Anti-TNF therapy for other inflammatory conditions

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ABSTRACT

The use of biological agents in inflammatory conditions is rapidly increasing. TNFα blocking treatments have changed the course of rheumatoid arthritis, Crohn's disease, juvenile rheumatoid arthritis and psoriatic arthritis. Open label studies with TNFα inhibitors in other inflammatory conditions such as adult Still's disease, uveitis, Wegener's granulomatosis, Behçet's disease, scleroderma, Sjögren's syndrome, sarcoidosis, pyoderma gangrenosum, polymyositis/dermatomyositis have shown promising results. However, whether anti-TNFα therapy can be safely and efficaciously applied to these other inflammatory disorders requires further controlled studies.

Introduction

TNF is considered one of the major proinflammatory cytokines involved in the pathogenesis of many immune mediated disorders. Recently, two biological agents that inhibit TNF have become available: a soluble receptor antagonist (etanercept) and a chimeric anti-TNF monoclonal antibody (mAb) (infliximab). The Food and Drug Administration (FDA) of the United States has approved etanercept and infliximab for use in the treatment of rheumatoid arthritis (RA); infliximab is also approved for use in refractory and fistualizing Crohn's disease; and etanercept is approved for use in juvenile rheumatoid arthritis (JRA), and psoriatic arthritis (PsA).

RA is a systemic, inflammatory disorder characterized by symmetrical additive, erosive, and potentially deforming arthritis. Joint inflammation leads to erosive articular damage, which limits physical activities and reduces quality of life. Over the past decade, advances in understanding the pathogenesis of RA have led to the identification of a number of noteworthy molecular targets; of these, therapy-targeting TNF has been best validated. Recently published studies confirm that anti-TNF therapy can improve the signs and symptoms of RA, retard the progression of joint erosions and joint space narrowing and improve quality of life (1-3).

Observations of improvement of coexisting conditions (e.g. pyoderma gangrenosum or psoriasis in Crohn's disease), coupled with an accumulating body of information suggesting a role for TNF in the pathogenesis of other immune mediated conditions has created considerable enthusiasm for using these and other biologic agents in patients with diverse diseases. Case reports and small open-label studies have revealed promising results, suggesting that anti-TNF therapy may be a useful treatment option.

Adult Still's disease

Adult Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology, characterized by high spiking fever, arthritis, neutrophilic leukocytosis and transient cutaneous rash. Even though the type of articular involvement is distinct from RA, the long-term morbidity may similarly be dependent upon the chronicity and severity of arthritis. Of note, high serum levels of TNF have been demonstrated during the acute phase of AOSD (4,5). Suppression of fever and the acute phase response in patients with JRA treated with anti-TNF mAb has provided supporting evidence for potentially using anti-TNF therapy in AOSD (6).

In a pilot study, five AOSD patients received 25 mg etanercept twice weekly. All the patients showed improvement in fever, rash and joint pain/ swelling within 3 weeks. Four of the five patients completed 6-12 months of therapy; they remained in clinical remission with decreased prednisone dosing (7). In a six-month open-label study, twelve patients with AOSD received 25 mg etanercept twice a week or up to three times a week for

eight weeks. Eight of the patients reached an ACR20 response, five out of twelve reached an ACR50, and two out of twelve reached ACR70 response. Only one of the three patients with fever and rash had shown improvement in these symptoms. Tender and swollen joint count improved 54% and 63% respectively (8). Six patients with AOSD were treated with 3 to 5mg/kg infliximab in an open label study at weeks 0, 2, 6 and then every 6 to 8 weeks. They were followed for 2 to 18 months. Resolution of fever, arthralgia, myalgia, splenomegaly and rash was noted in all patients (9).

TNF blocking therapy appears to be well tolerated and improves articular and systemic manifestations in AOSD. Nevertheless, the long term effects and optimal regimen of anti-TNF therapy is still to be determined.

Uveitis

Uveitis is frequently associated with systemic inflammatory diseases. TNF has been implicated in the pathogenesis of various forms of uveitis and has been extensively studied in several animal models (10,11). An up-regulation of the TNF gene in the iris/cytoid body and high levels of TNF in the aqueous humor may contribute to intraocular inflammation and parallel the disease course (12). Mice lacking the p55 and p75 TNF receptors develop less ocular inflammation after challenge (13). However, there are contradictory reports about the effect of anti-TNF therapy on uveitis in rats. Dick *et al.* demonstrated that inhibition of TNF by the administration of a TNF receptor IgG fusion protein delayed the onset and decreased the severity of uveitis in rats (14). In contrast, De Vos *et al.* reported that anti-TNF therapy caused an exacerbation of endotoxin-induced uveitis in rats (15).

Case reports regarding the use of TNF blockers in patients with inflammatory uveitis are inconclusive. Although TNF blockers help achieve remission in patients with certain subgroups of inflammatory eye disease (16-18), some reports demonstrate insufficient response or even worsening of the symptoms (19).

Vasculitis

The vasculitides constitute various clinical and pathological syndromes, which create a therapeutic challenge. Vasculitis is characterized by infiltration of vessel walls by various cells including macrophages, and T lymphocytes, with the production of many cytokines that are largely responsible for the signs and symptoms of the disease. By immunohistochemical techniques, TNF has been demonstrated in up to 60% of the cells in all areas of inflamed temporal arteries of patients with giant cell arteritis (20). Although the effectiveness of biological agents in systemic vasculitis is unproven, their introduction may provide a new avenue for treatment. Cases of TNF blockade (infliximab) in giant cell arteritis have been reported (21).

Wegener's granulomatosis

Wegener's granulomatosis (WG) is characterized by a multifocal inflammatory illness that most often affects the upper and lower respiratory tracts and kidneys. Evidence from a variety of sources suggests that abnormal regulation of TNF may play a major role in WG. In animal models, granuloma formation, a classic pathological marker of WG, was markedly impaired by antibodies directed against TNF (22). Also, transcription of the TNF gene has been shown to be enhanced in peripheral blood mononuclear cells from patients with WG (23). CD4+ T cells isolated from patients with WG produce elevated levels of TNF (24). Serum levels of soluble receptors for TNF are elevated in patients with active WG, and normalize with remission (25). Studies of renal biopsy tissue by immunohistochemistry, polymerase chain reaction and in situ hybridization from patients with pauciimmune glomerulonephritis confirm that TNF-positive cells infiltrate histologically active renal lesions (26). In a six-month open-label study, etanercept was well tolerated by patients with WG. Twenty patients were given 25 mg of etanercept twice a week in addition to their standard therapies for WG. The Birmingham Vasculitis Activity Score (BVAS/WG) was used to determine the clinical response.

BVAS/WG scores improved at the end of six months, but intermittently active disease was observed in fifteen out of twenty patients (27). While early data are encouraging, definitive assessment of the efficacy of TNF blockers in WG will require controlled clinical trials.

Behçet's disease

Behçet's disease (BD) is a vasculitis of unknown cause that is characterized by recurrent genital and oral ulcers, skin lesions and ocular lesions. Arthritis, neurological and gastrointestinal manifestations may also occur. A Th1-biased immune response seems to play a critical role in BD (28). TNF and other proinflammtory cytokines produced by monocytes may be an important part of the inflammatory cascade in BD (29). The MHC class I molecule HLA-B51 has been widely reported as a risk factor for BD; HLA-C and TNF polymorphisms have also been implicated (30,31). In a study of 102 patients with ocular BD and 105 controls, a primary role for TNF gene polymorphism in BD was not identified, but co-expression of the TNF 2 allele with HLA-B51 was found to contribute to the severity of the disease (32).

Patients with refractory BD showing different system involvement have been treated with TNF blockers. A patient with recalcitrant orogenital ulceration was treated with two doses of infliximab (10 mg/kg) over one month. The patient's symptoms dramatically improved following the first infusion, and he was still in remission twelve months after the second infusion (33). In another case of orogenital ulcers, 5 mg/kg infliximab infusions were given at weeks 0, 2, and 6 and the patient's ulcers cleared for the first time in ten years (34). Additional reports of patients with refractory ocular and gastrointestinal BD reveal that infliximab led to rapid and complete resolution of the patients' symptoms (17,18, 35, 36).

Given the significant morbidity and limited success with current therapeutic modalities in BD, the results of these pilot studies support a rationale for randomized controlled trials of TNF blocking agents.

Scleroderma

Progressive systemic sclerosis (SSc) is a connective tissue disease affecting various organs, including skin, gastrointestinal tract, lung, kidney, and heart with a primary fibrotic process often preceded by inflammation. The cause of SSc is unknown; it is regarded as an autoimmune disease that involves cellular and humoral immunity. Cellular infiltrates including CD4+, CD8+ T cells, B cells, and macrophages have been demonstrated in various organs. The mechanism of fibrosis in SSc is not understood, although soluble mediators such as transforming growth factor , platelet-derived growth factor, interleukin (IL)-4, IL-6, TNF can affect the behavior of fibroblast growth (37). It has also been shown that serum concentrations of soluble TNF receptor type 1 (sTNF R1) correlate with the severity of the disease (38). There is still no single agent or combination therapy that has a clear impact on the disease process or outcome.

In an open-label, single arm study of ten SSc patients, etanercept was administered twice a week for six months (39). The Rodnan skin score was the primary outcome measure. It improved in four patients and did not change in five. One patient had experienced worsening of fingertip ulcerations and discontinued the study, while the others (n = 3) with digital ulcers showed improvement. Pulmonary function tests remained stable through out the study. Patient and Physician Global Assessment scores, and HAQ improved 42.8%, 32.2%, and 12.7% respectively compared to baseline. Oral aperture and hand extension remained unchanged. Still there are a lot of unknowns in the pathophysiology of SSc. Further research needs to be conducted.

Sjögren's syndrome

Sjögren's syndrome (SS) is a systemic autoimmune attack on the exocrine system characterized by dysfunction of the lacrimal and salivary glands leading to xerophtalmia and keratokonjunctivitis sicca. Histologically, it is characterized by the eventual total replacement of the acinar structure by marked lymphocytic infiltrates. Infiltration of lung, liver, pancreas, sweat glands and renal tubules may also occur.

TNF expression in minor salivary gland duct cells in SS patients has been documented by many authors (40, 41). Animal models of SS also have shown that PEGylated recombinant methionyl human soluble TNF receptor I prevents lymphocytic infiltration into lacrimal and salivary glands and blocks the development of SS in the NOD mouse model (42). TNF and IL-1 treated normal human salivary cell clones with acinar phenotype demonstrate high metalloproteinase activity in protein and mRNA levels. Further in vitro studies demonstrated that blockade of signal transduction pathways of TNF or IL-1 can suppress cytokine-induced proteolytic enzyme activity (43). These observations suggest that the divergent response to cytokines in salivary gland may result in the histopathologic manifestations of SS. It was also shown that the balance of cytokines including TNF in the tear fluid and conjunctival epithelium is altered in SS (44). In this study ELISA was used to detect the epidermal growth factor (EGF) levels in tear fluid and RNA transcript levels encoding inflammatory cytokines. IL-6, IL-8, TNF , transforming growth factor 1 (TGF 1) and housekeeping gene (G3PDH) were evaluated in conjunctival cytology specimens taken from 10 subjects with SS and 10 healthy controls. EGF concentration was decreased and the inflammatory cytokine levels were increased in the conjunctival epithelium of the patients with SS compared to healthy controls. The severity of keratokonjunctivitis sicca correlated with high levels of inflammatory cytokine levels. These findings provide insight into the pathogenesis of keratokonjunctivitis and may open a therapeutic option in SS.

In order to determine the short-term efficacy and safety of infliximab in patients with primary SS, sixteen patients, with active SS received three infusions of 3 mg/kg infliximab at 0, 2, and 6 weeks. Patients were followed for fourteen weeks. There was statistically significant improvement in patient and physician global assessment, ESR, dry eyes and dry mouth. The treatment was well tolerated in all patients, and no significant adverse events were seen (45).

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder in which the cell-mediated immune response is activated by persistent exposure to one or more stimuli. Prolonged exposure leads to granulomatous inflammation that may cause fibrosis and progressive organ dysfunction most commonly in the lung

Many studies have confirmed elevated TNF production in sarcoidosis and have shown that TNF plays an important role in granuloma formation (46, 47). There are also reports with inconsistent results about the role of TNF polymorphism in sarcoidosis. A higher frequency of the uncommon TNF 2 allele was found in patients with Loefgren syndrome, which is an acute disease resembling sarcoidosis (48). In a different study, TNF and gene polymorphisms have been investigated in 26 patients with cardiac sarcoidosis. The results of this study showed that there was a significant increase in TNF 2 suggesting that the TNF gene may contribute to the genetic susceptibility to cardiac sarcoidosis (49). However, Yamaguchi et al. found no evidence of TNF gene polymorphism increasing the susceptibility to sarcoidosis (50). In contrast to the other reports, they found that the patients with allele TNF- 1 had a prolonged clinical course. Different results might be related to different patient populations or different forms of the disease.

In a case report, three patients with chronic, resistant sarcoidosis were treated with infliximab 5 mg/kg at weeks 0, 2, 4 and 12 weeks. In two patients the index lesion of lupus pernio significantly improved. The third patient had restrictive lung disease, which showed 26% improvement in the vital capacity from the baseline values (51). In a patient with sarcoidosis presenting with protein-losing enteropathy, and proximal myopathy, 5 mg/kg infliximab infusion at weeks 0, 2 and 6 resulted in resolution of symptoms (52).

Pyoderma gangrenosum

Pyoderma gangrenosum (PG) is a destructive inflammatory skin disease frequently associated with RA or inflammatory bowel disease, but can exist as an isolated lesion. PG develops in approximately 3-5% of patients with ulcerative colitis and 1% of patients with Crohn's disease. The lesions usually begin as small pustules but then ulcerate. Subsequently, the lesions develop erythematous margins with inflammation, which undermines the edges. Disturbances of immunoregulation and immunologic effector functions are involved in some patients with pyoderma gangrenosum; however no consistent pattern of disturbed cellular immune response has emerged. Treatment with immunosuppressive agents is not always successful and may cause side effects.

Two cases of PG with Crohn's disease treated with infliximab had complete resolution of most ulcers and this response lasted 2 to 2 1/2 months (53).

Polymyositis/dermatomyositis

Polymyositis (PM) and Dermatomyositis (DM) are inflammatory muscle disease characterized clinically by systemic proximal muscle weakness, cutaneous lesions (in DM), and systemic manifestations. Little is known about the ethiopathogenesis of these conditions. The role of pro-inflammatory cytokines such as TNF , IL-1 and IL-6 in PM/DM has not been clearly documented. However, muscle biopsy specimens from PM/DM patients have revealed that TNF -positive macrophages and lymphocytes are expressed around blood vessels in tissue sections with myositis (54, 55). Levels of soluble TNF receptor in peripheral blood mononuclear cells from patients with active-stage PM/DM were also demonstrated to be elevated compared to normal controls and inactive patients with PM/DM (56). In a report of 2 cases treated with infliximab, improvement in strength correlated with a decrease in muscle fiber inflammation and necrosis (57).

Case reports

Anecdotal data has been published regarding the use of TNF blockers in patients with many other autoimmune diseases who have been refractory to traditional treatments. A case of hidradenitis suppurativa occuring in a patient with Crohn's disease showed dramatic improvement after treatment with infliximab (58). Two patients with SAPHO syndrome (cluster of findings including synovitis, acne, palmoplantar pustulosis, hyperostosis and osteitis, where the upper anterior chest wall is most commonly involved) presenting with chest pain limiting normal activity despite treatment with NSAIDs and second line therapies, received infliximab (5 mg/kg) at weeks 0, 2, and 6. Signs and symptoms regarding SAPHO syndrome disappeared and have not reappeared two months after the last infusion (59). Graft-versus-host disease (GVHD) is recognized to be due to an immunologic reaction of engrafted lymphoid cells against the tissues of the host; inflammatory cytokines may contribute to the tissue damage seen (60). In a number of pilot studies patients with acute or chronic refractory GVHD were treated with infliximab (62). The results of these studies were encouraging, although inconclusive. Nevertheless, they justify further exploration of anti-TNF therapy in GVHD.

Multicentric reticulohystiocytosis is a rare disorder of cutaneous nodules and arthritis which rapidly leads to joint destruction and generally is unresponsive to therapy. Histologic analysis of skin and joint lesions reveals multinucleated giant cells and high levels of TNF. Treatment with TNF blockade has been promising (two cases; Morgan personal communication).

The treatment of the autoinflammatory syndrome TRAPS (TNF-receptor associated periodic syndrome) has also been reported with TNF blockade (62). In this syndrome abnormal shedding of TNF receptors leads to increased inflammatory response and this can be blocked with anti-TNF therapy.

Conclusion

There is no doubt that anti-TNF treatment provides a major advance in better targeting the inflammatory response and consequently improving the patient outcomes in autoimmune inflammatory conditions. TNF inhibitors can be safely added to other systemic agents to achieve better responses in some recalcitrant inflammatory diseases. The range of disorders in which TNF blockade may be beneficial need to be clearly identified in controlled trials. In addition, potential adverse effects of TNF inhibition must be weighed against potential clinical benefits. Finally, the high cost of these agents also warrants careful patient selection.

One consideration relevant to the potential use of TNF inhibitors in conditions other than RA relates to the agents themselves; will clinically important differences in safety or efficacy be observed among the various TNF inhibitors? Through 2002, there have been two TNF inhibitors approved for use worldwide; the chimeric anti-TNF-monoclonal antibody (mAb) infliximab, and the soluble p75 TNF-receptor IgG1-Fc fusion construct etanercept. In addition to sharing the ability to inhibit TNF, these molecules have other characteristics in common. Both are engineered macromolecules, with a volume of distribution that suggests largely intravascular distribution; both are administered parenterally. However, there are characteristics that vary between these two agents. Monoclonal antibodies are target specific, so anti-TNF- antibodies bind to TNF- , but not to the homologous cytokine lymphotoxin-a (LT- ; previously known as TNF-). In contrast, soluble forms of the TNF inhibitor bind both TNF- and LT- . MAb efficiently bind both soluble and cell bound forms of TNF, whereas the soluble receptor binds soluble cytokine more efficiently. While both compounds bind their target with high affinity, the avidity of the mAb binding to target may be greater. Although the half lives of the currently available agents are similar (etanercept ~ 4.5 days, infliximab ~ 9.5 days), inflximab is administered intravenously and has a large peak post-dosing followed by a steady state, whereas etanercept is administered subcutaneously and achieves a steady state without a large peak after several days. Finally,

mAb tend to be more efficient at effecting activities through their Fc piece, for example cell lysis and induction of apoptosis, although the extent to which this occurs *in vivo* is not certain. Whether these differences will result in variable efficacy or safety remains to be determined for the various diseases in which TNF inhibition has been tried. Of note, several other inhibitors of TNF in various stages of clinical development may be introduced in the future. Some are macromolecules, including the human anti-TNF- mAb adalimumab (previously known as D2E7), the PEGylated human anti-TNF-mAb Fab' fragment CDP870, and a PEGylated soluble p55 TNF receptor construct. A variety of other strategies are also being tested with the ultimate goal of inhibiting the function of TNF, including p38-MAPkinase inhibitors and NF- B inhibitors. While novel, the macromolecule TNF inhibitors might be predicted to have many characteristics similar to the current TNF inhibitors. However, the small molecule kinase inhibitors in development may be found to possess characteristics quite distinct from current agents. The impact of these differences on potential efficacy and tolerability remains to be seen.

The future challenge for us is to design clinical trials that will allow us to discover the unknown about the optimal usage, long-term benefits, and safety of TNFa blockers in patients with various inflammatory disorders. Although there are many questions to be answered, these biological agents will serve as a new hope in the management of refractory inflammatory conditions.

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