Biologics in Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic progressive disease of the joints associated with significant morbidity, deformity, and impaired quality of life. A satisfactory remission of disease is seldom achieved, so therapy is aimed at controlling joint damage and pain with preservation of joint mobility. Until recently, NSAIDs, followed by DMARDs, was considered the treatment of choice. However, many patients fail to gain a satisfactory response to DMARDs or response declines over time. Biologics such as IL-1 receptor antagonist (anakinra), and anti TNF-α agents (Etanercept, Infliximab, and Adalimumab) are now available. The anti TNF and IL-1 therapies exert their anti-inflammatory action by neutralizing the activities of TNF-α and IL-1 respectively. In contrast to older DMARDs, these agents have rapid onset of action with fewer side effects and have pronounced disease reducing activity in patients who have previously been treated with other DMARDs, when administered as monotherapy or in combination with methotrexate. They have been shown to be at least as effective as methotrexate in reducing clinical disease activity and reducing radiographic progression. Biological agents are generally well tolerated, although their long term safety needs to be determined. Some concerns have been raised that anti TNF-α therapy can increase the risk of serious infections, since TNF-α plays an important role in host defense. In light of limitations of cost and lack of long-term safety and efficacy data, newer agents for the time being are used as second- or third-line agents in patients with active RA. The dilemma is that which patients with RA are most suitable for such therapy, since it is still not possible to accurately predict which patient with RA will develop severe disease. One alternative approach may be to limit the use in patients who can afford it, and who are at high risk of radiographic progression and disability.

Rheumatoid arthritis (RA) is a chronic progressive disease that affects about 1% of the population worldwide and is associated with reduced life-expectancy. It can affect people at any age, but is common among those aged 40-70 years. The predominant symptomatology is pain, stiffness and swelling of multiple peripheral joints. Clinical course of the disease is highly variable and may range from mild, self-limiting arthritis to progressive erosive joint disease causing significant morbidity and mortality. Recent studies indicated that though inflammatory symptoms may be controlled in majority of the patients with early and aggressive therapy with conventional disease modifying antirheumatic drugs (DMARDs), such as methotrexate, sulfasalazine, and hydroxychloroquine, radiographic progression may continue despite the improvement in inflammatory markers and mobility. This has led to the development of more specific and effective therapies to halt joint damage and maintain functional mobility during the past few years.

With better understanding of inflammatory mediators involved in the disease process, drugs designed to target pathways active in inflammation and apparently relevant to RA pathogenesis have been developed. Cytokines, like tumour necrosis factor-α (TNF-α) and interleukins particularly interleukin-1 (IL-1) are recognized to be important mediators of inflammation and joint destruction in RA. Primarily produced by activated monocytes and macrophages, TNF-α mediates both inflammatory synovitis and articular matrix degradation. TNF-α induces the production of proinflammatory cytokines, stimulates endothelial cells to express adhesion molecules that attract leucocytes into affected joints, and increases the rate of synthesis of metalloproteinases by synovial macrophages, fibroblasts, osteoclasts, and chondrocytes. It also inhibits the synthesis of proteoglycans in cartilage. Studies in both experimental animal models and patients suggest that IL-1 plays an important role in promoting tissue inflammation and remodeling. IL-1 may contribute to joint damage by stimulating the release of matrix metalloproteinases, by...
inhibiting cartilage repair and by enhancing bone resorption through activation of osteoclasts.7,8 Treatment of murine models of arthritis with antibodies against TNF-α or IL-1 or with soluble TNF receptor ameliorates disease.9 Moreover, mice transgenic for TNF-α and those with dysregulated TNF-α production develop arthritis. These animal data provided a rationale for clinical trials of these agents in human disease. Clinical studies have proved their efficacy and few of these biologics are already approved for use in RA. This article reviews the role and place of these agents in the treatment of RA.

**TNF-α Antagonists**

There are two distinct TNF-α receptors (TNFR), the p55 or type-1 and p75 or type-2. Both forms are present in soluble form in synovial fluid of RA patients. The soluble receptors compete with the cell surface receptors for binding to TNF-α thereby inhibiting TNF-α activity. Both the receptors bind TNF-α with comparable affinities.

**Etanercept**

Etanercept was the first specific anti-cytokine agent approved for use in patients with RA. It is a recombinant form of the p75 TNF-α receptor that is linked to the Fc portion of human immunoglobulin G1. It binds to TNF-α and attenuates its biological effects. Efficacy of etanercept in RA has been demonstrated in clinical trials. Initial studies showed significant decrease in disease activity as manifested by reduction in swollen and painful joint counts and inflammatory markers.10 In a placebo-controlled trial of etanercept, given 25 mg subcutaneously twice weekly as monotherapy, produced ACR20 response in 62% of patients compared to 23% in placebo group at 3 months and 59% vs 11% at 6 months. Moreover, ACR50 response achieved at 6 months was 40% and 5% in etanercept and placebo group respectively.11 Etanercept given in combination with methotrexate was found to be superior to methotrexate monotherapy.12 Monotherapy with etanercept was found to be as efficacious as methotrexate in improving arthritis activity and in retarding the joint destruction in patients with early RA.13 Etanercept is a safe drug with good tolerability profile. It can cause injection site reaction in the form of erythema, itching, pain or swelling. Anti TNF-α therapy may be associated with serious infections due to impaired defense against pathogenic microorganisms. Infections were the most frequently reported adverse events in placebo-controlled trials with etanercept. However, the overall frequency of infections was similar in placebo and treatment group with the exception of upper respiratory tract infections.11,12

Patients of RA show dose dependent increase in serum concentration of etanercept and the serum half-life varies between 92-115 hours. It is approved for use in patients with moderate to severe active arthritis as monotherapy or in combination with methotrexate. Recommended dose in adults is 25 mg twice weekly administered subcutaneously.

Etanercept is contraindicated in patients with known hypersensitivity to the drug and in presence of active infection. Discontinuation of treatment is recommended if recipient develops serious infection during treatment.

**Infliximab**

Infliximab is a chimeric monoclonal antibody with 75% human and 25% mouse protein that binds to both soluble as well as transmembrane forms of TNF-α. The efficacy of infliximab infusion in RA has been assessed in several trials either alone14 or along with methotrexate.10,11 In a 4-week multicentric trial14 infliximab given in a dose of 1 or 10 mg/kg as single infusion was significantly more effective than placebo through week 1 to 4. Multiple doses of infliximab (3mg/kg every 4 and 8 weeks; and 10 mg/kg every 4 and 8 weeks) with concomitant methotrexate produced ACR20 response in 50% patients among all treatment groups at week 2 and over 90% at week 6. Thereafter total response rates were sustained at level between 50 and 60% up to 30 weeks. Additionally, significantly greater percentage of infliximab treated patients achieved ACR50 and ACR70 response at 6 months.15 Similarly single dose studies with background methotrexate use showed greater improvement in clinical response with infliximab than placebo plus methotrexate recipients.16 Superiority of the above combination has also been proved in another trial.17 In each of these trials patients had significantly more improvement in their signs and symptoms in infliximab plus methotrexate group than in placebo plus methotrexate group. Moreover, duration of symptom-free period increased with the increase in infliximab dose.

Limited data is available on pharmacokinetics of infliximab. The estimated elimination half-life (t1/2) is 8 to 9.5 days at 3 mg/kg dose. Infliximab is not metabolized by CYP450 enzymes thereby it has a reduced potential for drug interactions. Most frequent adverse effects are headache, nausea, upper respiratory tract infections (URTI) and infusion-related reactions (fever, chills, chest pain, hypotension, and dyspnoea).15 Incidence of infections including serious ones were reported significantly more with infliximab as compared to placebo. It is contraindicated in the presence of active infection, and known hypersensitivity to the drug. Dosage recommended by FDA is 3 mg/kg intravenously at week 0, 2 and 6, to be repeated every 8 weeks thereafter.

**Adalimumab (D2E7)**

It is a fully humanised monoclonal antibody against TNF-α.

**Table 1 : BSR (British Society for Rheumatology) guidelines for anti TNF-α therapy**23

<table>
<thead>
<tr>
<th>Active disease:</th>
<th>DAS &gt; 5.1</th>
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<tbody>
<tr>
<td>Pretreatment:</td>
<td>Failure of at least two DMARDs after adequate trial</td>
</tr>
<tr>
<td>Exclusion:</td>
<td>Pregnancy or breast feeding</td>
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<tr>
<td></td>
<td>Active infection</td>
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<tr>
<td></td>
<td>High risk of infections (various identified)</td>
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<tr>
<td></td>
<td>Malignancy or premalignancy</td>
</tr>
<tr>
<td>Withdrawal:</td>
<td>Adverse events</td>
</tr>
<tr>
<td></td>
<td>Lack of effect, DAS not improved by &gt; 1.2 at &gt; 3months</td>
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DAS: Disease Activity Score
α that was finally approved by FDA in December 2002. The molecule is less immunogenic than infliximab with a longer half-life, having the potential for less frequent dosing. Preliminary results with adalimumab in patients with established RA were encouraging.19 Response to treatment was rapid and evident within 24 hours to 1 week after administration. Results of ARMADA trial have proved efficacy and tolerability of adalimumab in severe active RA in dose range of 20-80 mg given subcutaneously every other week. An ACR20 response at week 24 was achieved by a significantly greater proportion of patients in the 20 mg, 40 mg, and 80 mg adalimumab plus methotrexate groups (47.8%, 67.2% and 65.8%) vs 14.5% (placebo plus methotrexate). The ACR50% responses were 31.9%, 55.2%, and 42.5% in 20mg, 40mg, and 80 mg adalimumab plus methotrexate groups respectively against 8.1% in placebo against TNF-α.

Anakinra

Anakinra is approved for the treatment of moderate to severe active RA in adults over 18 years of age who have established RA were encouraging.19 Response to treatment was rapid and evident within 24 hours to 1 week after administration. Results of ARMADA trial have proved efficacy and tolerability of adalimumab in severe active RA in dose range of 20-80 mg given subcutaneously every other week. An ACR20 response at week 24 was achieved by a significantly greater proportion of patients in the 20 mg, 40 mg, and 80 mg adalimumab plus methotrexate groups (47.8%, 67.2% and 65.8%) vs 14.5% (placebo plus methotrexate). The ACR50% responses were 31.9%, 55.2%, and 42.5% in 20mg, 40mg, and 80 mg adalimumab plus methotrexate groups respectively against 8.1% in placebo against TNF-α.

Infliximab

Results of another large, multicentric, international, placebo-controlled safety study demonstrated that anakinra is safe and well tolerated in a diverse population of patients with RA including those with co-morbid conditions and those using multiple combinations of concomitant therapies.26

Major concern with anakinra use is the risk of serious infections. It is contraindicated in the presence of active infection and should be discontinued if patient develops the same during treatment. Most commonly reported adverse event with anakinra was injection site reaction (pain, erythema, pruritus and rash).22,23 Anakinra shows absolute bioavailability of 95% after subcutaneous administration. Peak levels are observed between 3 and 7 hours with terminal half-life of 4 and 6 hours.

Anakinra is approved for the treatment of moderate to severe active RA in adults over 18 years of age who have
failed to respond to one or more DMARDs. It can be used alone or in combination with DMARDs other than TNF-\(\alpha\) inhibitors. Recommended dose in RA is 100 mg once daily administered subcutaneously at the same time everyday.

**Proserba column**

The US food and drug administration (FDA) has approved proserba column for use in patients with long-standing moderate to severe RA, who have failed or intolerant to DMARDs. Plasmapheresis to remove IgG and IgG containing complexes from plasma is an established therapeutic procedure in RA. This is achieved using a column containing an inert silica matrix and a covalently attached highly purified staphylococcal protein A. Treatment requires apheresis with about 1200 mL of plasma circulating over the column per treatment session of two hours. The standard treatment regimen constitutes 12 weekly apheresis sessions. The mechanism of protein A immunoadsorption remains largely unclear. The entire treatment course has moderate efficacy in RA.27 If no response is seen with first apheresis session, a second course is unlikely to be beneficial. Most common side effects are chills, musculoskeletal pain, headache, nausea, and gastrointestinal problems. There may be flare in joint pain and swelling during first four or five apheresis sessions in small number of patients. It is a proven and effective alternative therapeutic option in patients with severe RA refractory to several DMARDs.28

**Miscellaneous Agents**

**Rituximab**

Rituximab, is a chimeric monoclonal antibody that depletes B cells. B lymphocyte depletion in rheumatoid arthritis has so far proved to be safe and associated with improvement in symptoms of RA.29 These observations provide an initial basis for the design of formal trials of B cell depletion and other B cell directed treatments.

**CTLA4Ig**

This antibody binds to CD80 and CD86 receptors on antigen presenting cells preventing interaction with CD28 receptors (ligand) resulting in inhibition of T cell activation and proliferation. Clinical trials are underway to determine safety and efficacy in RA.30

**Vaccine therapy**

T-cell receptor peptide vaccine has been evaluated for prevention of RA. Although a trend towards improvement in signs and symptoms of RA was demonstrated the results were not significantly different from placebo.31

**Anti IL-6 antibody**

Anti IL-6 antibody has shown significant improvement in sign and symptoms of RA and normalization of acute phase reactants.32

**CDP-870**

It is Fab fragment of an antibody that is produced by recombinant DNA technology that is highly specific for TNF-\(\alpha\). In an initial randomized placebo controlled clinical trial CDP-870 at a dose of 400 mg produced response rate of 60%, 40%, and 29% according to ACR20, ACR50, and ACR70 criteria at 12 weeks.

**PEGylated soluble TNF receptor type 1 (Pegsunercept)**

It is produced by recombinant DNA technology that is stabilized by attaching a PEG molecule. This compound is in early phase of clinical trial and has shown encouraging results.

**Others**

Adhesion molecules like E-selectin and ICAM-1 are important mediators that modulate the disease activity. They appear to be promising targets for drug development. Serum VEGF levels are relatively elevated in patients with RA and bear good correlation with disease activity and blocking VEGF expression could be an attractive treatment approach. Moreover, humanized monoclonal antibody against cytokines like CD11 is under development.

**Conclusions**

Based on earlier treatment approach, use of conventional DMARDs in RA was indicated when a) the disease is progressive; b) objective evidence of joint erosions is seen. However, benefits of early therapy with conventional DMARDs in patients with potential progressive disease have now been realized, but there remains concern regarding their partial effectiveness and poor tolerability in long term. In recent years, better appreciation of the concept of inflammatory processes and mediators involved in the pathogenesis of RA, has led to the development of newer biological agents in an attempt to modify disease process. They can be used either in combination with methotrexate or as monotherapy when response with DMARDs is inadequate. TNF-\(\alpha\) and IL-1 antagonists have proved to be as efficacious as conventional DMARDs but their enormous cost and potential to cause long term side-effects needs to be assessed. Although these agents are faster acting in terms of controlling disease activity, and have better tolerability profile than conventional DMARDs, they are not capable of curing the disease. Moreover, they are needed to be taken on long term basis to keep the disease activity under control. Keeping in mind the financial impact of such therapy in chronic disease like RA that requires prolonged treatment, it is highly unlikely that they will gain wide public acceptance in the therapy of RA in developing countries like ours. Till date, experience with these agents has been promising and long-term outcomes in terms of efficacy and safety will eventually establish their place in pharmacotherapy of RA.

**References**


31. Moreland LW, Morgan EE, Adamson TC, et al. T cell receptor peptide vaccination in rheumatoid arthritis: a placebo-
Dr. F. P. Antia was born in Mumbai on August 10, 1916 in a religious Parsee family; his father was a priest. He passed BSc (1938), MBBS (1941), MD (1944) and MRCP (London) in 1946. He obtained MS (Illinois, USA) in 1949. He was awarded FRCP (London) in 1969 and FAMS (India) in 1978.

He had the most envitable, extensive, experience in the field of gastroenterology, with the stalwarts in UK and USA and was one of the most well-trained gastroenterologists in the world. He worked as a Clinical Assistant to Sir Francis Avery Jones at Central Middlesex Hospital, London (1946), did a course in endoscopy at Harvard Medical College, Boston (1947), worked at Postgraduate School, University of Pennsylvania under Dr H L Bockus (1948), and as United States Government Research Fellow with Dr A C Ivy at University of Illinois (1949). Later on, he attended a course in Radiosotope Technique at University of Columbia (1958) and fiberoptic colonoscopy (CME), Jefferson Medical college, USA in September 1974.


He published about 150 publications and the earliest were on gastric secretion with Ivy (1949) and Grossman MI (1951). Dr Antia was the Editor of Indian Journal of Gastroenterology from 1983 for a period of 5 years. He published an unique book “Clinical Dietetics and Nutrition”, Oxford University Press in 1966 and subsequent editions were published in 1973, 89, 97. He also wrote a chapter on Amoebiasis in Conn’s Current Therapy (1971, 1981) and on Gastrointestinal Emergencies in a book written by Vakil and Udwadia (Oxford University Press 1972, 75, 89). He was the Sectional Editor (Gastroenterology) for API Text book of Medicine (1969, 72, 79, 86, 92). He published about 150 publications and the earliest were on gastric secretion with Ivy (1949) and Grossman MI (1951). He was Hon. Gastroenterologist and Head at TN Medical college and BYL Nair Ch. Hospital, for about 20 years and Tata Memorial Hospital, Parsee General Hospital for about 30 years. He was consulting Physician at Radiation Medicine Centre, Bhabha Atomic Research Centre, since its inception. On his retirement, no farewell functions were held at any institute, as he would never agree to it. In recongisation of his extensive experience in UK and USA, Dr. Antia was offered a post in departments of Gastroenterology in USA but decided to return, to develop the speciality of gastroenterology in India, which became his life’s mission. With a donation of Rs 5000/= (Rupees Five Thousand Only.) from Pai family, obtained by a physician Dr S S Rao, he started the first separate department of Gastroenterology at B Y L Nair Charitable Hospital in 1954. Later on, this department received Shakuntala Amirchand Prize (ICMR) (1973), Pfizer Amirchand Trophy (ISG) (1978), for outstanding research work and gained recognition for DM and DNB degrees (1986). One incident of 1963, when I was his non-resident registrar, needs to be mentioned. An IVP was to be performed on me by his radiologist friend at 6.00 a.m. The radiologist and I reached at 6.00 a.m., but Dr. Antia had reached there 5 minutes earlier, waiting outside the radiologist’s office. He was a strict disciplinarian, with a serious exterior but was a large hearted human being, with an abundant subtle sense of humour.

Dr Antia’s determination to develop speciality of gastroenterology on returning to India, his far sighted vision to start the first separate department of gastroenterology in Mumbai, his development of subspecialty such as hepatology, endoscopy, his contribution in training young gastroenterologists, his research activities, the editorship of the journal of ISG and publishing his book on dietetics, provides ample proof of his unparallel contribution to the speciality of gastroenterology.

Though Dr. Antia is no more with us, Antia’s era will not end on 19 October, 2003. Several gastroenterologists from India, who have come in contact with this great gastroenterologists and a fine, wonderful, unconventional human being, will continue to follow the path shown by him. Dr. Antia’s rich legacy of hardwork, honesty, humour, helping others and hating hypocrisy will remain amongst us for a long - long time.

Good bye my respected Guru.

Mumbai, October 31, 2003

HG Desai