Emerging role of anti-tumor necrosis factor therapy in rheumatic diseases

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Abstract

Tumor necrosis factor alpha (TNF-α) is an inflammatory cytokine that has been implicated in a variety of rheumatic and inflammatory diseases. New understanding of the importance of TNF-α in the pathophysiology of rheumatoid arthritis and Crohn's disease led to the development of a new class of targeted anti-TNF therapies. Anti-TNF-α agents including etanercept (a fusion protein of the p75 TNF receptor and IgG1) and infliximab (a chimeric monoclonal antibody specific for TNF-α) have been approved for the treatment of rheumatoid arthritis. In addition, infliximab has been approved in the treatment of patients with active or fistulating Crohn's disease. A new appreciation of the importance of TNF-α in other rheumatic and inflammatory diseases has led to a broadening of the application of anti-TNF agents. Both etanercept and infliximab have been used in open-label and randomized studies in patients with psoriatic arthritis. Although larger randomized trials are needed to confirm early results, both these anti-TNF-α agents, etanercept and infliximab, have demonstrated activity in improving the signs and symptoms of psoriatic arthritis and psoriasis. Infliximab has also been shown to be effective in patients with other rheumatic diseases, including ankylosing spondylitis, and may be effective in adult-onset Still's disease, polymyositis, and Behçet's disease. Further investigations will fully elucidate the role of infliximab in these and other rheumatic diseases.

Keywords: anti-tumor necrosis factor, cytokine, infliximab, rheumatic disease, tumor necrosis factor

Introduction

Significant advances in recent years have improved the understanding of the pathogenesis of rheumatoid arthritis (RA). It is thought that TNF-α resides at the apex of an inflammatory cytokine cascade that is responsible for the pathophysiology of RA. The central role for TNF-α in RA is supported by several findings. Secreted by cultured synoviocytes, TNF-α is elevated in sera and synovial fluid of RA patients [1–3]. In addition, anti-TNF-α antibodies have been shown to prevent polyarthritic disease in two mouse models [4,5].

The new appreciation of the importance of TNF-α in the pathophysiology of RA has led to the clinical development of a new class of targeted therapeutic agents. Etanercept (Enbrel®; Immunex, Seattle, WA, USA) is a fusion protein of the extracellular ligand-binding portion of the p75 TNF receptor and the Fc portion of IgG1. Etanercept binds to

ACR = American College of Rheumatology response criteria; AOSD = adult-onset Still's disease; AS = ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; Fc = crystallizable fragment; IL = interleukin; MTX = methotrexate; PASI = Psoriasis Area and Severity Index; PGA = physician's global assessment; PsA = psoriatic arthritis; RA = rheumatoid arthritis; TNF-α = tumor necrosis factor alpha.

soluble TNF-α and lymphotoxin-α, thus blocking the activation of TNF receptors. Infliximab (Remicade®; Centocor, Malvern, PA, USA) is a chimeric (human/mouse) antibody that binds with high affinity and specificity to both the soluble and membrane-bound forms of TNF-α. In addition, infliximab also binds to TNF-α already engaged with the TNF receptor. Infliximab thus neutralizes soluble and membrane-bound TNF-α and can inhibit the activation of TNF receptors before and after TNF-α engages with the receptor.

Both etanercept and infliximab have demonstrated efficacy in reducing the signs and inflammatory symptoms of RA and in inhibiting joint erosion in clinical trials [6–10]. In addition, infliximab has been shown to significantly inhibit joint space narrowing [10].

Etanercept and infliximab have both been approved for the treatment of RA by the US Food and Drug Administration and by the European Agency for the Evaluation of Medicinal Products. In addition, infliximab has been approved for the treatment of Crohn's disease in patients with moderately to severely active or fistulating disease [11,12]. Success in the treatment of these inflammatory diseases with anti-TNF agents has prompted the investigation of this therapeutic modality in the treatment of other rheumatic diseases, including psoriatic arthritis (PsA), ankylosing spondylitis (AS), adult-onset Still's disease (AOSD), and polymyositis.

Current diseases under investigation

The use of anti-TNF agents in the treatment of PsA, AS, AOSD, and polymyositis has been based on evidence suggesting that TNF plays a role in these inflammatory rheumatic diseases. In the present article, the evidence of activity of anti-TNF-α therapy in the treatment of these diseases will be reviewed.

PsA and psoriasis

Psoriasis is reported to affect between 1 and 3% of adults in the United States, and PsA occurs in approximately 6–20% of psoriasis patients [13]. PsA is an inflammatory arthropathy that may present in a symmetric or an asymmetric polyarticular form, with or without onycholysis. The current therapeutic approaches for PsA are similar to those for RA and include nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs (DMARDs), and immunosuppressive agents. Only two DMARDs, methotrexate (MTX) [14] and sulfasalazine [15], have demonstrated efficacy in the treatment of PsA. These agents are, however, associated with significant adverse events, and many patients do not respond to these treatments. Other therapeutic options are therefore needed.

TNF-α has been linked to the pathogenesis of PsA and psoriasis because of its ability to upregulate adhesion molecules and to trigger an inflammatory cytokine cascade. TNF-α induces the expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, both of which are involved in lymphocyte trafficking to inflammatory lesions [16]. Circulating T lymphocytes and macrophages isolated from PsA patients produce an increased amount of TNF-α compared with macrophages isolated from healthy controls [17]. Furthermore, the levels of TNF-α are elevated in the synovial fluid [18,19] and skin lesions [20,21] in PsA patients, with TNF-α levels correlated with disease activity [22,23].

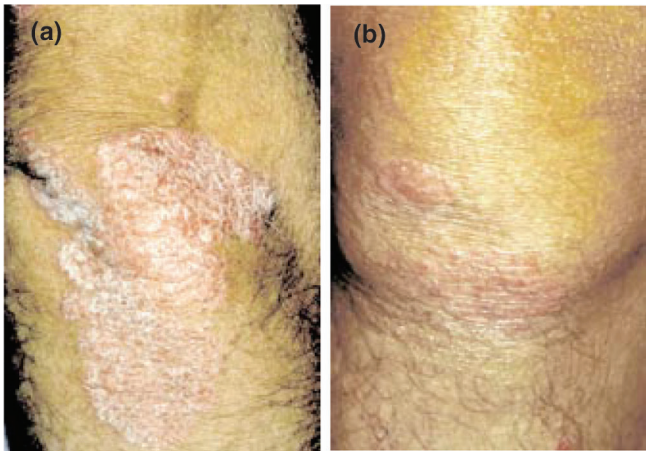
Several open-label studies have investigated the use of anti-TNF-α agents in the treatment of PsA and psoriasis [24–28]. In a single-center, open-label report on the treatment of spondyloarthopathies, Van den Bosch *et al*. [24] reported that nine PsA patients treated with 5 mg/kg infliximab (weeks 0, 2, and 6) experienced significant improvement in physician's global assessment (PGA) scores, erythrocyte sedimentation rates (ESRs), and C-reactive protein (CRP) levels. Of these nine patients, eight had psoriasis at baseline. After 12 weeks of infliximab treatment, baseline Psoriasis Area and Severity Index (PASI) scores were significantly decreased (improved). The clinical improvements in all PsA and psoriasis disease manifestations were maintained over a 1-year follow-up period [25].

In another open-label study, eight out of 10 heavily pretreated PsA patients experienced improvements in Health Assessment Questionnaire scores and PGA scores after 12 months of treatment with 25 mg etanercept (subcutaneously, twice per week). All four patients in this trial with active psoriasis had significant improvement in their psoriatic lesions, including complete resolution in three patients [26].

In our open-label experience, infliximab treatment was efficacious and safe in both PsA and psoriasis [27,28]. With infliximab treatment (5 mg/kg at weeks 0, 2, and 6), all 10 patients in our study achieved 20% improvement in arthritis per the American College of Rheumatology response criteria (ACR) by week 2. After 10 weeks of treatment, eight patients achieved 70% improvement per the ACR, with six patients maintaining this improvement after 54 weeks. In addition, magnetic resonance imaging showed an 82% reduction in inflammation in peripheral joints, and mean PASI scores were reduced by 71% at week 10. After 10 weeks of infliximab therapy, six patients experienced nearly complete clearing of erythematous psoriasis plaques (Fig. 1). Furthermore, histopathologic analysis of psoriatic plaques showed a reduction in epidermal hyperplasia and inflammation by week 10 (Fig. 2).This reduction in hyperplasia was associated with a decrease in plaque size and was evident from the near-normal epidermal structure after infliximab treatment.

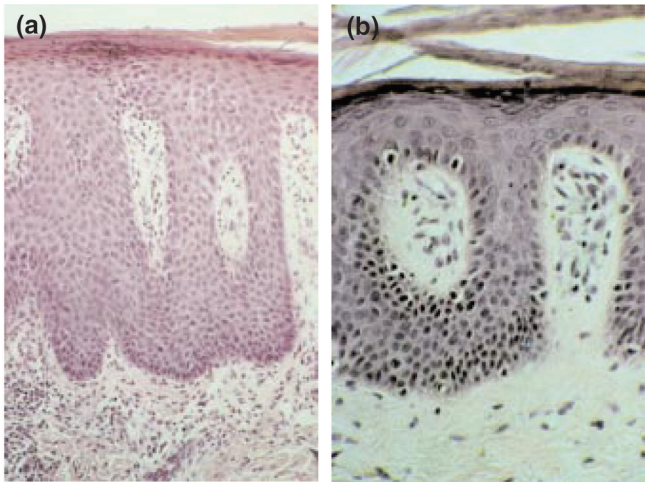
The use of anti-TNF agents in treating PsA and psoriasis has also been investigated in randomized, double-blinded,

Figure 1



Psoriasis plaques on patient skin. Depicted is a representative set of patient plaques **(a)** before and **(b)** 10 weeks after infliximab treatment. Note the characteristic sharply circumscribed erythematous psoriasis plaque covered by silvery scales prior to infliximab therapy.

Figure 2



Histopathologic psoriasis plaques. Epidermal and dermal characteristics of psoriasis plaques from a representative patient **(a)** before and **(b)** 10 weeks after infliximab treatment.

placebo-controlled studies. Mease *et al*. [29] reported that 87% of patients receiving 25 mg etanercept (subcutaneously, twice per week) achieved Ps ACR response criteria, compared with 23% of placebo patients ($P < 0.0001$). Seventy-three per cent of etanercept-treated patients achieved 20% improvement of the ACR, compared with 13% of placebo-treated patients ($P < 0.0001$). Of 19 patients in each treatment group with active psoriasis, the median improvement in PASI scores was significantly higher in etanercept-treated patients than that in placebo-treated patients. Of the psoriasis patients treated with etanercept, 26% achieved a 75% improvement, compared with no patients treated with placebo. In an open-label extension study, etanercept continued to effectively reduce clinical signs and symptoms of PsA and psoriasis for up to 36 weeks [30].

Chaudhari *et al*. [31] recently described the first reported placebo-controlled, randomized study designed to investigate the efficacy of an anti-TNF agent in psoriasis patients. In this study, 30 patients were randomized to receive 5 mg/kg or 10 mg/kg infliximab or placebo. Nine of 11 (82%) patients treated with 5 mg/kg infliximab achieved good, excellent, or clear ratings on PGA, compared with only two of 11 (18%) patients receiving placebo ($P = 0.0089$). In addition, 10 of 11 (91%) patients treated with 10 mg/kg infliximab achieved these ratings ($P = 0.0019$, compared with placebo). A significantly higher proportion ($P = 0.0089$, 5 mg/kg infliximab versus placebo; $P = 0.03$, 10 mg/kg infliximab versus placebo) of patients treated with infliximab obtained a 75% improvement in PASI scores compared with those receiving placebo. The results of these studies suggest that TNF-α plays a pivotal role in the pathogenesis of PsA and psoriasis. In addition, anti-TNF-α therapy offers patients with PsA and psoriasis a new therapeutic option for the control of their disease.

Ankylosing spondylitis

AS is an inflammatory arthropathy that preferentially affects the axial skeleton, usually manifesting in the sacroiliac joints and then ascending to involve the axial skeleton [32,33]. Treatment for AS includes nonsteroidal anti-inflammatory drugs and sulfasalazine, the only DMARD that shows activity, albeit limited, in the disease [34].

Only limited evidence exists to support a role for TNF-α in the pathophysiology of AS. Braun *et al*. [35] showed that TNF-α mRNA and protein were present in inflamed sacroiliac joints of AS patients. Lange *et al*. [36] recently reported significantly increased TNF-α plasma levels in AS patients, with a positive correlation between TNF-α plasma levels and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). In addition, the strong link between AS and inflammatory bowel disease (where 20–60% of spondyloarthropathy patients have gastrointestinal lesions resembling those in Crohn's disease) provides circumstantial evidence for a role of TNF-α in AS [37].

Despite a general lack of evidence for a role of TNF-α in the pathophysiology of AS, clinicians are beginning to investigate the use of anti-TNF therapies in this inflammatory disease. In an open-label study, 11 patients with AS of short duration were treated with 5 mg/kg infliximab at weeks 0, 2, and 6 [38]. Improvements in activity, in function, and in pain scores of ≥50% were reported in nine of 10 eligible patients. The median CRP level decreased to normal levels and the median improvement in BASDAI scores after 4 weeks was 70%.

In another open-label study of patients with different subtypes of spondyloarthropathy, 10 AS patients treated with 5 mg/kg infliximab every 14 weeks achieved significant improvements in morning stiffness, tender and swollen joint counts, ESR, CRP, and BASDAI, Bath Ankylosing Spondylitis Functional Index, and Bath Ankylosing Spondylitis Metrology Index scores. Improvement in ESR and CRP was significant at day 3 after infliximab treatment and was maintained to day 84. Improvements in the other endpoints were significant at day 14 and were also maintained to day 84. The significant improvements in the global, peripheral, and axial disease manifestations were maintained over a 1-year follow-up period [25].

In a larger open-label study, 48 patients with severe AS were treated with infliximab. Significant improvements in mean disease activity, global pain, BASDAI, Bath Ankylosing Spondylitis Functional Index scores, and CRP levels were observed at week 8 [39].

The results of the aforementioned open-label studies were recently confirmed in a double-blind, placebo-controlled, phase III clinical trial [40]. A total of 70 patients with active AS were enrolled in the study and were randomized to receive placebo ($n = 35$) or to receive 5 mg/kg infliximab ($n = 35$) at weeks 0, 2, and 6, and then every 6 weeks until week 48. At the time of the report, 66 patients had completed 3 months of treatment. A 50% improvement in BASDAI was achieved by 53% of patients treated with infliximab, compared with 9% of patients treated with placebo ($P < 0.01$).

Adult-onset Still's disease

AOSD is a rare systemic inflammatory disorder of unknown etiology. Clinical symptoms of this disease are high spiking fever, arthritis, transient cutaneous rashes, and sore throat [41]. AOSD is considered identical to the systemic form of juvenile RA [42]. A markedly elevated serum ferritin correlates with disease activity [43,44], and several inflammatory cytokines (e.g. IL-18) are elevated in these patients [45–47]. Furthermore, Hoshino *et al*. [46] reported elevated serum levels of TNF-α in AOSD patients. Kawashima *et al*. [47] recently demonstrated that the proinflammatory cytokine IL-18 is markedly elevated in the serum of AOSD patients during the acute phase of their disease. Because it has been shown that TNF-α induces the expression of IL-18 in synovial tissues [48], anti-TNF agents may lead to a reduction of IL-18 in AOSD patients. Bombardieri *et al*. [49] recently demonstrated that infliximab reduced IL-18 serum levels in RA patients. Studies to determine whether infliximab also reduces IL-18 serum levels in AOSD are therefore warranted.

The current treatment for AOSD is mostly limited to the use of nonsteroidal anti-inflammatory drugs and, in severe cases, of prednisone. However, many patients become dependent on high-dose prednisone or are refractory to corticosteroid treatment. In a retrospective analysis of 26 AOSD patients, MTX was an effective second-line treatment for patients who had not responded to prednisone [50]. However, controlled studies of MTX and other DMARDs in the treatment of AOSD have not been performed.

Interest in using anti-TNF therapy in treating AOSD increased following a report that infliximab was effective in suppressing fever and acute phase response in a patient with juvenile chronic arthritis [51]. Furthermore, thalidomide, a known inhibitor of TNF-α, was reported to markedly improve clinical symptoms in a patient with treatment-resistant AOSD [52]. Systematic investigation of anti-TNF-α therapy in AOSD is in its early stages. An open-label trial evaluated the efficacy of infliximab in the treatment of AOSD refractory to conventional therapy [53]. Three patients with chronic and active AOSD who were unresponsive to corticosteroids and MTX were administered 3 mg/kg infliximab at weeks 0, 2, and 6, and then every 8 weeks thereafter, along with concomitant 15 mg/week MTX. Disease activity had improved in all three patients at 50 weeks of follow-up, and two patients experienced reductions in ESR, CRP, prednisone dose, and PGA score.

In a recent pilot study conducted at our institution, six AOSD patients treated with infliximab reported marked improvements in the clinical signs and symptoms of AOSD [54]. Patients were treated with 5 mg/kg infliximab at weeks 0, 2, and 6, and thereafter at intervals of 6–8 weeks. Fever, arthralgias, myalgias, splenomegaly, and rash were resolved in all six patients within the first three courses of infliximab treatment. A summary of the serologic and disease activity parameters is presented in Table 1. Although the results of these open-label trials need to be confirmed in randomized, placebo-controlled studies, the preliminary results suggest infliximab is effective in managing relapse in refractory AOSD patients.

Polymyositis

Polymyositis is an idiopathic inflammatory myopathy that is characterized by proximal muscle weakness, skeletal muscle inflammation and damage, and elevated serum levels of muscle-derived proteins such as creatinine kinase. Polymyositis is associated with lymphocyte invasion of muscle fibers, predominantly cytotoxic $CD8^+$ T lymphocytes, which leads to muscle fiber necrosis, degeneration, and fibrosis. The current first-line therapy for polymyositis is prednisone [55]. However, many patients only achieve partial response or do not respond at all to high-dose corticosteroids. Because early recognition and treatment of polymyositis is critical to prevent irreversible muscle damage, second-line therapies such as MTX or azathioprine should be administered to patients who fail corticosteroid treatment [55].

Table 1

Serologic and global assessment parameters in patients with adult-onset Still's disease receiving 5 mg/kg infliximab

	Baseline (mean)	8 weeks (mean)
C-reactive protein (mg/dL)	65	5
Erythrocyte sedimentation rate (mm/h)	53	16
Serum ferritin (mg/dL)	2952	58
Tender joint count	15	2.7
Swollen joint count	9	1.8

Tateyama *et al*. [56] demonstrated, using monoclonal antibodies to TNF-α, that TNF-α-positive macrophages and lymphocytes invade the endomysium in the muscles of polymyositis patients. In addition, there was a correlation between TNF-α levels in the endomysium and muscle fiber atrophy. Kuru *et al*. [57] also demonstrated infiltration of TNF-α-positive $CD8^+$ lymphocytes and macrophages into the muscle fibers of polymyositis patients.

The apparent involvement of cytokine-producing T lymphocytes in polymyositis initiated interest in treating these patients with anti-TNF agents. There have been no published accounts of the efficacy of anti-TNF therapy in polymyositis, but a number of case studies have been presented. We recently treated a patient with polymyositis refractory to immunosuppressive regimens with 4 mg/kg infliximab every 6 weeks and concomitant MTX therapy. This patient showed a significant response on infliximab treatment, including a significant improvement in mobility. The skeletal muscle-specific enzymes returned to normal serum levels, indicating a substantial reduction in inflammation. Although this is a single case study, it suggests that anti-TNF-α therapy may be a viable treatment alternative for patients with refractory polymyositis. Further studies to fully investigate the potential for anti-TNF-α therapy in treating polymyositis are warranted.

Behçet's disease

Behçet's disease is a chronic autoimmune disorder characterized by systemic vasculitis. This disease is associated with mucocutaneous, ocular, articular, vascular, gastrointestinal, and central nervous system manifestations. Approximately 70% of patients experience relapsing ocular inflammation that can lead to blindness [58]. The etiology of Behçet's disease is unknown; however, some evidence suggests that increased levels of TNF and soluble TNF receptors are associated with active disease [59–61]. Interestingly, thalidomide, which has been used successfully in the treatment of Behcet's disease, inhibits TNF-α by accelerating the degradation of TNF-α mRNA [62]. Other anti-TNF therapies may therefore benefit these patients.

Anti-TNF therapy has recently been used for the treatment of patients with Behçet's disease. Travis *et al*. [63] reported the successful use of infliximab in two patients with Behçet's disease with rare gastrointestinal ulcerations. Within 10 days of infliximab treatment, the ulcers had healed and all extraintestinal manifestations had resolved. Furthermore, five patients with relapsing panuveitis were successfully treated with infliximab. Remission of ocular inflammation was evident within the first 24 hours, and complete suppression was observed within 7 days of infliximab therapy [64]. The rapid and effective response of this handful of patients with Behçet's disease to infliximab clearly warrants further studies of the use of anti-TNF therapy in treating this disease.

Conclusions

Anti-TNF-α therapy is currently approved for the treatment of RA (infliximab in combination with MTX, and etanercept) and of Crohn's disease (infliximab). This brief summary of study data supports a role for anti-TNF therapy in the treatment of PsA, psoriasis, AS, AOSD, polymyositis, and Behçet's disease. Success in the treatment of these inflammatory disorders suggests that anti-TNF therapy may also be effective in treating other inflammatory diseases, including ulcerative colitis, uveitis, and Felty's syndrome. Future investigations will determine the breadth of application of anti-TNF therapy in the treatment of autoimmune and inflammatory disorders.

Note added in proof

In January 2002, etanercept was awarded an additional indication by the US Food and Drug Administration. Etanercept was approved as monotherapy or in combination with methotrexate for reducing the signs and symptoms of psoriatic arthritis.

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