

# TNF-alpha inhibitors: Current indications

Rashmi Sharma, Chaman Lal Sharma\*

## Abstract

Advances in the DNA hybrid technology led to the development of various biologicals that specifically target TNF- $\alpha$ . There are currently three anti-TNF- $\alpha$  drugs available- etanercept, infliximab and adalimumab. Etanercept is approved by FDA for rheumatoid arthritis (RA) in 2000 followed by its approval for ankylosing spondylitis, psoriasis and psoriatic arthritis. Infliximab and adalimumab are approved by FDA in 2002 for RA. Infliximab is also approved for ankylosing spondylitis, psoriasis, psoriatic arthritis, crohn's disease and ulcerative colitis and adalimumab for psoriatic arthritis and ankylosing spondylitis. Other conditions like bronchial asthma, diabetes mellitus, malignancies, septic shock, behcet's disease, bullous dermatitis, neutrophilic dermatitis, toxic epidermal necrolysis, systemic vasculitis, pyoderma gangrenosum, pustular dermatitis, alcoholic hepatitis, cerebral malaria, hemolytic uremic syndrome, pre-eclampsia, allograft rejection, uveitis, otitis media, snakebite, erythema nodosum, myelodysplastic syndromes, graft versus host disease, dermatomyositis and polymyositis are the potential targets for anti-TNF- $\alpha$  therapy. There are recent reports of serious infections like tuberculosis with the use of anti-TNF therapy. In developing country like India these agents should be used with strict pharmaco-vigilance and chemo-prophylaxis for tuberculosis.

**Key words:** Adalimumab, ankylosing spondylitis, etanercept, infliximab, psoriasis, rheumatoid arthritis, tuberculosis

Tumour Necrosis Factor (TNF)- $\alpha$ , a potent cytokine is a soluble 17-Kd protein with three identical subunits. TNF is produced by the body and is involved in normal inflammatory and immune responses.<sup>[1]</sup> It is both autocrine and paracrine inducer of other cytokines like IL(interleukin)-1, IL-6, IL-8, platelet derived growth factor-B, eosinoids, platelet activating factors and granulocyte monocyte colony stimulating factor. Anti TNF- $\alpha$  therapy down-regulates the monocyte capacity to produce pro-inflammatory cytokines and induces a shift to produce

more anti-inflammatory TH2 cytokine. Anti-inflammatory cytokines are IL-4, IL-10, IL-11, IL-13, IL-16, transforming growth factor  $\beta$ , soluble TNF-receptor and soluble interleukin-1 receptor.<sup>[2]</sup>

With the development of biologicals against TNF- $\alpha$ , our therapeutic approach to inflammatory diseases has dramatically changed. Advances in the DNA hybrid technology led to the development of various biologicals that specifically target TNF- $\alpha$ . There are currently three anti-TNF- $\alpha$  drugs available: - etanercept, infliximab and adalimumab [Table 1]. Etanercept is a recombinant fusion protein that consists of two soluble TNF- $\alpha$  p75 receptor moieties linked to the Fc portion of human IgG.<sup>[1]</sup> It was approved by FDA for rheumatoid arthritis (RA) in 2000, followed by its approval for ankylosing spondylitis, psoriasis and psoriatic arthritis.<sup>[3]</sup> Infliximab

**From:**  
Postgraduate Department of Pharmacology and Therapeutics, Govt Medical College, Jammu, \*Indian-III Hospital, UN Mission Congo (Monuc), Armed Medical Corps, India

**Correspondence:**  
Dr. Rashmi Sharma, 216-A, Last Mohr, Gandhi Nagar, Jammu-Tawi., J and K - 180 004, India. E-mail: rashmichams@yahoo.com

**Table 1: Comparative features of anti-TNF- $\alpha$  agents<sup>[1-4]</sup>**

Parameters	Etanercept	Infliximab	Adalimumab
FDA approval [diseases refractory to conventional therapy]	RA, AS, Psoriasis and PsA	RA, AS, Psoriasis, PsA, Crohn's disease and ulcerative colitis	RA, AS and PsA
Structure	Two soluble TNF- $\alpha$ p75 receptor moieties linked to the Fc portion of human IgG	Chimeric (25% mouse and 75% human) monoclonal antibody	A human-derived antibody
Half life	3-4.8 days	8-9.5 days	10-13.6 days
Binding target	TNF- $\alpha$ and lymphotoxin - $\alpha$	TNF- $\alpha$	TNF- $\alpha$
Dose	25 mg S/C twice weekly or 50 mg once weekly.	3 mg/kg intravenously followed by 2 and 6 weeks after 1st infusion then every 8 weeks	20-80 mg S/C weekly
Side effects	Erythema, pain, swelling, itches, infections etc. at the site of injection, infections.	Infections, *tuberculosis, SLE - syndrome, nausea, headache, sinusitis, rash and cough	Serious infections, neurologic effects and certain malignancies of the lymphoid system

RA - Rheumatoid arthritis, AS - Ankylosing spondylitis, PsA - Psoriatic arthritis, TNF - Tumor necrosis factor, S/C - Subcutaneously, \*Incidence of tuberculosis more than etanercept and adalimumab

[chimeric (25%mouse and 75%human)] and adalimumab [human-derived antibody] are the monoclonal antibodies against TNF- $\alpha$  and are approved by FDA in 2002 for RA.<sup>[2]</sup> Infliximab is also approved for ankylosing spondylitis, psoriasis, psoriatic arthritis, crohn's disease and ulcerative colitis; whereas; adalimumab is approved for psoriatic arthritis and ankylosing spondylitis.<sup>[3,4]</sup> In

the present article we are going to summarize various therapeutic indications for novel anti-TNF therapies [Table 2 and 3].

### Search Methodology

Prominent rheumatology and general/internal medicine journals (MEDLINE, EMBASE, PUBMED between 2000

**Table 2: Clinical evidences of anti-TNF- $\alpha$  agent's use in various clinical conditions**

Study	Disease	Active treatment	Control	Result
ATTRACT phaseIII RCT	RA	Infliximab+ MTX	MTX	Combination produced better effect. <sup>[2]</sup>
ASPIRE phaseIII RCT	RA	Infliximab+ MTX	MTX	Combination produced better effect. <sup>[2]</sup>
Double blind RCT	RA	Etanercept +MTX	Either drug alone	Combination produced better effect. <sup>[2]</sup>
BeSt Trial (Questionnaire)	RA	MTX + Infliximab	DMRDs	MTX + Infliximab better than other DMRDs. <sup>[2]</sup>
Double blind RCT	AS	Etanercept	Placebo	>Etanercept patients showed ASAS 50 responses. <sup>[9]</sup>
3 month RCT	AS	Infliximab	Placebo	Infliximab more effective than placebo. <sup>[9]</sup>
Anti-TNF RCT	AS	Etanercept	Placebo	At 24 weeks, etanercept more effective than placebo. <sup>[11]</sup>
Infliximab safety database	Pregnancy with CD (131)	Infliximab exposed	Non exposed	Pregnancy outcome same. <sup>[17]</sup>
Double blind RCT	PsA	Infliximab	Cyclosporine	Infliximab has efficacy and rapidity of onset of therapeutic effect similar to cyclosporine. <sup>[6,22]</sup>
Double blind RCT	PsA	Etanercept	Placebo	Improvement in the PASI was significantly more in etanercept group than placebo. <sup>[23]</sup>
Phase III, double blind trial	PsA	Infliximab	Placebo	Infliximab through 24 weeks significantly improved active PsA, including dactylitis and enthesopathy and associated psoriasis. <sup>[24]</sup>
Multicenter, double-blind, RCT	PsA with failure of at least 1 DMRD	Infliximab	Placebo	ACR20 response at week 16, was higher in infliximab group. <sup>[25]</sup>
Pilot study	AD	Infliximab	-	Induction therapy with infliximab significantly improved all clinical parameters. <sup>[27]</sup>
Pilot study	RU	Infliximab	-	Infliximab was found to be effective both as short-term (10 weeks) and long term therapy (50 weeks). <sup>[30]</sup>
ATLAS trial	AS	Adalimumab	Placebo	Adalimumab is more effective in reducing disease activity. <sup>[4]</sup>
Phase II, RCT	SPS	CytoFab	Human albumin as placebo	CytoFab promptly reduced plasma TNF- $\alpha$ and IL-6 concentrations compared with placebo. CytoFab increased mean ventilator-free days and ICU-free days at day 28. <sup>[35]</sup>

RCT - Randomized control trial, RA - Rheumatoid arthritis, AS - Ankylosing spondylitis, CD - Crohn's disease, PsA - Psoriatic arthritis, AD - Atopic dermatitis, RU - Refractory uveitis, DMRD - Disease modifying drug, MTX - Methotrexate, ASAS - The multicomponent assessments in ankylosing spondylitis, PASI - Psoriasis area and severity index, ACR - American College of Rheumatology preliminary criteria for improvement, SPS - Septic shock, CytoFab - Polyclonal ovine anti-TNF fragment antigen binding (Fab) fragments

**Table 3: Clinical studies of anti-TNF- $\alpha$  agents in Indian patients**

Study	Disease	Drugs	Number of patients	Result
Phase IIIb	RA	Etanercept along with concomitant use of other drugs	40	ACR 20% response in 70% of patients at the end of 16 weeks. <sup>[2]</sup>
Clinical trial	RA, AS, PsA and juvenile RA	Infliximab	-	ACR 20 responses were obtained in all patients of RA; 13% of the total patients developed TB. <sup>[99]</sup>
Clinical trial	AS	Infliximab	15	Clinically significant improvement was found in all patients without any incidence of TB after 52 weeks. <sup>[40]</sup>
Clinical trial	AS, polyarticular JIA, RA, undifferentiated SpA, IBD-related spondyloarthritis and PsA	Infliximab	176	Reactivated TB developed in 10.6% SpA patients treated with standard doses (5 mg/kg) of infliximab. <sup>[41]</sup> Infliximab showed expected efficacy in SpA, RA and JIA
Open label pilot study	PsA	Infliximab	3	All patients attained PASI 50 by 3.8 weeks. PASI 75 was attained at 9.6 weeks. Relapse occurred at a mean of 18.6 weeks after the first infusion. <sup>[42]</sup>

RA - Rheumatoid arthritis, AS - Ankylosing spondylitis, PsA - Psoriatic arthritis, SpA - Spondyloarthropathy, IBD - Inflammatory bowel disease, JIA - Juvenile idiopathic arthritis, PASI - Psoriasis area and severity index, ACR - American College of Rheumatology preliminary criteria for improvement

and 2006) were searched for review papers and clinical trials published on therapeutic uses of anti-TNF therapy. All the data was collected and important evidences regarding use of anti-TNF agents were summarized in the present article.

## Therapeutic Indications of Anti-TNF Drugs

### *Rheumatoid arthritis (RA)*<sup>[2,5]</sup>

The TNF plays an important role in both pathological inflammation and joint destruction that are hallmark of RA. Anti-TNF therapy has revolutionized the approach in management of RA. In phase-III RCTs (randomized control trials) like ASPIRE and ATTRACT infliximab (3 mg/kg or 10 mg/kg) regimen was found to be superior to MTX (methotrexate) alone. In a double blind RCT, on 686 patients with active RA the combination of etanercept 25 mg (subcutaneously twice a week) and oral MTX (up to 20 mg every week) was significantly better in reducing disease activity, improving functional disability and retarding radiographic progression than MTX or etanercept alone.

In a 52-week double blind clinical trial, patients with active RA were randomized to receive etanercept 25 mg twice weekly or MTX up to 20 mg weekly or combination therapy. Combination therapy with etanercept and MTX improved function, quality of life and satisfaction with medication significantly better than mono-therapy. In BeSt trial (where questionnaire was filled by each patient to give the responses in relation to different anti-rheumatic drug regimens), MTX and infliximab combination found to be benefiting greatly than other DMRDs (disease modifying drugs). In a study on total of 2662 patients

(infliximab = 141; etanercept = 853; and MTX = 1668), compliance with at least 80% of the expected dosages was significantly lower for etanercept and MTX patients than infliximab patients. Currently, anti-TNF therapy is recommended for patients, who fail to respond or tolerate at least 2 DMRDs including MTX.

### *Ankylosing spondylitis (AS)*

AS affects about 0.5%-1.0% of the population and typically begins between the ages of 15 and 40 years.<sup>[5]</sup> It causes painful stiffness of the spine, progressive disability and loss of independence during the prime productive years. Anti-TNF- $\alpha$  agents have been found to be very effective for the treatment of both peripheral and axial symptoms in patients with AS.<sup>[6,7]</sup> In a double blind RCT, out of 84 patients of AS, 45 received etanercept and 39 received placebo.<sup>[8]</sup> Significantly more etanercept patients reported ASAS (the multicomponent Assessments in AS) 50 responses at all times and ASAS 70 responses at weeks two, four and eight. Patients in the etanercept group reported lower composite and fatigue BASDAI (Bath AS Disease Activity Index) scores, lower acute phase reactant levels and improvement in spinal flexion.<sup>[8]</sup> In a three-month clinical trial, 18 of 34 patients (53%) treated with infliximab met the predefined response criterion, compared with three of 35 (9%) patients receiving placebo.<sup>[9]</sup> These improvements persisted during the open-label extension study in which all participants were given infliximab for an additional 42 weeks.<sup>[10]</sup> In another RCT, 277 patients with AS received either etanercept or placebo.<sup>[11]</sup> At 24 weeks, 59% of patients in the etanercept group and 28% patients of the placebo group met the ASAS-20 criteria for response. Data from Phase

III adalimumab trial evaluating long-term efficacy and safety in AS (ATLAS trial) on 315 patients demonstrated ASAS-20 response in 58% patients receiving adalimumab at 12 weeks.<sup>[4]</sup> At week 24, 42% of adalimumab-treated patients and 16% of those receiving placebo achieved a reduction of 50% or more in disease activity.<sup>[4]</sup> Recent trials have shown that anti-TNF therapy is more effective in AS than in RA.<sup>[12]</sup> However, patient's benefits from long-term treatment, effects on radiological progression and long-term safety of biologic therapy are still needed to be explored.

### **Crohn's disease and ulcerative colitis**

Stenoses and fistulas are frequent complications in patients with Crohn's disease (CD). Infliximab is effective in the treatment of patients with moderately to severely active Crohn's disease with an inadequate response to other treatment options or those with fistulizing disease.<sup>[13-15]</sup> It is administered intravenously, generally in a schedule with initial infusions at 0, 2 and 6 weeks, followed by administration once every eight weeks.<sup>[13,14]</sup> Clinical evidence suggested that a single intravenous infusion of infliximab may be effective for induction of remission in Crohn's disease.<sup>[16]</sup> The results of two trials suggested that CDP571, the genetically engineered human TNF monoclonal antibody, is also effective in reducing disease activity index at two weeks after an infusion.<sup>[16]</sup> Clinical experience suggests that infliximab is also effective when administered as corticosteroid-sparing therapy.<sup>[15]</sup> Data from the infliximab safety database suggest that infliximab exposure during pregnancy (of the 146 identified pregnancies, 131 involved women exposed directly to infliximab and outcome data were available for 96 of these women) results in outcomes that are similar to those in the U.S. population of pregnant women and pregnant women with CD not exposed to infliximab.<sup>[17]</sup> However, follow-up of larger numbers of pregnant women exposed to infliximab will be necessary to definitively exclude any fetal risk.

In a RCT, 20 patients of steroid-dependent ulcerative colitis received either three infusion of infliximab (5 mg/kg) at zero, two and six weeks and thereafter every eight weeks (group A) or methylprednisolone (0, 7-1 mg/kg) daily for one week followed by a tapering regimen up to the minimal dose to maintain a symptom-free condition (group B).<sup>[18]</sup> Infliximab seems to be as effective as steroids in the management of the disease. In another RCT on

patients with glucocorticoid resistant ulcerative colitis, no statistically significant difference was seen between the infliximab and placebo groups.<sup>[19]</sup> Hence, data do not support the use of infliximab in the management of moderately active glucocorticoid resistant ulcerative colitis. However, recently in a RCT patients with severe to moderately severe ulcerative colitis not responding to conventional treatment, were randomized to receive infliximab (24) or placebo (21).<sup>[20]</sup> Seven patients in the infliximab group and 14 in the placebo group had a colectomy ( $P=0.017$ ) within three months after randomization. Moreover, three patients in the placebo group required operation for septic complications. The study clearly indicated the role of Infliximab 4-5 mg/kg in patients experiencing an acute severe or moderately severe attack of ulcerative colitis not responding to conventional treatment.

### **Psoriasis and psoriatic arthritis (PsA)**

TNF- $\alpha$  inhibitors are among the new class of drugs that offer new options for psoriasis control.<sup>[21]</sup> TNF- $\alpha$  increases in the psoriatic skin lesion and in the synovium of the inflamed joint.<sup>[21]</sup> A double blind trail by Chaudhari *et al.*, showed a > 75% improvement in psoriasis, area and severity index score at week 10 in 82% patients receiving infliximab 5 mg/kg at weeks 0, 2 and 6.<sup>[22]</sup> Etanercept has also been shown to possess good efficacy in moderate to severe psoriasis. In a double-blind RCT (12 week study) 60 patients with PsA and psoriasis received either etanercept (25 mg twice-weekly subcutaneous injections) or placebo.<sup>[23]</sup> 26 (87%) of etanercept-treated patients met the Psoriatic Arthritis Response Criteria, compared with seven (23%) of placebo-controlled patients. The ACR20 (American College of Rheumatology preliminary criteria for improvement) was achieved by 22(73%) of etanercept-treated patients compared with 4(13%) of placebo-treated patients.<sup>[23]</sup> Improvement in the psoriasis area and severity index (PASI) was significantly more in etanercept group than placebo. In a phase III, double blind trial 200 patients with active PsA unresponsive to previous treatment were randomized to infusions of infliximab 5 mg/kg or placebo at weeks 0, 2, 6, 14 and 22. At week 14, 58% of patients receiving infliximab and 11% of those receiving placebo achieved an ACR20 response ( $P<0.001$ ).<sup>[24]</sup> 64% patients receiving infliximab had at least 75% improvement in PASI compared with 2% patients receiving placebo at week 14 ( $P<0.001$ ).<sup>[24]</sup> These therapeutic effects were maintained till week 24.



In a multicentre RCT, 104 patients with PsA (with prior failure of at least 1 DMARD therapy) received infusions of infliximab (5 mg/kg) or placebo at weeks 0, 2, 6 and 14.<sup>[25]</sup> After week 16, all patients received infliximab 5 mg/kg every eight weeks through week 50. 65% of infliximab-treated patients and 10% of placebo-treated patients achieved an ACR20 response at week 16. Moreover, 46% and 29% of infliximab-treated patients achieved ACR50 and ACR70 responses respectively; no placebo-treated patient achieved these end points. Hence, clinical experience so far clearly indicated the role of anti-TNF drugs in the management of psoriasis and PsA refractory to other DMARDs.

### **Systemic vasculitis<sup>[26]</sup>**

There are encouraging uncontrolled data in humans with infliximab for anti-neutrophil cytoplasm antibody (ANCA)-associated systemic vasculitis (AASV). TNF- $\alpha$  plays an important role in the pathogenesis of experimental autoimmune vasculitis and blockade of this cytokine is effective in treating established vasculitis. The therapeutic action of anti-TNF- $\alpha$  agents may be mediated by suppression of the enhanced leukocyte-endothelial interactions in this disorder. However, clinical trials are needed to establish their role in systemic vasculitis.

### **Atopic dermatitis<sup>[27]</sup>**

Chronic use of standard therapies for atopic dermatitis (AD) is associated with variable efficacy and potential side effects. Targeted therapeutic approaches, such as the inhibition of TNF- $\alpha$ , may be a novel option. In a pilot study, nine patients with moderate or severe AD received infliximab 5 mg/kg by intravenous infusion at weeks zero, two, six, 14, 22, 30 and 38 and patients were followed for 46 weeks. Induction therapy with infliximab significantly improved all clinical parameters, but this improvement was not sustained through maintenance therapy. Only two patients with severe AD achieved an excellent clinical response by 46 weeks. Hence, long term RCTs are required to further establish the role of infliximab and other anti-TNF- $\alpha$  agents in atopic dermatitis refractory to standard therapies.

### **Congestive heart failure (CHF)<sup>[22,28,29]</sup>**

Elevated TNF- $\alpha$  levels have also been observed in patients with CHF and clinical trials have been performed to examine the effects of TNF- $\alpha$  inhibitors, such as etanercept and infliximab, in such a population.

TNF- $\alpha$  exerts negative inotropic effect, recapitulates cellular and biochemical abnormalities, uncouples  $\beta$ -adrenergic receptors from adenylate cyclase, activates metalloproteinases and provokes a hypertrophic growth response in cardiac myocytes. Hence, anti-TNF- therapy seems to hold promises in treatment of CHF. Two large-scale trials of etanercept in more than 2000 patients with heart failure did not indicate any increased risk of mortality or morbidity. In a clinical trial, 150 patients with stable New York Heart Association class III or IV heart failure and left ventricular ejection fraction  $\leq 35\%$  were randomly assigned to receive placebo (n=49), infliximab 5 mg/kg (n=50) or infliximab 10 mg/kg (n=51) at zero, two and six weeks. It was found that neither dose of infliximab improved clinical status at 14 weeks. However, the combined risk of death from any cause or hospitalization for heart failure through 28 weeks was increased in the patients randomized to 10 mg/kg infliximab. Hence, recent evidences clearly indicated adverse effect of anti-TNF therapy in patients with CCF.

### **Refractory uveitis<sup>[30]</sup>**

In a study, 23 patients of refractory uveitis received three infliximab infusions at weeks zero, two and six. Clinical success was ascertained at week 10 and patients meeting initial criteria for success received an infusion at week 14 and every eight weeks thereafter (dose escalation permitted for breakthrough inflammation). Infliximab was found to be effective both as short-term (week 10) and long term therapy (50 weeks of therapy). However, further studies are required to establish the safety of anti-TNF therapy in refractory uveitis.

### **Bronchial asthma and allergic conditions<sup>[6,31,32]</sup>**

It has been seen that recruitment of neutrophils and eosinophils associated with allergic condition is mediated via TNF- $\alpha$ . TNF- $\alpha$  is released in allergic responses, from mast cells and macrophages via IgE dependent mechanisms. Anti-TNF- $\alpha$  therapy may be useful as a glucocorticoid sparing asthma therapy. Anti-TNF- $\alpha$  therapy may also be effective in the treatment of certain allergic conditions including Jarisch-Herxheimer reaction. Asthma is regarded as a Th2 type disorder, especially when associated with atopy. However, TNF $\alpha$  production is increased in severe corticosteroid-dependent asthma. Improvements in clinical and physiological measures of asthma following 12 weeks treatment with etanercept were observed in an open label uncontrolled clinical study.

Etanercept treatment was associated with improvement in asthma symptoms, lung function and bronchial hyper-responsiveness. However, further long term RCTs are required to establish the status of anti-TNF therapy in refractory bronchial asthma and allergic conditions.

### **Sepsis and shock**

TNF- $\alpha$  is involved in virtually all features of septic shock and multiple organ failure. Anti-TNF- $\alpha$  strategies are thus appealing and have been effective at reducing inflammation and morbidity.<sup>[33]</sup> Evidences from various RCTs targeting TNF during sepsis, showed a small but significant benefit with anti-TNF therapeutic strategies. Strategies using monoclonal antibodies are more effective than are strategies using TNF receptor proteins.<sup>[34]</sup> A study in 2634 septic patients using a murine anti-TNF antibody showed a 3.6% significant benefit in reducing mortality.<sup>[34]</sup> Afelimomab, the F(ab')<sub>2</sub> fragment of a murine anti-TNF- $\alpha$  antibody has been found to be efficacious and well tolerated in 7300 patients with septic shock.<sup>[33,34]</sup> In a Phase II, RCT, 81 septic patients with either shock or two organ dysfunctions were randomized to receive CytoFab (polyclonal ovine anti-TNF fragment antigen binding (Fab) fragments), infused as a 250-units/kg loading dose, followed by nine doses of 50 units/kg every 12 hours or 5 mg/kg human albumin as placebo.<sup>[35]</sup> CytoFab promptly reduced plasma TNF- $\alpha$  ( $P=0.001$ ) and IL-6 concentrations ( $P=0.002$ ) compared with placebo. CytoFab also significantly decreased TNF- $\alpha$  in bronchoalveolar lavage (BAL) fluid ( $P<0.001$ ). The number of shock-free days did not differ between CytoFab and placebo. CytoFab increased mean ventilator-free days and ICU (intensive care unit)-free days at day 28. However, 41% of CytoFab-treated patients developed detectable plasma levels of human anti-sheep antibodies.<sup>[35]</sup> However, better characterization of patients and a more multimodal approach by concomitantly targeting other mediators involved in sepsis may be helpful in enlarging the clinical benefit of anti-TNF therapy.

### **Diabetes Mellitus<sup>[36]</sup>**

TNF- $\alpha$  related apoptosis is involved in  $\beta$  cell damage in type I diabetes, resulting into insulin resistance, impaired insulin signaling and formation of atherosclerotic vascular lesions in diabetic patients. It has been documented that anti-TNF- $\alpha$  therapy may be beneficial in reducing the complications of diabetes. In a study on 4 women (52-76 years) with type 2 diabetes in danger of vision

loss due to severe macular edema on hypoglycemic therapy, two infusions of infliximab (5 mg/kg) in 1-month intervals intravenously showed significant regression in macular edema. Long term RCTs are needed to establish the role of infliximab like drugs in preventing diabetic complications.

### **Neuro-degenerative conditions<sup>[37]</sup>**

Increased TNF- $\alpha$  levels in the cerebral post-ischemic inflammatory response lead to stimulation of adhesive molecules expression, neuronal necrosis and neuro-degeneration through inhibition of a vital survival signal, 1GF-I. The cytokine TNF- $\alpha$  is elevated in Alzheimer's disease, Parkinson's disease, stroke and amyotrophic lateral sclerosis. Its synthesis can be reduced via posttranscriptional mechanisms with novel analogues of the classic drug, thalidomide. Moreover, there is need to explore the role of anti-TNF agents in neuro-degenerative disorders.

### **Other Conditions<sup>[6,38]</sup>**

Monoclonal antibodies against TNF- $\alpha$  also have a potential in the management of cachexia of cancer, skin tumors such as basal cell carcinoma, colorectal cancers and ovarian cancers. In a study on 6 patients of active adult onset Still's syndrome (AOSD), the disease improved remarkably in all patients with and after treatment with infliximab. Conditions like behcet's disease, bullous dermatitis, neutrophilic dermatitis, toxic epidermal necrolysis, systemic vasculitis, pyoderma gangrenosum, pustular dermatitis, alcoholic hepatitis, cerebral malaria, hemolytic uremic syndrome, pre-eclampsia, allograft rejection, otitis media, snakebite, erythema nodosum, myelodysplastic syndromes, graft versus host disease, dermatomyositis and polymyositis are other potential targets for anti-TNF- $\alpha$  therapy.

### **Anti TNF-therapies and Indian patients**

Misra R, *et al.* in a phase IIIb study involving forty patients of RA over 18 years of age (6 male: 34 females), demonstrated ACR 20% response in 25%, 57.5% and 70% of patients at four, eight and 16 weeks respectively after etanercept 25 mg subcutaneous injection twice weekly for 16 weeks (along with concomitant use of prednisolone, MTX, non-steroidal anti-inflammatory drug, folic or folinic acid as prescribed earlier).<sup>[2]</sup> The mean scores of all aspects of Short Form-36 Health Survey assessment of patient physical and mental functioning

improved significantly from baseline.<sup>[2]</sup> Moreover, the data from this study have shown etanercept to be efficacious and well tolerated drug in Indian patients with RA.

In another study from Kolkata during 2002-2005 on patients of RA, AS, PsA and juvenile rheumatic arthritis, ACR 20 responses were obtained in all patients of RA with infliximab 3mg/kg dose at 0, 2 and 6 weeks; however, 13% of the total patients developed TB (tuberculosis).<sup>[39]</sup> However, an other study on 15 patients of AS treated with infliximab (3 mg/kg at every eight weeks for 52 weeks) showed clinically significant improvement in all patients without any incidence of TB.<sup>[40]</sup>

Data on infliximab from 176 patients (147 AS, nine polyarticular juvenile idiopathic arthritis, 12 RA, six undifferentiated spondyloarthritis, one inflammatory bowel disease-related spondyloarthritis and one PsA) showed development of reactivated TB in 5/47 (10.6%)

SpA patients treated with standard doses (5 mg/kg) of infliximab.<sup>[41]</sup> This amounted to 56 times increased risk compared to baseline (0.187%). None of the 129 patients treated with 3 mg/kg infusions at eight-weekly intervals with omission of the two-week and six-week doses of infliximab developed reactivation tuberculosis. Infliximab showed expected efficacy in SpA, RA and JIA. The lone study on etanercept showed good efficacy in 40 patients with RA.<sup>[41]</sup>

In an open label pilot study among three patients having moderate to severe plaque psoriasis, infliximab was administered in a dose of 5 mg/kg as an intravenous infusion over two hours, diluted into 500 ml of normal saline at zero, two and six weeks.<sup>[42]</sup> All patients attained PASI 50 by 3.8 weeks. PASI 75 was attained at 9.6 weeks.<sup>[42]</sup> The mean improvement in PASI at week 10 stood at 77.2%. Relapse occurred at a mean of 18.6 weeks after the first infusion. The first patient, who also

**Table 4: British society for rheumatology guidelines for prescribing TNF- $\alpha$  blockers in adults with rheumatoid arthritis<sup>[5]</sup>**

<p><b>Eligibility criteria for biologic therapy:</b> *Fulfill 1987 criteria of American college of Rheumatology for diagnosis of RA. *Active RA (DAS28 score &gt;5.1) at 2 points one month apart. *Failure to respond or tolerate at least 2 DMRDs (disease modifying drugs) including MTX (methotrexate). *When other DMRDs are contraindicated.</p>
<p><b>Exclusion criteria:</b> Pregnant and lactating mothers, active infection, septic arthritis in last 12 months, sepsis of prosthetic joint within last 12 months or indefinitely if joint remains in situ, New York Heart Association (NYHA) grade 3 or 4 of congestive cardiac failure (CCF) and Demyelinating disease. *Caution in patients with low immune status.</p>
<p><b>Conditions for with-drawal of biologic therapy:</b> *Drug related toxicity. *Failure to improve DAS28 score by 1.2 or to reduce it to a score of &lt;3.2 after 3 months of therapy. However, if there is decrease in dose of DMRDs, continue drug for 6 months and assess. *Severe inter-current infection and pregnancy (temporary with-drawal).</p>
<p><b>Choice of anti-TNF therapy:</b> *Patient's preference, practical issues like drug administration and delivery. *Etanercept and adalimumab can be given in patients intolerant to MTX. *Infliximab and etanercepts can be interchanged in case of failure to one of the therapy. DMRDs can be combined. Follow recommended dose.</p>
<p><b>Potential adverse effects and anti-TNF therapy:</b>  <b>Serious infections including tuberculosis (TB):</b> Stop therapy, restart when infection gets resolved, not recommended in HIV+ve and HBV infection, use with caution in HCV infection.            Prior to commencing treatment screen patient according to British Thoracic Society (BTS) guidelines. Treat active TB before starting anti-TNF therapy. Start prophylactic treatment in patients with evidence of potential latent disease. Monitor patients for TB during anti-TNF therapy and 6 months after discontinuation of infliximab due to prolonged elimination phase. Treat patients on anti-TNF therapy with active TB symptoms with full anti-tuberculosis chemotherapy and continue anti-TNF therapy if clinically needed. Resume anti-TNF therapy in accordance with BTS guidelines.</p>
<p><b>Surgical procedures:</b> With held therapy 2-4 weeks before major surgery and restart after complete wound healing.</p>
<p><b>Vaccination:</b> Live vaccines are to be given 4 weeks before commencing treatment or 6 months after last infusion of infliximab or 2-3 weeks after last dose of etanercept.</p>
<p><b>Malignancy:</b> No evidence of associated malignancy risk. Investigate patient for any potential malignancy and stop therapy if confirmed. Caution is required in patients with previous malignancy, no contraindication if no evidence of recurrence of malignancy for 10 years.</p>
<p><b>SLE-like disease:</b> Stop therapy and treat for SLE.</p>
<p><b>CCF/cardiovascular disease:</b> No therapy in NYHA grade 3/4CCF. Caution in mild CCF. Monitor for CCF and stop if increases in severity.</p>
<p><b>Demyelination disease (DD) and neurological complications:</b> Contraindicated in presence of clear history of DD, avoid if possible history of DD or family history of DD, withdraw therapy if DD occurs and refer patient to neurologist.</p>
<p><b>Haematological complications:</b> Periodic blood counts to be done and stop therapy if pan-cytopenia occurs.</p>
<p><b>Pregnancy and lactation:</b> Active contraception during therapy and stop treatment if pregnancy occurs. Discontinue infliximab 6 months before female becomes pregnant or male patient fathers. Avoid breast-feeding.</p>

had PsA, reported partial improvement in spinal stiffness and pain at two weeks and peripheral joint stiffness at six weeks. These improvements did not diminish at 22 weeks, end of the surveillance period.<sup>[42]</sup>

**Safety concerns with anti-TNF therapy<sup>[2,43-46]</sup>**

Reactivation of latent TB with TNF blockers is a cause of concern. More cases of TB have been reported with infliximab than with etanercept or adalimumab. This higher incidence of TB with infliximab could be because of its ability to disrupt granulomas leading to reactivation of TB and to fix the complement and lyse the cells presenting TNF- $\alpha$ . Moreover, infliximab has longer half-life (210h) and can produce continuous blockade of TNF- $\alpha$  in irreversible manner in contrast to etanercept. Another point differentiating infliximab and etanercept is blockade of both TNF- $\alpha$  receptor p55 and p75 mediated events by infliximab and only p75 blockade is blocked by etanercept.

However, considering the risk of serious infections with the use of anti-TNF therapy, FDA recommended a black box for TB on the product labeling of infliximab. According to British Thoracic Society recommendations following guidelines should be observed:

1. If there is prior history of TB, chest X-ray and clinical examination positive, first treat the patient with anti-

tuberculosis chemotherapy before starting anti-TNF therapy.

2. If anti-TNF therapy has to be initiated earlier, complete two months anti-tuberculosis treatment or ensure drug susceptibility of the organism before starting the anti-TNF therapy.
3. If there is evidence of past history of TB or abnormal chest X-ray with complete treatment carefully monitor with chest X-ray after every three months.
4. If history of inadequate anti-TB therapy or risk of TB is more than risk of chemoprophylaxis, a full course of chemoprophylaxis should be given before starting anti-TNF- $\alpha$  therapy.
5. Tuberculin test is considered reliable only if patient is not taking immunosuppressive drugs or stopped them (one month for steroids and three months for others).

However, in developing countries like India with prevalence rate of TB of about 44%, a negative Mantoux test does not rule out TB. It is recommended to consider prophylactic anti-TB therapy with Isoniazid 5 mg/kg in patients before starting anti-TNF- $\alpha$  therapy. As there is increasing trend towards multidrug resistant TB, hence prophylaxis with two or three antitubercular drugs should also be considered. SLE syndrome, demyelinating diseases, neurodegenerative diseases, pancytopenia,

**Table 5: Current therapeutic status of anti-TNF therapy**

Diseases	Present status of anti-TNF therapy
Rheumatoid arthritis (RA)	Patients, who fail to respond or tolerate at least 2 DMRDs (disease modifying drugs) including methotrexate.
Ankylosing spondylitis	Patients refractory to conventional therapy More effective than in RA.
Crohn's disease	Moderately to severely active Crohn's disease with an inadequate response to other treatment options or those with fistulizing disease.
Ulcerative colitis	Patients not responding to conventional and treatment; management of moderate to severe steroid-dependent ulcerative colitis.
Psoriasis and PsA (psoriatic arthritis)	Management of psoriasis and PsA refractory to other DMRDs.
Systemic vasculitis, atopic dermatitis, complications of diabetes mellitus	Encouraging uncontrolled data in humans with infliximab. No anti-TNF agent approved by FDA for use in this condition
Congestive heart failure (CHF)	Recent evidences clearly indicated adverse effect of anti-TNF therapy in patients with CCF.
Sepsis and shock	Strategies using monoclonal antibodies are more effective than are strategies using TNF receptor proteins. No anti-TNF agent approved by FDA for use in this condition.
Bronchial asthma and allergic conditions	Encouraging uncontrolled data in humans with etanercept. No anti-TNF agent approved by FDA for use in this condition.
Neuro-degenerative conditions, cancer, behcet's disease, bullous dermatitis, neutrophilic dermatitis, toxic epidermal necrolysis, systemic vasculitis, pyoderma gangrenosum, pustular dermatitis, alcoholic hepatitis, cerebral malaria, hemolytic uremic syndrome, preeclampsia, allograft rejection, otitis media, snakebite, erythema nodosum, myelodysplastic syndromes, graft versus host disease, dermatomyositis and polymyositis	Potential targets for clinical studies



cardiovascular diseases etc. are the other important adverse effects reported with anti-TNF $\alpha$  therapy. However, it has been recommended that anti-TNF drugs should not be used in pregnant and lactating mothers, active infection, septic arthritis in last 12 months, sepsis of prosthetic joint within last 12 months or indefinitely if joint remains in situ, NYHA grade 3 or 4 of CCF and demyelinating disease [Table 4].

## Conclusion

Anti-TNF- $\alpha$  agents have been found very effective for the treatment of various immuno-inflammatory conditions (table-5). Currently anti-TNF drugs are approved by FDA for use in RA, PsA, psoriasis, CD, ulcerative colitis and AS. Sepsis, bronchial asthma and allergic conditions are other diseases in pipeline for approval. However, their use is limited by cost and uncertainty over long-term efficacy and safety. Etanercept, infliximab and adalimumab can be given in patients intolerant or refractory to other DMRDs.<sup>[5]</sup> Infliximab and etanercept can be interchanged in case of failure to one of the therapy.<sup>[5]</sup> Genetic variability in the production and effector pathways of TNF- $\alpha$  determines the effect of anti-TNF therapy. Meta-analyses have suggested that etanercept shows modest superiority over infliximab or adalimumab.<sup>[47]</sup> Reactivation of latent TB with TNF blockers is a cause of concern. More cases of TB have been reported with infliximab than with etanercept or adalimumab. Etanercept [Rs 20800(\$451.20)/100 mg] and infliximab [Rs16500(\$357.50)/25 mg] are two biologics available in India.<sup>[2]</sup> It is recommended to consider prophylactic anti-TB therapy before starting anti-TNF- $\alpha$  therapy, as India has 44% prevalence rate of TB. However, extensive post-marketing surveillance is necessary to re-evaluate the risk-benefit ratio of these biologic therapies. Prescriber should evaluate all the available evidences before prescribing an anti-TNF- $\alpha$  agent for various potential indications.

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**Source of Support:** Nil, **Conflict of Interest:** None declared.