are occasionally used for PsA, although there are very few properly controlled studies. Gold salts (auranofin and sodium thiomalate) are probably no more effective than placebo. Azathioprine may be effective but larger trials are needed. Antimalarials should be avoided as they have been associated with severe exacerbations of psoriasis (39), and there is no convincing evidence of effectiveness for PsA. The use of combination therapy with traditional disease modifying agents has not been the subject of any well-designed prospective study in PsA.

## CONCLUSIONS

The advent of effective biological agents for the treatment of PsA has brought to attention the relative lack of evidence for conventional therapies. Conventional disease modifying agents should not be disregarded simply because they have been under-evaluated in PsA, and experience with their use in rheumatoid arthritis is generally reassuring in terms of long-term safety. Sulphasalazine has been studied more than others and has no more than modest efficacy, methotrexate needs further evaluation, and cyclosporin is limited by toxicity. Leflunomide is a useful addition to the list of disease modifying agents and will probably become more commonly used before consideration is given to a biologic agent.

## REFERENCES


1. Harrison BJ, Silman AJ, Barrett EM, Scott DG, Symmons DP. Presence of psoriasis does not influence the presentation or short-term outcome of patients with early inflammatory polyarthritis. J Rheumatol 1997; 24 (9): 1744-9.
2. Wright V, Moll JMH. Seronegative arthritis. North Holland Publishing Co, 1976.
3. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973; 3: 55-78.
4. McHugh NJ, Balakrishnan C, Jones SM. Progression of peripheral joint disease in psoriatic arthritis. Rheumatology (Oxford) 2003; 42: 778-83.
5. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: Development of new criteria from a large international study. Arthritis Rheum 2006; 54 (8): 2665-73.
6. Gladman DD, Stafford-Brady F, Chang CH, Lewandowski K, Russell ML. Longitudinal study of clinical and radiological progression in psoriatic arthritis. J Rheumatol 1990; 17 (6): 809-12.
7. Hanly JG, Russell ML, Gladman DD. Psoriatic spondyloarthropathy: a long term prospective study. Ann Rheum Dis 1988; 47 (5): 386-93.
8. Torre AJ, Rodriguez PA, Arribas CJ, Ballina GJ, Riestra NJ, Lopez LC. Psoriatic arthritis (PA): a clinical, immunological and radiological study of 180 patients. Br J Rheumatol 1991; 30 (4): 245-50.
9. Kavanaugh AF, Ritchlin CT. Systematic review of treatments for psoriatic arthritis: an evidence based approach and basis for treatment guidelines. J Rheumatol 2006; 33(7): 1417-21.
10. Soriano ER, McHugh NJ. Therapies for peripheral joint disease in psoriatic arthritis. A systematic review. J Rheumatol 2006; 33 (7): 1422-30.
11. Nash P. Therapies for axial disease in psoriatic arthritis. A systematic review. J Rheumatol 2006; 33 (7): 1431-1434.
12. Ritchlin CT. Therapies for psoriatic enthesopathy. A systematic review. J Rheumatol 2006; 33 (7): 1435-8.
13. Helliwell PS. Therapies for dactylitis in psoriatic arthritis. A systematic review. J Rheumatol 2006; 33 (7): 1439-41.
14. Lassus A. A comparative pilot study of azapropazone and indomethacin in the treatment of psoriatic arthritis and Reiter's disease. Curr Med Res Opin 1976; 4 (1): 65-9.

15. Lonauer G, Wirth W. [Controlled double blind study on the effectiveness and adverse effects of acemetacin and indomethacin in the treatment of psoriatic arthritis]. Arzneimittelforschung 1980; 30 (8A): 1440-4.
16. Leatham PA, Bird HA, Wright V, Fowler PD. The run-in period in trial design: a comparison of two non-steroidal anti-inflammatory agents in psoriatic arthropathy. Agents Actions 1982; 12 (1-2): 221-4.
17. Hopkins R, Bird HA, Jones H, Hill J, Surrall KE, Astbury C et al. A double-blind controlled trial of etretinate (Tigason) and ibuprofen in psoriatic arthritis. Ann Rheum Dis 1985; 44 (3): 189-93.
18. Wanders A, Heijde D, Landewe R, Behier JM, Calin A, Olivieri I et al. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum 2005; 52 (6):1756-65.
19. Griffiths CEM. Therapy for psoriatic arthritis: sometimes a conflict for psoriasis. Brit J Rheumatol 1997; 36: 409-12.
20. Rubin RL. Autoantibody specificity in drug-induced lupus and neutrophil-mediated metabolism of lupus-inducing drugs. Clin Biochem 1992; 25: 223-34.
21. Jones G, Crotty M, Brooks P. Interventions for psoriatic arthritis. Cochrane Database Syst Rev 2000; (3): CD000212.
22. Farr M, Kitas GD, Waterhouse L, Jubb R, Felix-Davies D, Bacon PA. Sulphasalazine in psoriatic arthritis: a double-blind placebo-controlled study. Br J Rheumatol 1990; 29 (1): 46-9.
23. Fraser SM, Hopkins R, Hunter JA, Neumann V, Capell HA, Bird HA. Sulphasalazine in the management of psoriatic arthritis. Br J Rheumatol 1993; 32 (10): 923-5.
24. Gupta AK, Grober JS, Hamilton TA, Ellis CN, Siegel MT, Voorhees JJ et al. Sulfasalazine therapy for psoriatic arthritis: a double blind, placebo controlled trial. J Rheumatol 1995; 22 (5): 894-8.
25. Combe B, Goupille P, Kuntz JL, Tebib J, Liote F, Bregeon C. Sulphasalazine in psoriatic arthritis: a randomized, multicentre, placebo-controlled study. Br J Rheumatol 1996; 35 (7): 664-8.
26. Clegg DO, Reda DJ, Mejias E, Cannon GW, Weisman MH, Taylor T et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. Arthritis Rheum 1996; 39 (12): 2013-20.
27. Clegg DO, Reda DJ, Abdellatif M. Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondylarthropathies: a Department of Veterans Affairs cooperative study. Arthritis Rheum 1999; 42 (11): 2325-9.
28. Clegg DO, Reda DJ, Weisman MH, Blackburn WD, Cush JJ, Cannon GW et al. Comparison of sulfasalazine and placebo in the treatment of ankylosing spondylitis. A Department of Veterans Affairs Cooperative Study. Arthritis Rheum 1996; 39 (12): 2004-12.
29. Black RL, O'Brien WM, Vanscott EJ, Aeurbacj R, Eisen AZ, Bunim JJ. Methotrexate therapy in psoriatic arthritis; double-blind study on 21 patients. JAMA 1964; 189: 743-7.
30. Willkens RF, Williams HJ, Ward JR, Egger MJ, Reading JC, Clements PJ et al. Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. Arthritis Rheum 1984; 27 (4): 376-81.
31. Whiting-O'Keefe QE, Fye KH, Sack KD. Methotrexate and histologic hepatic abnormalities: a meta-analysis. Am J Med 1991; 90 (6): 711-6.
32. Wollina U, Stander K, Barta U. Toxicity of methotrexate treatment in psoriasis and psoriatic arthritis-short- and long-term toxicity in 104 patients. Clin Rheumatol 2001; 20 (6): 406-10.
33. Newman M, Auerbach R, Feiner H, Holzman RS, Shupack J, Migdal P et al. The role of liver biopsies in psoriatic patients receiving long-term methotrexate treatment. Improvement in liver abnormalities after cessation of treatment. Arch Dermatol 1989; 125 (9): 1218-24.
34. Zachariae H, Heickendorff L, Sogaard H. The value of amino-terminal propeptide of type III procollagen in routine screening for methotrexate-induced liver fibrosis: a 10-year follow-up. Br J Dermatol 2001; 144 (1): 100-3.
35. Salvarani C, Macchioni P, Olivieri I, Marchesoni A, Cutolo M, Ferraccioli G et al. A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. J Rheumatol 2001 Oct; 28 (10): 2 274-82 28 (10): 2274-82.
36. Spadaro A, Riccieri V, Sili-Scavalli A, Sensi F, Taccari E, Zoppini A. Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study. Clin Exp Rheumatol 1995; 13: 589-93.
37. Kaltwasser JP, Nash P, Gladman D, Rosen CF, Behrens F, Jones P et al. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. Arthritis Rheum 2004; 50 (6): 1939-50.
38. Grundmann-Kollmann M, Mooser G, Schraeder P, Zollner T, Kaskel P, Ochsendorf F et al. Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. J Am Acad Dermatol 2000; 42 (5 Pt 1): 835-7.
39. Wolf R, Ruocco V. Triggered psoriasis. Adv Exp Med Biol 1999; 455: 221-5.