



# Biologics and Beyond in Rheumatic Diseases

**URK Rao**

President, Indian Rheumatology Association, Sri Deepti Rheumatology Centre,  
6-2-45/8, A.C. Guards, Hyderabad 500004.

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## ABSTRACT

In the last few years, advances in biotechnology have lead to the introduction of new classes of therapeutic agents. No drug class has shown as much growth and impact as the cytokine directed therapies to treat various immunoinflammatory rheumatic disorders. As regulatory and terminal effector molecules, cytokines amplify deregulatory immune response that results in the magnitude and chronicity of inflammatory diseases. The success of cytokine therapies underscores the merit of approaching these disorders with more complete and specific targeting. The objective of therapy in these disorders has been to improve pain, avoid articular (radiographic) damage, preserve function and to improve the quality of life. However, use of these novel compounds is often restricted by cost and safety concerns.

Every patient with confirmed rheumatoid arthritis (RA) should receive disease-modifying anti-rheumatoid drugs (DMARDs). Methotrexate has become the gold standard against which all new therapies are being judged. Biologic response modifiers (BRMs), some of them available in our country, should be considered in rheumatic disorders of aggressive nature and should not be reserved for those with long-standing and end-stage disease. Judicious patient selection and the appropriate monitoring of these agents by rheumatologists will optimize patient outcomes, ensure the cost-effectiveness of therapy and limit the incidence of rare or troublesome adverse events.

### INTRODUCTION

The last decade has witnessed an unprecedented expansion of therapeutic options for the treatment of various rheumatic diseases; most recent and notable have been the biologic response modifiers (BRM). The traditional disease modifying anti-rheumatic drugs (DMARDs) are non-specific immunomodulators, each of which has substantial drawbacks in terms of efficacy and safety. The human system comprises both soluble and cellular elements that defend against pathogenic antigens. Immune cells interact either by cell-to-cell interaction or through secreted mediators called cytokines.

### CYTOKINES AND CYTOKINE ANTAGONISTS

Cytokines are small molecules that act as messengers between cells. They are involved in many processes but have especially important roles in inflammation. Cytokines are proteins, which are found in abundance at the sites of active inflammation, including the synovial joints in rheumatoid arthritis (RA). Their roles in inflammation have been studied extensively. Some cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- $\alpha$ ) are pro-inflammatory while others like tissue

growth factor-beta and IL-10 are anti-inflammatory. Blocking pro-inflammatory cytokines or increasing anti-inflammatory cytokines is a possible treatment strategy. The validity of the former approach is confirmed by the clinical benefit of TNF- $\alpha$  inhibitors and recombinant IL-1 receptor antagonists in RA. The production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 (IL-1) is overwhelming in several immuno-inflammatory arthritides such as rheumatoid arthritis (RA). Many cells of the body, predominantly macrophages secrete TNF- $\alpha$ , one of the most important cytokines in the pathogenesis of RA. Once a cytokine binds to its receptor on a target cell, it sets of signal cascade and alteration of gene transcription producing various inflammatory mediators. The receptors for cytokines are present as surface receptors and soluble receptors. The anti-inflammatory substances produced endogenously in RA include soluble TNF receptors, IL-1 receptor antagonists (IL1-Ra) and IL-10. The BRMs blocking the biological effects of inflammatory cytokines include antibodies directed against the TNF- $\alpha$  (Infliximab, Adalimumab), soluble receptor (Etanercept), and IL-1 receptor antagonist (Anakinra). Various clinical trials indicate that BRMs are more effective than placebo and traditional DMARDs as they

**Table 1 : Some BRMs tested in clinical trials for the treatment of Rheumatic Disorders**

	Structure	Composition	Mechanism of action
Etanercept	sTNFR + Fc IgG1	Human	High affinity binding to two TNF molecules
Infliximab	Anti-TNF Ab + IgG1	66% human	High affinity binding to trimeric TNF molecules
CDP571	CDR of anti-TNF + IgG4	95% human	High affinity binding to trimeric TNF molecules
Adalimumab	IgG1 specific for human TNF	Human	Binds to circulating and cell surface TNF and blocks interaction with p55 and p75 cell surface TNF receptors
Rituximab	Monoclonal anti-CD20 antibody	Chimeric	B-cell cytotoxicity
MRA	Fc portion of IgG1	Human	Binds to human IL-6 R

can alter joint remodeling in addition to attenuating symptoms and retarding radiological damage. Some important properties of the currently available BRMs are highlighted in Table 1.

## RECOMMENDATIONS FOR BIOLOGICAL AGENTS IN RA

RA is a debilitating, progressive, immune-mediated disease reducing the quality and span of the life. The fundamental goal in the management of RA is the elimination of the synovitis and disease activity. Early DMARD therapy is mandatory. Methotrexate, unless contraindicated, forms base-line therapy. BRMs are appropriate depending upon the disease activity and response to DMARD therapy. They need not be reserved for only the advanced or DMARD resistant disease, but instead used in rapidly advancing aggressive disease.<sup>1</sup> One of the more compelling reason for using these agents is the euphoria or born again feeling of many patients upon receiving TNF inhibiting therapy.

### Various BRMs and approved indications for their use

Among the four commonly used BRMs namely Etanercept, Infliximab, Adalimumab and Anakinra; Etanercept (Enbrel) and Infliximab (Remicade) are available in India. Apart from RA, they are also indicated in other rheumatic diseases (Table 2).

### Tumor Necrosis Factor (TNF) Inhibitors

#### *Etanercept*

Etanercept is a recombinant form of the human 75(p75) kd TNF receptor (TNFR) that is fused to the Fc fragment of human immunoglobulin G1 (IgG1). It is prepared from mammalian cells by using DNA recombinant technology. Etanercept binds to TNF before TNF can interact with cell surface TNFRs. In addition to directly inhibiting TNF, Etanercept can modulate biologic responses that are induced or regulated by TNF, including expression of adhesion molecules, serum concentrations of matrix metalloproteinase-3, and cytokines. Cells that express transmembrane TNF that bind Etanercept are not lysed in vitro in the presence or absence of complement. Etanercept is given as 25 mg subcutaneous (sc) twice a week. It has half-life of 4-5 days. Since several clinical studies support the efficacy of Etanercept alone or combined with methotrexate in RA, its use has been approved in various rheumatological disorders.<sup>2</sup> There are several ongoing studies to see the effect of Etanercept in active Wegener's

granulomatosis, Behcet's disease and adult-onset Still's disease. Etanercept is being used in active RA in India.<sup>3</sup>

#### *Infliximab*

Infliximab is a chimeric monoclonal antibody consisting of 75% human IgG1k and 25% mouse protein sequences. The mouse portion consists of antigen binding fragment of Fab region; the human portion is used to reduce antigenicity. Infliximab binds to soluble and also to the membrane-bound TNF with high affinity and specificity to human TNF. Infliximab is given in a dose of 3 mg/kg as an IV infusion at '0', '2', '6' weeks repeated every two months thereafter. It has a half-life of 8-12 days. Several trials including ATTRACT trial (Anti-TNF Therapy of Rheumatoid Arthritis with Combination Therapy) have established the usage of Infliximab in aggressive RA and early RA. It is also used as monotherapy for the treatment of Crohn's disease, ankylosing spondylitis (AS), psoriasis and psoriatic arthritis (PsA).<sup>4</sup> It is also shown to be effective in Behcet's syndrome, Wegener's granulomatosis and other Vasculitides.

#### *Adalimumab*

Adalimumab (HUMIRA) is a recombinant human immunoglobulin G1 monoclonal antibody that is specific for human tumour necrosis factor. Adalimumab binds specifically to circulating and cell surface TNF- $\alpha$  and blocks its interaction with the P55 and P75 cell surface TNF receptors. The recommended dose of Adalimumab in adults with RA is 40 mg administered every other week as a single dose by sc injection. Adalimumab can be given alone or with concomitant methotrexate. Its half-life is 10-20 hours.

### Other TNF Inhibitors under Clinical Trials:

- CDP870*: It is a novel second-generation TNF inhibitor comprised of a humanized Fab fragment linked with two polyethylene glycol molecules (20kDa each). The size and composition of this construct should potentially limit its immunogenicity yet prolong its duration of effect. Its half-life is 12-15 days. It may be administered monthly as a subcutaneous or intravenous infusion.
- Pegsunercept*: It is a monomeric P55 soluble TNF receptor 1(sTNFR1) that links polyethylene glycol to sTNFR1 (PEGsTNFR1) to enhance its half-life.

**Table 2: Indications for the use of cytokine Inhibitors**

Indication	Etanercept	Infliximab	Adalimumab	Anakinra
Rheumatoid arthritis	Yes	Yes	Yes	Yes
Crohn's disease	-	Yes	-	-
Polyarticular juvenile RA	Yes	-	-	-
Psoriasis and psoriatic arthritis	Yes	-	-	-
Ankylosing spondylitis	Yes	Yes	-	-

- iii. *Weaker tumor necrosis factor inhibitors:* These include thalidomide and pentoxifylline. The mechanisms by which these agents inhibit TNF have not been elucidated.
- iv. *TNF- $\alpha$  converting enzyme inhibitors:* TNF- $\alpha$  converting enzyme is a transmembrane protein that cleaves cell surface bound TNF- $\alpha$  to release soluble cytokine. Inhibition of this metalloproteinase reduces lipopolysaccharide stimulated TNF production in whole blood by 95 percent. Several orally bioavailable TNF- $\alpha$  converting enzyme inhibitors are currently in preclinical trials.

### Interleukin-1 blocking agents

#### *Anakinra*

IL-1 is a key mediator of immune and inflammatory processes by recruiting neutrophils, activating macrophages and T and B cells and induction of other cytokines and chemokines. IL-1 receptor antagonist (IL-Ra) occurs naturally and is a specific inhibitor of IL-1. When IL-1 Ra binds to the IL-1 receptor, the association between the receptor and its accessory protein is prevented and thus further signaling is blocked. Anakinra (Kineret) is a recombinant non-glycosylated form of native human IL-1 Ra. It differs from native IL-1 Ra by the addition of a single methionine residue at its amino terminus. It is given subcutaneously in a dose of 100 mg daily. The efficacy and safety of anakinra in patients with RA was investigated as monotherapy and in combination with methotrexate and other DMARDs.<sup>5</sup> The combination of anakinra with other TNF blockers is not indicated at present.

### Other Targeted Therapies

IL-6 is pleiotropic cytokine with diverse biologic effects. The therapeutic potency of a humanized anti-IL-6R monoclonal antibody (MRA) is tested in clinical trials. Chemokine and chemokine receptors control the recruitment of leukocytes to sites of inflammation. Pre-Clinical studies in arthritis models suggest that inhibiting IL-18 activity via neutralizing monoclonal antibodies or recombinant human IL-18 binding protein can effectively reduce inflammation. IL-1 Trap is a fusion protein that links the extracellular domain of the type 1 IL-1 receptor and the IL-1 receptor accessory protein with the Fc region of IgG1. This construct has a strong binding affinity for IL-1  $\alpha$  and IL-1  $\beta$  and has a prolonged half-life (range 128-214 hours) to permit once weekly subcutaneous dosing. IL-1 converting

enzyme (also known as ICE or caspase-1) is required for the release of IL-1 and IL-18 from the cell surface. Prainacasan is a synthetic, orally administered ICE inhibitor that is under evaluation for RA and inflammatory bowel disease. The limited experience with gene therapy in RA has focused usage of IL-1 Ra. IL-1 Ra is a leading candidate for gene therapy as a means of controlling inflammation.

T cell costimulatory molecules are cell surface proteins that play important role in activation of T cells. Clinical efforts to treat various inflammatory and immune diseases by inhibiting costimulatory signals with monoclonal antibodies (anti-CD 40 ligand) and recombinant naturally occurring molecules CTLA4 (Cytotoxic T-lymphocyte antigen 4 –immunoglobulin) are ongoing. T cell surface complex CD11a/CD18 (also called LFA-1) interacts with its ligand intercellular adhesion molecule-1 (ICAM-1) as part of a costimulatory pathway for T cell activation. A humanized, monoclonal antibody against CD11a (called efalizumab) has been developed to study its effects in psoriasis and RA with considerable improvement.

### B-Cell directed therapy

Rituximab (anti-CD20 antibody) is a chimeric monoclonal antibody that selectively depletes B cells bearing the CD20 surface marker. Plasma cells do not express CD20; therefore, immunoglobulin levels are not significantly affected by anti-CD20 treatment. Rituximab is currently being tried in systemic lupus erythematosus (SLE) and RA, administered by way of slow infusion for several hours 1 gm every 2 weeks.<sup>6</sup>

### SAFETY OF BIOLOGIC RESPONSE MODIFIERS

Side effects of BRMs include infusion reactions, infections especially tuberculosis, hematological, cardiovascular, demyelinating, autoimmune and malignancies. Because many of these serious toxicities occur at rates of one or fewer cases for 1000 patients' years of use, it appears that proper patient selection and prevention measures are needed to further limit this risk.<sup>7</sup>

### Bone Marrow Transplantation and Stem Cell Therapy

Several groups have used autologous T-cell-depleted stem cell transplantation in small open label studies in patients with rheumatoid arthritis with refractory RA, juvenile rheumatoid arthritis, SLE and systemic sclerosis. Although autologous bone marrow transplantation produced promising results in patients with refractory RA, treatment was associated with high frequency of side effects.

A hematopoietic stem cell transplant from a healthy woman to her sister with severe and refractory RA has safely induced disease remission in the patient, researchers report in the August issue of Arthritis and Rheumatism.<sup>8</sup>

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