

Psoriatic Arthritis Management Update – Biotherapeutic Options

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ABSTRACT. Psoriatic arthritis (PsA) is a seronegative spondyloarthropathy (SpA) occurring in up to 30% of patients with psoriasis. It has a wide variation of annual incidence (median 6.4, range 0.1–3.1 per 10⁵ people), based on analysis of 13 incidence and prevalence reviews published between 1987 and December 2006. Conventional treatments with antiinflammatory and disease modifying or antirheumatic drugs are not efficacious in all patients, in particular those with axial disease. This review examines new pharmacological developments in the treatment of PsA with a focus on biologic therapies. (J Rheumatol 2009;36 Suppl 83:65-68; doi:10.3899/jrheum.090229)

Key Indexing Terms:
PSORIATIC ARTHRITIS
MANAGEMENT

SPONDYLOARTHROPATHY
BIOTHERAPEUTICS

Psoriatic arthritis (PsA) is a seronegative spondyloarthropathy (SpA) occurring in up to 30% of patients with psoriasis¹. It has a wide variation of annual incidence (median 6.4, range 0.1–23.1 per 10⁵ people), based on analysis of 13 incidence and prevalence reviews published between 1987 and December 2006². Conventional treatments with antiinflammatory and disease modifying or antirheumatic drugs are not efficacious in all patients, in particular those with axial disease. This review will examine new pharmacological developments in the treatment of psoriatic arthritis with a focus on biologic therapies.

PsA is characterized by several unique clinical features that differentiate it from rheumatoid arthritis (RA). Attempts to identify immunopathologic mechanisms, some shared with psoriasis, that underlie these differences from RA have been most challenging. Recently, however, research studies highlight novel findings in PsA at the molecular, cellular, and tissue level that form the basis for a new understanding of this relatively common form of inflammatory arthritis. In particular, the availability of new biologic anti-tumor necrosis factor- α (TNF- α) therapies allows further insight into the immunopathology of psoriasis and PsA.

Treatment comprises a non-drug therapy (physiotherapy and rehabilitation) and drug therapy, administered locally or systemically. Conventional treatments have been useful for peripheral arthritis, but have proven of minimal benefit in spinal disease. In this review, we will focus on recent advances and novel drugs. The major advance is in biotherapeutics, including anti TNF- α agents. The efficacy of the various agents is compared in Table 1.

Corticosteroids. Corticosteroids are the most powerful antiinflammatory agents used in the treatment of PsA. Intraarticular injection may provide rapid, effective treatment for peripheral arthritis and sacroiliac (SI) joint inflammation^{3,4}. Magnetic resonance imaging (MRI) guidance offers an important and useful method of delivery to the SI joints. Gunaydin, *et al*⁵ reported in a pilot study that MRI-guided corticosteroid injection of inflamed SI joints is effective and safe.

Table 1. Drugs used to treat psoriatic arthritis and efficacy in peripheral and axial disease.

	Efficacy	
	Peripheral Arthritis	Axial Disease
Antiinflammatory drugs		
Conventional NSAID	+	+
Corticosteroids:		
Local	++	++
Systemic	+/-	+/-
Disease-modifying drugs		
Sulfasalazine / mesalazine	+ / ++	-
Methotrexate	+ / ++	-
Infliximab	++ / +++	++ / +++
Etanercept	++ / +++	++ / +++
Adalimumab	++ / +++	++ / +++

-: none; +: mild; ++: moderate; +++: good.
NSAID: nonsteroidal antiinflammatory drugs.

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Supported by the Health Research Board of Ireland and The Science Foundation of Ireland.

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Table 2. Comparison of anti-tumor necrosis factor (TNF) biologic therapies used in psoriatic arthritis.

TNF Inhibitor	Structure	Mechanism
Infliximab (Remicade)	Chimeric monoclonal anti-TNF antibody	Blocks TNF- α receptor interactions, also cytotoxic for TNF-expressing cells
Etanercept (Enbrel)	Soluble TNF receptor-FC fusion protein	Binds TNF- α , blocking interactions with the receptor and targets TNF- β
Adalimumab (Humira)	Human monoclonal anti-TNF antibody	Blocks TNF- α and blocks p55 and p75 receptor interaction

Anti-TNF agents. Anti-TNF- α therapy has been shown to be effective in RA^{6,7} and in inflammatory bowel disease (IBD)⁸. TNF- α is a key proinflammatory cytokine that has been detected in the inflamed bowel mucosa of patients with chronic IBD and the synovium from SI joints of patients with SpA including PsA. These findings suggest that anti-TNF- α therapy directed at neutralizing the TNF molecule may be effective in PsA. The main biologic agents targeting TNF- α are the chimeric (mouse/human) monoclonal IgG1 antibody infliximab (Remicade) and the 75 kDa IgG1 fusion protein etanercept (Enbrel). Since 2008, the US Food and Drug Administration has also approved adalimumab (Humira; HUMAN Monoclonal antibody In Rheumatoid Arthritis), a recombinant human IgG1 monoclonal antibody specific for human TNF- α for use in SpA. A comparison of the anti-TNF therapies available is summarized in Table 2.

Infliximab binds directly to both the circulating and membrane bound TNF- α molecule, whereas etanercept binds soluble, circulating TNF- α . There are now positive data for infliximab in the treatment of SpA and for both etanercept and infliximab in the treatment of PsA. Van den Bosch, et al⁹ evaluated the safety and efficacy of a loading dose regimen of 3 infusions of infliximab in 21 patients with active SpA (10 AS, 9 PsA, and 2 undifferentiated SpA). This was a single center, open-label, 12-week pilot study in which the patients received infliximab 5 mg/kg at weeks 0, 2, and 6. Active disease was defined as at least one manifestation of peripheral arthritis or enthesitis, or inflammatory back pain. No disease modifying antirheumatic drugs (DMARD) were permitted, although stable doses of nonsteroidal antiinflammatory drugs (NSAID), corticosteroids (< 10 mg/day), and intra-articular steroid injections were allowed. Clinical and laboratory evaluation included patient global assessment of duration of morning stiffness and pain, physician assessment of swollen/tender joint counts and axial involvement, and laboratory markers of inflammation. In addition, in patients with psoriasis, the extent of skin disease was measured with the Psoriasis Area and Severity Index (PASI). A significant reduction in tender and swollen joint count was seen from day 3 onwards, and

morning stiffness and pain in the peripheral joints, which was evaluated at day 14, showed significant improvement compared with baseline. There was also significant improvement in skin disease by day 14 in those patients with psoriasis. Although the symptoms of back pain improved, the Schober's test and intermalleolar distance remained unchanged, suggesting the presence of fixed back disease or persistent inflammation. All patients received a second and third infusion and had sustained and significant improvement in all variables assessed up to week 12 compared with baseline. No clinical or laboratory adverse reactions attributable to the infusion were noted. In conclusion, the treatment of longstanding SpA (mean = 17 yrs) with infliximab led to a rapid, sustained, and significant improvement in both axial and peripheral joint involvement as assessed by global disease measures.

Subsequent to the above mentioned study, Kruithof, et al¹⁰ reported the safety and efficacy of a maintenance regime of 5 mg/kg infliximab given every 14 weeks, in the same patients with active SpA as in the initial open-label trial, over a 1 year period. Nineteen out of 21 patients completed the study, with a statistically significant decrease of global, peripheral, and axial disease manifestations. Two patients changed to another dosing regime due to partial lack of efficacy but were followed up for analysis of safety. Partial relapse of symptoms was reported by 3 patients (16%) at week 20, 13 patients (68%) at week 34, and 15 patients (79%) at week 48, with the time of recurrence between 10 and 14 weeks after retreatment, indicating that the inflammatory disease activity cannot be controlled continuously with the maintenance regime of 5 mg/kg infliximab every 14 weeks. Adjustment of the maintenance regime is warranted, but it is not clear whether this can be achieved by decreasing the interval between doses or by increasing the dosage. Twelve minor infectious episodes were observed, but no withdrawals occurred due to adverse events. Twelve of 21 patients (57%) developed antinuclear antibodies, out of which 4/21 (19%) also had detectable anti-dsDNA antibodies; however, no lupus-like symptoms were described. This concluded that infliximab is a safe and effective drug in the treatment of SpA in this 1 year followup study.

Although recurrence of symptoms was noted before each retreatment, no loss of efficacy was observed after retreatment. Further, in patients with PsA and severe psoriasis, we have shown that infliximab given over a short time period can induce a rapid clinical response in skin and joints^{11,12}, which is associated with significant pathological changes at a molecular level in the affected skin.

The potential beneficial effects of anti-TNF- α therapy on peripheral arthritis in SpA was further evaluated by Baeten, et al¹³. This open-label pilot study of 8 patients (3 AS, 4 PsA, and 1 undifferentiated SpA) examined the effect of intravenous infliximab infusions (5 mg/kg) at baseline, week 2, and week 6. All 8 patients had active synovitis of at least one knee joint, and synovial biopsies were obtained for histologic and immunohistochemical analysis at baseline, week 2 (just prior to infliximab infusion), and at week 12. Clinical and laboratory evaluation included patient global assessment of pain and morning stiffness, physician assessment of tender and swollen joint counts, and laboratory markers of inflammation. Overall, there was significant improvement in all variables of patient and physician global assessment, including peripheral synovitis, regardless of the SpA subtype. Histologic analysis of synovial biopsy tissues showed reduction in synovial lining layer thickness and CD55+ synoviocytes. A reduction in vascularity in the sublining layer and vascular cell adhesion molecule-1 was noted; however, E-selectin, PECAM-1, and intercellular adhesion molecule-1 expression was unchanged. The overall degree of inflammatory infiltration remained unchanged although the number of neutrophils and CD68+ macrophages in the sublining layer was decreased. This could be due to the lymphocyte infiltration as only CD4+ cells decreased, while CD20+ lymphocytes and plasma cells were increased. In conclusion, reduction histologically of inflammatory cells and molecules in the joint tissue was observed, in addition to the clinical benefit of anti-TNF- α therapy on peripheral synovitis in SpA. This study also revealed immunomodulatory mechanisms involving adhesion molecule expression and lymphocyte infiltration, which were different from previous observations in RA and therefore suggested that anti-TNF- α has a distinct immunomodulatory mechanism in SpA; these findings may warrant further evaluation in a larger study.

Mease, et al¹⁴ recently reported their study with etanercept in the treatment of patients with psoriasis (median duration 18 yrs) and active PsA (median duration 10 yrs) defined as ≥ 3 swollen joints and ≥ 3 tender or painful joints. They treated 60 patients in a randomized, double blind, placebo-controlled 12 week study with etanercept 25 mg or placebo subcutaneously twice weekly. All patients enrolled had active PsA with insufficient

response to NSAID. Patients were allowed to continue on stable doses of methotrexate (≤ 25 mg/week) but all other DMARD were discontinued. Stable doses of steroids (< 10 mg/day) were also allowed. In all, 87% of patients treated with etanercept met the Psoriatic Arthritis Response Criteria, compared with 23% of control patients treated with placebo. The American College of Rheumatology (ACR) preliminary criteria for improvement (ACR20) were achieved by 73% of patients treated with etanercept, compared with 13% of placebo-treated patients. Of the 19 patients in each treatment group who could be assessed for psoriasis, 26% of etanercept-treated patients achieved a 75% improvement in the PASI, compared with none of the placebo-treated patients. C-reactive protein and erythrocyte sedimentation rate were significantly decreased in the etanercept-treated group compared with the placebo group. Etanercept was well tolerated with no serious adverse effects noted. Some minor infections occurred in both groups except that more patients receiving placebo developed an influenza like syndrome. The results showed that etanercept is safe and effective in the short term treatment of PsA and psoriasis.

Adalimumab is the third anti-TNF agent approved for the treatment of SpA after infliximab and etanercept. It binds TNF- α , preventing it from binding receptors, and plays a major role in downregulating the inflammatory reactions associated with autoimmune diseases. Alonso Ruiz, et al¹⁵ looked at 7087 patients across 13 randomized controlled studies for treatment of inflammatory arthritis with TNF- α therapies (infliximab, etanercept, adalimumab), using ACR efficacy response criteria. Positive and undesired effects were estimated using combined relative risks (RR), number needed to treat (NNT), and number needed to harm (NNH). Heterogeneity was evaluated by Cochrane's Q and I² statistics. Anti-TNF- α drugs are effective in PsA patients, with apparently similar results irrespective of the drug administered. The main factor influencing therapeutic efficacy is the prior response to DMARD treatment. The effect of treatment with etanercept or adalimumab does not differ from that obtained with MTX.

The anti-TNF therapies currently approved for use in PsA (infliximab, etanercept, and adalimumab) have shown greater clinical efficacy than any other treatment to date in the various clinical aspects of PsA. Safety surveillance for infection remains a priority, but no new concerns have arisen in patients with PsA. Studies over the last few years have also demonstrated the cost effectiveness of anti-TNF- α in PsA¹⁶⁻¹⁸.

Other biologic agents in early trials are alefacept (anti-T cell human fusion protein), efalizumab (anti-T cell monoclonal antibody), and abatacept (recombinant human fusion protein, binds CD80/86 and blocks CD28

receptor on T cells). Some of these agents appear more effective in psoriasis and therefore use may be restricted to the dermatological manifestations of psoriasis.

CONCLUSIONS

It is clear from the small open studies in SpA and the one substantial controlled study of PsA that anti-TNF- α therapies show considerable promise in the treatment of peripheral and axial disease. Indeed, these biologic agents are the first disease modifying drugs to show a significant benefit for both spinal and peripheral arthritis in SpA. Further, these treatments have been associated with a low incidence of adverse events within these study protocols. However, vigilance for cases of *Mycobacterium tuberculosis* infection¹⁹, malignancies such as rare lymphomas, and polyneuritis is still required as these adverse effects are potentially serious.

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