Cytokine blockers in psoriatic arthritis

P J Mease

Abstract

The cellular events underlying the pathogenesis of psoriatic arthritis (PsA) and psoriasis have not yet been fully elucidated. Nevertheless, some clues to these conditions are beginning to emerge. In particular, a growing body of data supports the role of proinflammatory cytokines, such as tumour necrosis factor (TNF), in the pathophysiology of PsA and psoriasis. Raised levels of these cytokines are found in the joints of patients with PsA, as well as in psoriatic skin lesions. Physiotherapy, non-steroidal anti-inflammatory agents, corticosteroids, and disease modifying antirheumatic agents, such as methotrexate, are the most commonly used treatments for PsA. However, the data supporting the effectiveness of these treatments are limited, and disease resolution is usually incomplete. This study examined the effects of etanercept, a TNF inhibitor, in patients with PsA. Etanercept treatment was well tolerated and resulted in significant improvement in the signs and symptoms of PsA and in psoriatic skin lesions. Infliximab, another TNF inhibitor, has also been shown to be effective in patients with PsA. Such studies confirm the importance of proinflammatory cytokines in PsA, and hold out hope for patients who require new options for the treatment of their disease.

(*Ann Rheum Dis* 2001;**60**:iii37–iii40)

Psoriatic arthritis (PsA) is a complication of psoriasis, a skin disorder. Psoriasis is present in 1–3% of the general population,[1 2] and approximately 5–30% of patients with psoriasis develop PsA.[1 3–5] Patients with PsA may develop considerable joint damage or even deformity.[6] The cause and pathogenesis of PsA are not yet understood, but disease progression appears to be associated with inflammation early in the course of the disease.[7] PsA is often treated in the same manner and with the same agents as are used for rheumatoid arthritis (RA), but there is no evidence that these drugs prevent disease progression, and the adequacy and safety of these treatments have also been called into question in this patient group.[8]

Several studies have shown that proinflammatory cytokines, including tumour necrosis factor (TNF), are raised in the skin lesions and serum of patients with psoriasis[9] and in the synovial fluid and synovium of patients who additionally have PsA.[9–12] These findings provide a rationale for the use of TNF blockers in the treatment of these diseases. Recent studies have shown that TNF inhibitors relieve the signs and symptoms of PsA.[13 14] These findings, and their implications for the treatment of PsA, are discussed here.

Background

PsA typically strikes patients between 30 and 55 years of age. Approximately 50% of patients with PsA are male.[3] The presentation of a patient with PsA can be quite variable, involving any number of joints in an asymmetrical or symmetrical pattern. Specific areas may be affected, such as the distal interphalangeal joints or the spine, or the arthritis may be widespread. Polyarthritis in PsA may be similar to RA and is asymmetrical in about half of the cases.[8] Most patients (about 75%) develop the skin lesions of psoriasis before PsA, but approximately 10–15% show signs of both at the same time, and in another 10–15% PsA symptoms appear first.[3]

In recent years the potentially severe consequences associated with PsA have begun to be appreciated. Functional impairment is common, and deformity may occur. In one study the extent of impairment at the time of referral to the rheumatology clinic was assessed. More than half (57%) of these patients were found to have erosive arthritis, and 19% showed moderate to severe functional impairment.[15] The finding that a high number of effusions upon first presentation is associated with future progression of joint damage, together with a correlation between low erythrocyte sedimentation rate and diminished disease progression,[7] suggests that inflammation may be a predictor of disease progression, especially early in the course of the disease. Most PsA-induced joint damage seems to occur early, and the rate of disease progression slows over time.[6] Nevertheless, a prospective study found that the proportion of patients with five or more damaged joints doubled from 19% to 41% during the five year study,[6] suggesting that damage that occurs early in the disease may not be manifested as functional impairment until later stages.

TNF, interleukin 1 (IL1), IL6, IL8, and other proinflammatory cytokines are found at high levels in the synovial fluid and membranes of affected joints and in synovial explants.[9–12] The levels of these cytokines do not seem to be quite as high in PsA as in RA, but the overall pattern of cytokine expression is similar, suggesting that these intracellular messengers may be general mediators of joint inflammation and destruction.[10 11] IL2, interferon γ, lymphotoxin α, and other cytokines produced primarily by T helper 1 (Th1) cells are also found in increased levels in the synovial fluids and tissues of patients with PsA.[12 16] It is thus likely that interactions between T cells and

Seattle Rheumatology Associates and Division of Clinical Research, Swedish Hospital Medical Centre, and University of Washington, Seattle, Washington, USA
P J Mease

Correspondence to:
Professor P J Mease, Seattle Rheumatology Associates, 1101 Madison Street, Seattle, WA 98104, USA
pmease@u.washington.edu

Accepted 27 June 2001

monocytes/macrophages, the primary producers of proinflammatory cytokines, play a part in the pathogenesis of PsA.[12]

Treatment for PsA depends on the extent of joint manifestations. Non-steroidal anti-inflammatory drugs (NSAIDs) or physiotherapy may be sufficient for patients with mild joint symptoms.[17] More severe disease is likely to require treatment with corticosteroids or disease modifying antirheumatic drugs (DMARDs). Methotrexate (MTX) is the most commonly used DMARD in PsA (Chang DJ, personal communication), together with cyclosporin A, gold, sulfasalazine, azathioprine, and antimalarial drugs. The use of these agents is largely based on their success in the treatment of RA, but their role in PsA has not been well studied. A double blind, placebo controlled trial of low dose pulse MTX (7.5–15.0 mg/week) in 37 patients with PsA found that the doctor assessment of arthritis activity and skin surface area with psoriasis improved slightly in response to MTX treatment compared with placebo. However, MTX did not result in significant improvements in patient assessment of arthritis activity, joint pain/tenderness and swelling count or score, grip strength, morning stiffness, or skin erythema, inflammation, or scaling relative to placebo. MTX was generally well tolerated. Although MTX treated patients had a statistically significant increase in serum total bilirubin, the overall increase was small and no patients withdrew from the study because of adverse drug effects.[18]

Treatment with intramuscular gold thiomalate was found to result in significant improvements in Ritchie articular index, visual analogue pain score, and erythrocyte sedimentation rate compared with placebo in a study of 82 patients with PsA, but no significant changes were seen in those receiving auranofin.[19]

In a double blind, placebo controlled study of sulfasalazine (SSZ) in 30 patients with PsA, the improvement of the SSZ group was greater than that of the placebo group. However, SSZ did not improve skin lesions, and treatment was discontinued in 26% of patients because of mild side effects.[20] A larger study of 221 patients with PsA concluded that SSZ 2000 mg/day is well tolerated and may be more effective than placebo.[21] When the Psoriatic Arthritis Response Criteria (PsARC; table 1) were used to judge treatment response, SSZ was found to increase the response significantly compared with placebo (SSZ 57.8% *v* placebo 44.6%; p=0.05). However, none of the individual criteria achieved significance.[21]

Although there are data supporting the effectiveness of cyclosporin in the treatment of psoriasis,[22] only a single abstract has been published on the use of this drug in patients with PsA. In this report, cyclosporin had a good effect on the skin lesions but produced "less dramatic changes" in PsA (Doyle D, personal communication).

In response to the current sparsity of options for the effective treatment of PsA, clinicians and scientists have begun to investigate other possible agents. In addition to drugs that provide symptomatic control, there is a marked need for drugs that slow or prevent disease progression, thus potentially improving long term outcomes. Much attention has been focused on agents that inhibit the activity of proinflammatory cytokines, which are believed to have a primary role in joint destruction. TNF neutralisers were the first such agents to reach clinical trials. TNF inhibitors have shown significant clinical efficacy in RA,[23–26] and are now being examined for use in patients with PsA.[13 14] We tested etanercept, one of these TNF neutralisers, in the treatment of PsA.

*Table 1 Psoriatic arthritis response criteria**

- Improvement in two of the following four criteria, one of which must be tender or swollen joint score
  - Doctor global assessment (1 unit on 0 to 5 Likert scale)
  - Patient global assessment (1 unit on 0 to 5 Likert scale)
  - Tender joint score (30% improvement)
  - Swollen joint score (30% improvement)
- No worsening in any criteria

*From Clegg 1996.[21]

Methods

This study was a placebo controlled, randomised clinical trial of 60 patients with PsA who were randomly allocated to receive either etanercept (25 mg subcutaneously twice weekly) (n=30) or placebo (n=30) for 12 weeks.[13] Patients in this study had had psoriasis for a mean of approximately 20 years and PsA for a mean of 11.5 years. Patients achieving partial benefit with MTX were allowed to continue treatment with it. This subgroup, which contained 28 (47%) of the patients enrolled in the study, was evenly distributed between the placebo and etanercept groups. All other DMARDs and topical medicines for psoriasis were discontinued. Background use of NSAIDs or prednisone ⩽10 mg/day was allowed.

The primary arthritis efficacy response measure in this study was the PsARC. The ACR 20, 50, and 70 responses, modified for use in PsA, were the secondary arthritis measures. Evaluation of skin response required a minimum of 3% body surface area affected with psoriasis. In eligible patients, skin response was evaluated with the Psoriasis Area and Severity Index (PASI) and the target lesion score. The PASI is a composite measure based on scale, erythema, and induration, and is weighted by severity and body surface area.[27] A single, preselected lesion is used to determine the target lesion score, which is based on the amount of scale, erythema, and plaque.

Results

At the study end point (12 weeks), 26 (87%) etanercept treated patients were determined to have a response according to PsARC criteria, compared with seven (23%) placebo treated patients (fig 1).[13] For most patients, the response was quite rapid: by four weeks, 23 (77%) etanercept treated patients qualified as responders. At 12 weeks, four (13%) patients had no tender joints and seven (23%) patients

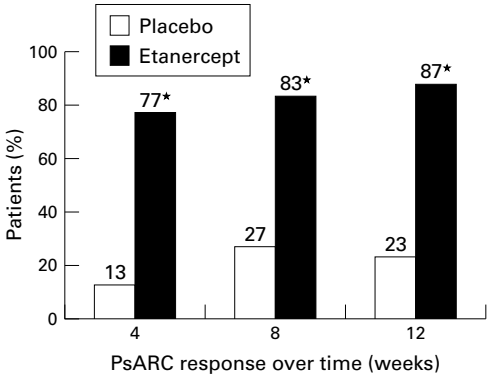

Figure 1 Clinical response as assessed by Psoriatic Arthritis Response Criteria (PsARC) in patients with psoriatic arthritis treated with etanercept or placebo. p<0.0001 v placebo. Adapted from Mease,[13] with permission.

had no swollen joints. Similar dramatic responses were noted with ACR 20, 50, and 70 criteria. Nineteen patients in each group met the criterion for skin response evaluation, and greater improvement in psoriasis lesions was observed in etanercept treated than in placebo treated patients. The median improvement in PASI score in etanercept treated patients at three months was 46%, compared with 9% in the placebo group, while for the target lesion score the median improvement was 50% for the etanercept group versus 0% for the placebo group. A 75% PASI response, which represents nearly complete resolution of skin disease, occurred in 26% of etanercept treated patients and in none of the patients receiving placebo. Figure 2 shows a representative response of psoriatic lesions to etanercept.

Etanercept was well tolerated during this trial. No patient in the etanercept group discontinued treatment. Mild reactions at the injection site occurred in six (20%) of the etanercept treated patients. These reactions resolved with continued use; interruption of treatment was not necessary. Other adverse events occurred in comparable numbers in the etanercept and placebo groups.[13]

Discussion

The data from this study show that etanercept is a safe and effective treatment for PsA. Significant improvements were seen not only in the arthritis symptoms but also in the psoriatic lesions. Etanercept treatment was well tolerated during the 12 week period of observation.

Infliximab, another TNF inhibitor, has also been tested in the treatment of PsA (Antoni C, personal communication). In a small open label study of six patients with severe PsA despite MTX treatment, infliximab (5 mg/kg once every two weeks) was added to the MTX regimen. At the six week study end point, there was an 88% improvement in swollen joint counts and an 86% improvement in tender joint counts. Magnetic resonance imaging data suggested that inflammation was reduced.

Infliximab was also found to be effective in patients with PsA over a period of one year. Ten patients were treated with 5 mg/kg of infliximab at weeks 0, 2, and 6; most also received concomitant DMARD treatment (MTX (n=7); SSZ, (n=1)). At the 10 week assessment, all patients showed reduced signs and symptoms of PsA and decreased serological activity. Infliximab treatment was then given to meet individual patients' needs. At one year, patients continued to show at least an ACR 50 response (using RA criteria not modified for PsA), and six patients had no tender or swollen joints (Dechant C, personal communication).

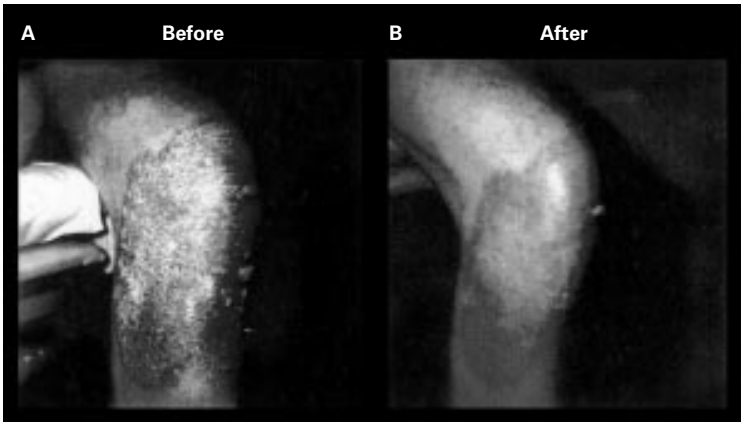

Figure 2 Area of skin affected by psoriatic lesions in a patient with PsA. (A) Before etanercept treatment; (B) after 12 weeks of etanercept treatment.

Conclusions

Early results with TNF neutralising agents in the treatment of PsA and psoriasis are encouraging. The symptomatic improvements seen in these studies were profound and sustained, and adverse effects were minimal. Inhibitors of TNF thus seem to have excellent potential for treating PsA and psoriasis. Whether these agents will be able to improve long term outcomes, such as disability, is not yet known. The ability of etanercept and infliximab to slow joint damage in patients with RA has been convincingly demonstrated[24 26]; hopefully, these findings will prove true in PsA as well. Given the close association between early signs of inflammation and subsequent joint damage in patients with PsA,[7] early control of inflammation through the use of TNF neutralisers may positively impact future functional ability.

The clinical benefits of TNF neutralisers in patients with PsA and psoriasis support the key role of proinflammatory cytokines in the pathophysiology of these diseases, and raise the question as to whether other cytokine inhibitors will have similar effects. Agents that neutralise IL1 are currently being tested in clinical trials of RA, and may also be useful in the treatment of PsA and psoriasis. As our understanding of the pathophysiology of PsA and psoriasis improves, the options for treating these difficult and often devastating conditions will hopefully expand as well.

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