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ORIGINAL ARTICLE / RESEARCH

Biologicals in Ankylosing Spondylitis: Current Concepts

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ABSTRACT

Ankylosing spondylitis (AS) is a systemic inflammatory rheumatic disease involving spinal and sacroiliac joints. Anti-TNF (tumour necrosis factor)-α agents have been found very effective for the treatment of both peripheral and axial symptoms in patients with AS. Etanercept, infliximab and adalimumab are approved by Food and Drug Administration (FDA) for AS. Systemic Lupus Erythematosus syndrome, demylinating diseases, neurodegenerative diseases, pancytopenia, severe infections, cardiovascular diseases etc. are some of the important side-effects reported with TNF-α blockers. TNF-α plays an important role in the host defense against mycobacterial infection, particularly in granuloma formation and inhibition of mycobacterial dissemination. There are recent reports of reactivation of tuberculosis after anti-TNF therapy. FDA recommended a black box for tuberculosis on the product labeling of infliximab. It is highly recommended to consider prophylactic anti- tubercular therapy (with isoniazid or isoniazid and rifampicin combination) before starting anti- TNFα therapy in patients with evidence of past history of tuberculosis or abnormal chest x-ray suggesting tuberculosis. However, extensive post-marketing surveillance is necessary to re-evaluate the risk-benefit ratio of these biologic therapies.

Key words: Etanercept, infliximab, adalimumab, ankylosing spondylitis

Ankylosing spondylitis (AS) is a systemic inflammatory rheumatic disease involving spinal and sacroiliac joints. This condition is responsible for back pain, stiffness and discomfort AS affects about 0.5%–1.0% of the population [1]. .Prevalence estimates vary between 0.1% and 2% in different populations with male:female ratio of around 5:1 and the peak age of onset is at 15-35 years [2]. Recently, there have been 2 major developments in the management of AS : use of magnetic resonance imaging to visualize the inflammatory changes in the sacroiliac joint and the axial spine and the demonstration that TNF (tumor necrosis factor) blocking agents are highly efficacious in reducing spinal inflammation and slowing radiographic progression [3]. Treatment for AS focuses on relieving pain and stiffness, reducing inflammation, keeping the condition from getting worse and enabling patient to continue daily activities [4]. Early diagnosis and treatment may reduce pain, stiffness, inflammation and deformity.

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Drug Treatment for AS

Initial treatment for AS may include patient education regarding nature of the disease and ways to control complications, physiotherapy, non-steroidal antiinflammatory drugs (NSAIDs), assistive devices like canes or walkers and alternative therapies like yoga or acupuncture [4],[5]. Several NSAIDs are available, but phenylbutazone is considered the NSAID of choice in AS [1]. However, all NSAIDs share common gastrointestinal toxicity and they

should be administered during periods of flare-up of the disease [6] However, additional, stronger medications like corticosteroids and Disease-modifying antirheumatic drugs (DMARDs) may be needed for some parients. The DMARD most often studied and prescribed for AS is combination of 5 amino salicyclic acid and sulfapyridine [4]. DMARDs are required in cases of longstanding severe or refractory AS. Drugs like methotrexate or gold salts require properly designed controlled studies to evaluate their effectiveness in the treatment of AS, while immunosuppressive agents have little to offer in the management of patients with AS and require further studies [1]. Enthesopathy may be treated with local injection of corticosteroids; sacroiliac joint pain may be managed by corticosteroid injection performed under fluoroscopic control or guided by computed tomography [1]. Recent evidences showed efficacy of pamidronate as antiinflammatory agent in AS [7],[8]. However, in ankylosing spondylitis there is an unmet medical need, since there are almost no DMARDs available for severely affected patients, especially those with spinal manifestations [7]. Anti-TNF-α agents have been found very effective for the treatment of both peripheral and axial symptoms in patients with AS [9],[10].

Biological agents in AS

TNF-α is a potent cytokine produced by the body and is involved in normal inflammatory and immune responses [11]. It also induces other cytokines like IL(interleukin)-1, IL-6, IL-8, platelet derived growth factor-B, ecosanoids, platelet activating factors and granulocyte monocyte colony stimulating factor [11]. Anti TNF-α therapy down-regulates the monocyte capacity to produce proinflammatory cytokines and induces a shift to produce more anti-inflammatory cytokine [11]. Etanercept (July 2003), infliximab (December 2004) and adalimumab are approved by FDA (Food and Drug Administration) for AS ([Table/Fig 1]) [11],[12].

[Table/Fig 1] Characteristics of TNF- α blockers for ankylosing spondylitis [11]

Drug	Structure	Half-life	Dose	Side-effects
Etanercept	Two soluble TNF- α p75 receptor moieties linked to the Fc portion of human IgG	3-4.8 days	25 mg subcutaneously twice weekly or 50 mg once weekly	Erythema, pain, swelling, itches,etc. at injection site. Infections.
Infliximab	Chimeric (25%mouse-75%human) monoclonal antibody	8-9.5 days	3 mg per kg intravenously at 0, 2 and 6 weeks, then every 8 weekly.	Infections (incidence of tuberculosis more than etanercept and adalimumab), SLE, etc.
Adalimumab	Human derived antibody	10-13.6 days	20-80 mg subcutaneously weekly	Serious infections, neurologic effects, malignancies of lymphoid system.

Etanercept

It is a recombinant fusion protein that consists of two soluble TNF-α p 75 receptor moieties linked to the Fc portion of human IgG; it binds two TNF-α molecules [13],[14]. It is usually administered in a dose of 25mg subcutaneously twice weekly. Erythema, pain, swelling, itching etc. at the site of injection are common with its use [13],[14].

In a double blind RCT (randomized control trial), out of 84 patients of AS, 45 received etanercept and 39 received placebo [15]. Significantly more etanercept patients reported ASAS (the multicomponent Assessments in Ankylosing Spondylitis) 50 responses at all times and ASAS 70 responses at weeks 2, 4, and 8. Patients in the etanercept group reported lower composite and fatigue Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores, lower acute phase reactant levels and

improvement in spinal flexion [15]. In another anti-TNF RCT on 277 patients with AS at 24 weeks, 59% patients of the etanercept group and 28% of the placebo group met the ASAS-20 criteria for response [16].

Infliximab

It is a chimeric (25%mouse and 75%human) monoclonal antibody that binds with high affinity and specificity to human TNF- α [13],[14]. It is given in a dose of 3-10mg/kg intravenously at 0,2 and 6 weeks, followed by infusion every 8 weeks. Risk of serious infections, activation of tuberculosis, production of human anti-chimeric antibodies, nausea, headache, sinusitis, rash, cough and reversible drug induced lupus-like illness are reported with its use [13],[14]]. In an open-labelled, prospective trial 18 patients of AS, after induction with infliximab at 5 mg/kg at week 0 and 2 (induction period), were given 3 mg/kg at week 6 and then 8-weekly (maintenance period) to 22 weeks [17]. Thirteen of these patients were on concurrent DMARDs. It was observed that half of the patients (9/18) achieved ASAS20 and ASAS40, whereas 61.1% (11/18) achieved ASAS5/6 at the end of the study.

In a 3-month clinical trial, 18 of 34 patients (53%) treated with infliximab met the predefined response criterion, compared with 3 of 35 (9%) patients receiving placebo [18]. These improvements persisted during an open-label extension study in which all participants were given infliximab for an additional 42 weeks [19]. In an open, observational, 2-yr extension study of an open-label study of three induction infusions of infliximab in refractory AS (fourth infusion was performed only in case of relapse) out of 50 patients, 46 patients judged efficacious and well tolerated. However, a fourth infusion was performed because of a flare of the disease, after a mean interval of 20.3±9.9 weeks (range 7.3–57.9) [20]. Side-effects were similar to those noted in shorter-term studies; seven patients suffered serious adverse events. There were no deaths, no malignancies and no tuberculosis [20]. In another study from Kolkata, India during 2002-2005 on patients of RA, AS, psoriatic arthritis 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 tuberculosis [21]. However, an other study on 15 patients of ankylosing spondylitis treated with infliximab (3mg/kg at every 8 weeks for 52 weeks) clinically significant improvement was found in all patients without any incidence of tuberculosis [22].

Data on infliximab from 176 patients [147 AS, 9 polyarticular juvenile idiopathic arthritis (JIA) , 12 RA, 6 undifferentiated spondyloarthropathy (SpA), 1 inflammatory bowel disease-related spondyloarthritis and 1 psoriatic arthritis] showed that reactivated tuberculosis developed in 10.6% SpA patients treated with standard doses(5 mg/kg) of infliximab [23] Infliximab showed expected efficacy in SpA, RA and JIA.

Adalimumab

It is a human-derived antibody that binds to TNF-α. It is administered as a single subcutaneous injection (20-80mg) every other week [13],[14]. Serious infections, neurologic effects, and certain malignancies of the lymphoid system are the serious adverse effects associated with it [13],[14].

Data from Phase III Adalimumab trial evaluating long-term efficacy and safety in AS (ATLAS trial) on 315 patients demonstrated ASAS-20 in 58% patients receiving adalimumab at 12 weeks [24]. At week 24, 42% of adalimumab-treated patients vs 16% of those receiving placebo achieved a reduction of 50% or more in disease activity. At week 24, adalimumab-treated patients achieved a mean 50% change in enthesitis symptom score, as measured by Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) [24]. In a study from UK the incremental cost-effectiveness ratio (ICER) of adalimumab vs conventional therapy was estimated to improve with longer time horizons (48 weeks to 5 and 30 yrs) [25]. In this study it was estimated that, over 30 yrs, adalimumab therapy yielded 1.03 more quality-adjusted life-years (QALYs) per patient initiating therapy. The 30-yr ICER of adalimumab vs conventional therapy was estimated at £23 097/QALY and on inclusion of indirect costs, ICER improved to £5093/QALY [25].

Safety Concerns with TNF-α Blockers

Systemic Lupus Erythematosus syndrome, demylinating diseases, neurodegenerative diseases, pancytopenia, severe infections, cardiovascular diseases etc. are some of the

important side-effects reported with TNF-α blockers [1],[26]. TNF-α plays an important role in the host defense against mycobacterial infection, particularly in granuloma formation and inhibition of mycobacterial dissemination [27].

In a clinical trial the incidence of serious infection was estimated as 0.181/anti-TNFα therapy/year versus 0.008 in the 2 year preceding anti-TNFα therapy [28]. There are recent reports of reactivation of tuberculosis after anti-TNF therapy. FDA recommended a black box for tuberculosis on the product labeling of infliximab. It has been shown that 3mg/kg infliximab therapy along with methotrexate can produce a significant rise in infection rate (53%) as compare to placebo [28]. According to British Thoracic Society's recommendations in presence of prior history of tuberculosis, chest X-ray and clinical examination positive, first patient should be treated with anti-tuberculosis chemotherapy before starting anti-TNF therapy; 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 ; if there is evidence of past history of tuberculosis or abnormal chest X-ray with complete treatment it is important to carefully monitor the patient with chest X-ray after every three months; on presence of inadequate anti-tuberculosis therapy or risk of tuberculosis is more than risk of chemo- prophylaxis, a full course of chemo-prophylaxis should be given before starting anti-TNF-α therapy and Tuberculin test should be considered reliable only if patient is not taking immunosuppressive drugs or stopped them (one month for steroids and three months for others) [11]. However, in developing countries like India with prevalence rate of tuberculosis of about 44%, a negative Mantoux test does not rule out tuberculosis [11].

It is highly recommended to consider prophylactic anti- tuberculosis therapy (with isoniazid or isoniazid and rifampicin combination) before starting anti- TNFα therapy in patients with evidence of past history of tuberculosis or abnormal chest x-ray suggesting tuberculosis [1]. Other serious infections reported with etanercept include sepsis secondary to Listeria monocytogenes and Histoplasma capsulatum [27]. Severe disseminated opportunistic infections have been reported in the HIV positive patients [27].

Future Trends

Anakinra (recombinant form of nonglycosylated human interleukin-1 receptor antagonist), abatacept (a recombinant fusion protein, which selectively modulates the CD80 or CD86-CD28 co-stimulatory signal required for full T-cell activation) and rituximab (genetically engineered human-mouse chimeric monoclonal antibody against the CD20 antigen) are other biologicals under trials for management of AS [11–14]. The risk of infection rate with anakinra use is found to be 4.3cases/100patient years [29].

According to evidence based recommendations for the management of AS by the 'Assessment in AS' international working group and the European League Against Rheumatism, recommended the use of NSAIDs, DMRDs, biological agents, simple analgesics, local and systemic steroids, non-pharmacological treatment (including education, exercise, and physiotherapy), and surgical interventions for management of AS [30]. Recent trials have shown that anti-TNF therapy is more effective in AS than in RA [Table/Fig 2]. However, healthcare cost is another important aspect about TNF blocking agents. Etanercept [Rs 20800($451.20)/100mg] and infliximab [Rs16500($357.50)/25mg] are two biologics available in India [31].

Howe ever, the costs associated with having AS are difficult to quantify but increase steeply with increasing severity of disease. Withdrawal from work is three times higher in patients with AS in comparison with the general population. Patients often require hospital care for joint replacement surgery, spinal surgery, osteoporosis, cardiovascular morbidity, symptom severity or disability [32]. We need to know the extent to which biologic treatment might mitigate these costs [32]. Tumour necrosis factor inhibitors have good evidence supporting large treatment effects for spinal pain and function in AS over at least 6 months [33]. Experience with these agents in Indian patients is scanty; however various clinical trials are on. However, extensive post-marketing surveillance is necessary to re-evaluate the risk-benefit ratio of these biologic therapies.

[Table/Fig 2] Clinical trials with biological agents in ankylosing spondylitis

Study	Active treatment	Control	Result
3 month RCT	Infliximab	placebo	*Infliximab more effective than placebo. [18]*
Anti-TNF RCT	Etanercept	placebo	*At 24 weeks, 59% of the etanercept group and 28% of the placebo group met the ASAS-20 criteria [16]*
Double blind RCT	Etanercept	placebo	*Significantly more etanercept patients reported ASAS 50 responses at all times and ASAS 70 responses at weeks 2, 4, and 8. Lower BASDAI, lower acute phase reactant levels and improvement in spinal flexion in the etanercept group [15].*
Open, observational, 2-yr extension study of an open-label study	Infliximab	-	*Therapy was efficacious and well tolerated, Side-effects were similar to those noted in shorter-term studies; seven patients suffered serious adverse events [20].*
Pilot study on 15 patients	Infliximab	-	*Clinically significant improvement was found in all patients without any incidence of TB [22].*
Phase III ATLAS trial	Adalimumab	placebo	*ASAS-20 was reported in 58% patients receiving adalimumab at 12 weeks [8]. At week 24, adalimumab-treated patients achieved a mean 50% change in enthesitis symptom score [24].*
Cost-effectiveness ratio (ICER)	Adalimumab	conventional therapy	The 30-yr ICER of adalimumab vs conventional therapy was estimated at £23 097/QALY and on inclusion of indirect costs, ICER improved to £5093/QALY [25].

RCT= randomized control trial; TNF= tumor necrosis factor; ASAS = multicomponent Assessments in Ankylosing Spondylitis; BASDAI = Ankylosing Spondylitis Disease Activity Index; ATLAS = Adalimumab trial evaluating long-term efficacy and safety in Ankylosing spondylitis; TB = tuberculosis.

References

[1] Ledingham J, Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNF-α blockers in adults with Rheumatoid Arthritis (update of previous guidelines of april 2001). Rheumatol 2005;44:157-63.

[2] McVeigh CM, Cairns AP. Diagnosis and management of ankylosing spondylitis. Br Med J 2006;333:581-5 .

[3] Mansour M, Cheema GS, Naguwa SM, Greenspan A, Borchers AT, Keen CL, et al. Ankylosing Spondylitis: A Contemporary Perspective on Diagnosis and Treatment. Seminars in Arthritis and Rheumatism 2007;36(4) : 210-23.

[4] A-Z Health Guide from WebMD: Health Topics, Ankylosing Spondylitis. www.webmd.com, assessed on 15-08-2006.

[5] Langer HE. Patient education--a contribution to improvement of long-term management of patients with rheumatism. Rheumatol 1995 ;54(4):207-12.

[6] Kean WF, Buchanan WW. The use of NSAIDs in rheumatic disorders 2005: a global perspective. Inflammopharmacology. 2005;13(4):343-70.

[7] Braun J, Sieper J. Therapy of ankylosing spondylitis and other spondyloarthritides: established medical treatment, anti-TNF-alpha therapy and other novel approaches. Arthritis Res 2002;4(5):307-21.

[8] Akerkar SM, Bichile LS. Pamidronate - a promising new candidate for the management of spondyloarthropathy. Indian J Med Sci 2005;59:165-70.

[9] Singh J, Suruchi A. Anti-TNF-α strategy: Present status of this therapeutic paradigm. Ind J Pharmacol 2004;36:10-4.

[10] Boulos P, Dougados M, Macleod SM, Hunsche E. Pharmacological treatment of ankylosing spondylitis: a systematic review. Drugs 2005;65:2111-27.

[11] Sharma R, Sharma CL. TNF-alpha inhibitors: current indications. Indian J Crit Care Med 2007; 11 (3): 34-43.
[12] Arya V. Food and drug administration (FDA) approval status of biologicals used in Rheumatology. Ind J Rheumatol 2006;1(1):41.
[13] Mahajan A, Sharma R, Khajuria R, Bardi GH, Kapoor B, Gupta V. Rheumatoid arthritis: new developments in biologic therapy. J Ind Med Assoc 2006; 104 :327-30.
[14] Mahajan A, Sharma R, Singh JB. Biological therapy in Rheumatoid Arthritis: current status. Ind J Rheumatol 2006;1(1):13-9.
[15] Calin A, Dijkmans BA, Emery P, Hakala M, Kalden J, Leirisalo-Repo M, et al Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis 2004 ;63:1594-600.
[16] Davis JC Jr, van der Heijde D, Braun J, Dougados M, Cush J, Clegg DO, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum 2003; 48: 3230-36.
[17] Chan K Y, Lee K L, Hsu E, Ma K , Lee K W. Effectiveness of a modified dosing regimen with a lower maintenance dose of infliximab in the treatment of patients with ankylosing spondylitis and spondyloarthropathy. APLAR J Rheumatol 2006 ;9(2):131-5.
[18] Braun J, Brandt J, Listing J, Zink A, Alten R, Golder W, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 2002; 359: 1187-93.
[19] Braun J, Brandt J, Listing J, Zink A, Alten R, Burmester G, et al. Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebo-controlled trial. Arthritis Rheum 2003; 48: 2224-33.
[20] Gossec L, Le Henanff A, Breban M, Vignon E, Claudepierre P, Devauchelle V, et al. Continuation of treatment with infliximab in ankylosing spondylitis: 2-yr open follow-up. Rheumatology 2006 45(7):859-62.
[21] Narayanan K, Anand KP. Two year follow up of infliximab therapy in inflammatory arthritis. J Ind Rheumatol Assoc 2005;13(suppl 1):7-8.
[22] Singh S, Sinal VK, Chaturvedi V. Strategy to prevent tuberculosis during anti TNF therapy in juvenile ankylosing- spondylitis with low dose infliximab without loading schedule: a one year open label study of toxicity and efficacy in 15 patients. J Ind Rheumatol Assoc 2005;13 (suppl 1):5-6.
[23] Kumar A. Experience with anti-tumor necrosis factor-α therapy in India. APLAR J Rheumatol 2006; 9:136.
[24] Waknine Y. FDA Approvals: Duetact and Humira. Medscape Family Medicine/Primary Care MedPulse® Release Date: August 3, 2006 . Medscape_FamilyMed@mp.medscape.com. Assessed on 9-08-06.
[25] Botteman MF, Hay JW, Luo MP, Curry AS, Wong RL,Hout BAV. Cost effectiveness of adalimumab for the treatment of ankylosing spondylitis in the United Kingdom. Rheumatology 2007 46(8):1320-8.
[26] Hrycaj P, Korczowska I, Lacki JK. Severe parkinson's disease in rheumatoid arthritis patient treated with infliximab. Rheumatol 2003;42:702-3.
[27] Dogra A, Sachdeva S. Biologic therapy in psoriasis. Indian J Dermatol Venereol Leprol 2006;72:256-65.
[28] Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-α therapy. Rheumatol 2003;42:617-21.
[29] Chau LSY, Mok CC, Choy E. Non-tumor necrosis factor biological therapies for rheumatoid arthritis. APLAR J Rheumatol 2005;8:77-83.
[30] Zochling J, van der Heijde D, Burgos-Vargas R, Collantes E, Davis JC Jr, Dijkmans B, et al. ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2006 ;65(4):442-52.
[31] Moots R, Taggart A, Walker D. Biologic therapy in clinical therapy practice: enthusiasm must be tempered by caution. Rheumatol 2003;42:614-6.
[32] Jois RN,Gaffney K, Keat A. Anti-tumour necrosis factor therapy for ankylosing spondylitis—unresolved issues. Rheumatology 2007 46(6):899-901.
[33] Zochling J, Heijde DVD, Dougados M, Braun J. Current evidence for the management of ankylosing spondylitis: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. Ann Rheumatic Dis 2006;65:423-32.