Disease-modifying antirheumatic drug therapy for psoriatic arthritis

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ABSTRACT

As erosive and deforming arthritis is present in 40% of patients with psoriatic arthritis (PsA), early and aggressive treatment with disease-modifying antirheumatic drugs (DMARDs) may be as effective in controlling the progression of the disease as it is for rheumatoid arthritis (RA).

Methotrexate (MTX), sulfasalazine (SSZ), and cyclosporine (CsA) are the most widely used DMARDs in the treatment of PsA and are safe and effective in patients with active peripheral arthritis, although they do not appear to be effective on axial manifestations. No controlled study has evaluated the efficacy of these drugs on the progression of radiological damage.

It has recently been demonstrated that leflunomide and anti-tumor necrosis factor (TNF) agents are effective in PsA and psoriasis. The symptomatic improvement has been important and sustained and side effects minimal. In particular, inhibitors of TNF appear to have excellent potential to treat PsA. These agents are able to slow joint damage in rheumatoid arthritis and they are effective on spinal symptoms in ankylosing spondylitis. Hopefully, these findings will prove true in PsA as well.

Introduction

Psoriatic arthritis (PsA) used to be considered a relatively mild, non-deforming arthropathy. Its treatment consisted of non-steroidal anti-inflammatory drugs (NSAIDs) and local corticosteroid injections, with disease modifying antirheumatic drugs (DMARDs) being reserved for NSAID-resistant or progressively destructive forms of the condition. However, this view has been challenged over the last decade. One of the largest series of PsA patients studied has shown the development of erosive and deforming arthritis in 40% of cases (1,2). Therefore, early and aggressive treatment with DMARDs may be as effective in controlling the progression of PsA as it is in rheumatoid arthritis (RA).

Methotrexate (MTX), sulfasalazine (SSZ), and cyclosporine (CsA) are the most widely used DMARDs in the treatment of PsA, but only a few well-designed and controlled studies have been conducted so far (3-8), and the effect of such drugs on axial disease (7-9) and on the progression of the radiological damage has been evaluated only a few times (10-12).

A recent meta-analysis study has shown that parenteral high dose MTX and SSZ are the only two second-line agents with well-demonstrated, published efficacy in PsA (13). CsA was not considered because no controlled study met the inclusion criteria for the meta-analysis. In all of the trials included in the meta-analysis, the placebo groups showed significant improvement, which suggests that observational studies should be interpreted with prudence in decisions regarding the management of PsA.

Parenteral gold, antimalarial agents, azathioprine and retinoids are drugs less frequently used in PsA (14-18). Leflunomide and agents that neutralise tumor necrosis factor (TNF) have recently been shown to be effective in PsA and psoriasis (19-30). In particular, inhibitors of TNF appear to have excellent potential to treat PsA. These drugs are able to slow joint damage in RA (31) and are effective on spinal sympoms in ankylosing spondylitis (AS) (32).

In the first part of this article we will review the clinical studies of "traditional" therapies, in particular SSZ, MTX and CsA, while in the second part we will look at the encouraging early results of the "new" agents.

Traditional disease-modifying antirheumatic drugs

Six double blind, randomized, placebo

controlled studies have evaluated the efficacy and safety of SSZ in PsA patients (5-7, 33-35), especially in those with active peripheral arthritis.

In all of these studies SSZ was more effective than placebo. The two largest trials on the use of SSZ in PsA were a Department of Veteran Affairs Cooperative study (5) and a European-Australian study (7). In the first 221 patients with PsA were randomized to SSZ at a dosage of 2,000 mg/day or placebo and followed up for 36 weeks. SSZ was significantly more effective than placebo based on a composite index that included patient self-assessment, physician assessment, the joint pain/tenderness score and the joint swelling score. In the second study PsA was evaluated together with ankylosing spondylitis and reactive arthritis. Subgroup analysis showed that at the end of the 6-month study period SSZ was superior to placebo in PsA patients. In both studies side effects, consisting mostly of gastrointestinal complaints, were more frequent in the SSZ group than in the placebo group, but all were transient or reversible after cessation of treatment. SSZ did not appear to be effective on axial manifestations and in halting radiographic progression in PsA (9, 11).

Although some authors consider MTX the second-line drug of choice in PsA, few controlled studies have been conducted on its efficacy (3, 4). A pioneering double blind, placebo controlled study in 1964 evaluated the efficacy and safety of a series of three parenteral injections of MTX (from 1 to 3 mg per kilogram of body weight) at 10-day intervals in 21 patients with PsA (3). MTX was found to be effective in decreasing joint tenderness and swelling, improving the joint range of motion, and decreasing the erythrocyte sedimentation rate. Side effects mainly included anorexia or nausea and only one patient had severe pancytopenia. Twenty year later Wilkens *et al*. were not able to demonstrate the efficacy of low-dose pulse MTX (2.5 – 5.0 mg every 12 hours in 3 consecutive doses per week) in PsA in a double blind, placebo controlled study (4). However, the implications of this study are limited by its short duration (only 12 weeks) and the low number of patients enrolled (37 patients).

Two retrospective long-term studies that enrolled an adequate number of patients concluded that MTX is an effective and safe agent in PsA (36, 37). A better response seemed to be correlated with earlier treatment. The starting dose of MTX was 5 – 7.5 mg/week orally and was adjusted according to outcome and tolerance, the highest dose being 25 mg/week. One of these studies carefully evaluated the long-term toxicity of MTX, focusing on the role of liver biopsy in monitoring hepatotoxicity (37). Only two patients discontinued the medication because of side effects: leukopenia in one and stomatitis in the other. Liver function test abnormalities were observed in 11 patients and they resolved when the MTX dose was reduced. Seven patients had 11 liver biopsies; of these only one showed evidence of cirrhosis. No changes were observed in the histopathology in those patients with repeated biopsies. The case reported as cirrhosis occurred very early in the course of MTX therapy and the patient continued taking MTX without further deterioration of liver chemistry and/or histology. The authors concluded that MTX is a safe agent in PsA and that it is not necessary to perform liver biopsies on a routine basis.

In a case-control study that used the database of the University of Toronto Psoriatic Arthritis Clinic, MTX was not able to prevent the progression of radiological damage in the majority of PsA patients over a 24-month period (10). However, only a few patients were studied (19 patients) and the study was not a prospective therapeutic trial. No studies have evaluated the efficacy of MTX on axial manifestations in PsA.

In a recent study MTX was superior to intramuscular gold in terms of the likelihood of achieving a clinical response and in permitting an individual to continue long-term treatment (15).

In the 1980s, studies evaluating the use of CsA in severe cases of psoriasis documented improvement in the associated arthritis (38-40). Subsequent open prospective studies included patients with active peripheral arthritis (41-44). Improvement in clinical parameters was noted at CsA doses of 3-6 mg/kg/day.

Only three prospective controlled studies have been published. The first compared CsA with azathioprine (AZA) and placebo for six months, but the results suffered from poorly defined inclusion criteria, outcome variables, and side effects (45). The second showed that CsA and MTX were equally effective in the treatment of peripheral PsA, but the study was limited by the small number of patients who completed it (46).

The third was a multicenter Italian study that evaluated the 24-week efficacy and safety of CsA (3 mg/Kg/day) versus SSZ and symptomatic therapy alone (non-steroidal anti-inflammatory drugs, analgesic, and/or prednisone ≤ 5 mg/day) in the treatment of PsA with or without axial involvement (8). Patients treated with CsA and SSZ were allowed to receive a stable dose of symptomatic therapy. CsA was more effective than symptomatic therapy and SSZ in the treatment of peripheral PsA. However, the efficacy of CsA and SSZ on axial manifestations was not superior to that of symptomatic therapy. The efficacy of CsA on peripheral arthritis was evident as early as the 8th week of treatment, whereas the effect of SSZ was apparent only after 24 weeks.

Clegg *et al.* (5) found that the efficacy of SSZ in PsA was evident only after 36 weeks, and remained limited until week 28. The short duration of the treatment period in the Italian study could therefore partially explain the weak effect of SSZ. However, this study included an adequate number of patients with active PsA (99 patients) and a symptomatic treatment comparison group. This comparison is particularly important when assessing the efficacy of second line therapy in PsA. In their meta-analysis, Jones *et al.* (13) demonstrated that the placebo groups in all of the published controlled studies, usually on symptomatic therapy, improved considerably over baseline, and so the positive effect of symptomatic therapy in PsA clinical trials may be erroneously attributed to DMARDs.

Both SSZ and CsA were well tolerated,

and the rate of withdrawals due to adverse events was similar in the two groups. Although the most frequent side effect of CsA was reversible kidney dysfunction, no patient discontinued CsA because of nephrotoxicity.

Potential irreversible nephrotoxicity is a major concern with the long-term use of CsA. Low-dose CsA therapy in PsA has recently been reviewed. CsA seems to be effective and safe if monitoring guidelines are closely followed. Of the 170 CsA-treated patients in 16 published studies, only 10 (6%) discontinued the drug because of reversible nephrotoxicity (41).

Macchioni *et al*. evaluated the effect of 2 years of CsA treatment on peripheral joint damage in patients with PsA (12). CsA was capable of controlling progression of the radiological damage in 60% of patients. Normal levels of soluble IL-2 receptor after 6 months of therapy may have a prognostic value for good radiological outcome.

Combination therapy with CsA and MTX was explored in an open study (47) and, as in RA, will probably become a well established therapy in the future. Some authors have suggested combination therapy with SSZ and MTX, which has been found to be effective in RA (48).

Leflunomide and biological agents

Leflunomide, which has been demonstrated to be effective in RA (49), has also been evaluated in two preliminary open studies on PsA with polyarticular involvement (19, 20). In both studies the drug was effective on joint complaints and in one also on skin lesions (20). In this last study 5 out of 13 patients discontinued leflunomide due to side effects.

Both of the main biologic agents that block TNFα – the chimeric monoclonal IgG1 antibody infliximab and the 75kD IgG1 fusion protein etanercept – have been proven to be effective in different forms of spondyloarthritis (SpA) including AS (21-23, 32), undifferentiated SpA (50), arthritis associated to Crohn's disease (51), and PsA (21-26). The major argument in favor of using these agents in PsA is that TNFα and other pro-inflammatory cytokines play a role in the pathophysiology of the disease, as suggested by their raised levels in psoriatic skin lesions (52) and PsA joints (53).

The first study on infliximab in PsA was published as an abstract by Antoni and colleagues in 1999 and 2000 (24, 25). They treated 10 patients with severe PsA unresponsive to methotrexate treatment (15-25 mg/wk) with infliximab (5 mg/kg at weeks 0, 2, and 6). Patients had active polyarticular disease and remained on a stable dose of DMARD, steroids and NSAIDs. All patients showed an ACR50 response and 7 out of 10 an ACR70 response. Gadolinium uptake was reduced in the affected joints by 82%. The PASI of psoriatic lesions showed an improvement of 71%. Patients were re-treated every 8 weeks and showed a continuous response over 1 year.

Van den Bosch *et al.* designed a 12-week open-label trial with infliximab to investigate the efficacy of TNFα blockade in different subtypes of PsA (21). Twenty-one patients with active disease, 9 of whom had PsA, received three infusions of 5 mg/kg of infliximab at weeks 0, 2 and 6. A rapid and significant improvement in global, peripheral and axial manifestations was observed in all 21 patients, without major side effects. Moreover, a significant improvement in the PASI score in 8 patients with PsA was observed at day 14. All patients in the 12-week study were re-treated every 14 weeks (weeks 20, 34, and 48) (22). Of these 21 patients, 19 completed the 1-year follow-up for efficacy. The significant improvement of all disease manifestations was maintained during the entire follow-up period without major adverse events.

Other data on the effect of infliximab in PsA come from our 30-week open pilot study (26). We treated 16 patients with active and DMARD-resistant PsA with infliximab at a dose of 3 mg/kg at 0, 2, 6, 14, 22 and 30 weeks while continuing MTX. A significant improvement of both peripheral and axial symptoms was observed by week 2 that persisted throughout the study period. At day 14 the percentage of patients satisfying the ACR 20, ACR 50, and ACR 70 response criteria were 67%, 40% and 0, while at week 30 they were 64%, 57% and 57%, respectively. PASI improved by 37% at week 2 and by 86% at week 30. No patient dropped out due to treatment failure. Side effects were observed in 4 out of 16 patients, 2 of whom suspended the therapy due to a severe infusion reaction (dyspnea, bronchospasm and hypertension). We have also used infliximab to treat 2 patients with active and DMARD-resistant SAPHO (synovitis, acne, pustolosis, hyperostosis, osteitis) syndrome, which shares manifestations and clinical associations with PsA (54). One patient had palmoplantar pustolosis and the other acne conglobata. In both cases the drug was effective on the chest wall pain. At the beginning of the study the patient with acne conglobata had severe lesions, which showed dramatic improvement with infliximab therapy.

The first placebo-controlled, double blind study on infliximab in SpA has been published very recently (23). Forty patients with different forms of SpA, including 13 patients with PsA, were assigned to receive a loading dose of 5 mg/kg infliximab (weeks 0, 2, and 6) or placebo. Both primary endpoints, that is to say patient and physician assessments of global disease activity, improved significantly in the infliximab group compared with the baseline value, with no improvement in the placebo group. The difference between the values for the two endpoints in the infliximab group versus the placebo group became statistically highly significant at week 2 and persisted up to week 12. Minor adverse events not leading to discontinuation of therapy were observed in both treatment groups. One patient in the infliximab group developed disseminated tuberculosis.

Infliximab has also recently been tested in monotherapy in the treatment of moderate to severe plaque psoriasis (55). Thirty-three patients were assigned to placebo, infliximab 5 mg/kg, or infliximab 10 mg/kg at weeks 0, 2 and 6. The percentage of responders was significantly higher in both 5 mg/kg (82%) and 10 mg/kg (91%) infliximab groups compared with the placebo group (18%). The median time to response was 4

weeks in both active groups and no serious adverse events occurred.

Etanercept was studied in PsA by Mease *et al.* (27). They treated 60 patients with PsA and psoriasis in a randomized, double blind, placebo-controlled 12-week study. Twenty-six (87%) of the patients treated with etanercept (25 mg subcutaneous injections twice weekly) met the Psoriatic Arthritis Response Criteria compared to 7 (23%) of the patients treated with placebo. The ACR20 criteria were achieved by 22 (73%) in the first group and 13% in the second. Of the 19 patients in each treatment group who could be assessed for psoriasis, 26% of the etanercept-treated patients showed a 75% improvement of PASI compared with none of the placebo-treated patients.

Additional data on etanercept come from the studies by Yazici *et al.* (28, 29). Ten patients who were unresponsive to multiple DMARDs were treated with 25 mg subcutaneous etanercept twice weekly (28). At the 12-month follow-up 8 patients were still on etanercept and had maintained their initial response as observed at 3 months. Two patients stopped etanercept, one due to inefficacy and one owing to the diagnosis of osteomyelitis in her foot. All 8 patients were still taking etanercept 2 years after they began therapy (29). Disease activity scores remained the same as those at the 12-month follow-up. None experienced a worsening of the disease or loss of efficacy of etanercept. Of 4 patients with skin disease at the beginning of the study none had lesions after 2 years of therapy. There was no increase in adverse events with the extended exposure to etanercept.

The efficacy of etanercept on psoriasis has also been reported by Iyer *et al.*, who added etanercept to the treatment regimen of 6 patients with recalcitrant and resistant psoriasis (3 of whom had PsA) (30). Alefacept, an LFA3-Ig1 fusion protein which blocks LFA3-CD2 interactions resulting in the inhibition of T cell responses, has been successfully tested on plaque psoriasis in a placebo-controlled, double-blind study (56). A positive effect has also been observed on PsA in an open study (57).

As this review shows, evaluating DMARD trials of PsA is a complex problem. Many clinical trials are too short and enroll too few patients. Observational data are contaminated by a strong placebo effect and therefore should be interpreted with prudence. Future therapeutic trials for this condition will need to be controlled and multicentre in design.

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