

# Biologics in RA

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*Ved Chaturvedi, Molly Thabab*

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## INTRODUCTION

**R**heumatoid arthritis (RA) chronic multisystem disease affects almost 1% of the Indian population and is the most common inflammatory joint disease seen in clinical practice. The synovial inflammation leads to cartilage damage, bone erosions and subsequent joint destruction which cause significant morbidity. RA once diagnosed should be treated early because bone erosion begins in the first 2 years of disease. A delay of as little as 8-9 months in starting DMARDs (disease modifying anti-rheumatic drugs) could impact clinical outcome several years later <sup>1</sup>. The last decade witnessed a revolution in the treatment of RA with the development of biologics. The term biologics is used for therapeutic agents produced by biotechnology.

### **Pathophysiology of RA and basis of therapy using biologics in RA**

RA is a disease with a still unknown etiology. But it is likely that a still unidentified infective agent or another stimulus binds to receptors on dendritic cells and macrophages <sup>2</sup>. Dendritic cells then migrate to lymph nodes and they present the antigen to the T-cells resulting in T-cell activation. T-cell activation requires two signals; signal 1 is generated when MHC-complex-bound peptide on the antigen presenting cell (APC) stimulates the T-cell receptor, whereas signal 2 is generated by CD28 costimulation i.e, CD80 or CD86 on the APC interacts with CD28 on the T-cell. To prevent overshooting activation, T cells subsequently express cytotoxic T-lymphocyte antigen (CTLA) 4, which has a higher affinity to CD80 and CD86 than CD28 and conveys inhibitory signals. Abatacept, a recombinant fusion protein of CTLA 4, is used therapeutically to block CD80-mediated or CD86-

mediated co-stimulation and activation of T cells.

The activated T cells migrate to the joint; they proliferate and produce a host of inflammatory mediators. These stimulate macrophages, fibroblasts, chondrocytes and osteoclasts. Activated macrophages and fibroblasts release tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-15 (IL-15), interleukin-18 (IL-18) and other pro-inflammatory cytokines, which in turn recruit other cells like neutrophils, B cells and endothelial cells. B cells express various cell-surface molecules, especially their antigen receptor, immunoglobulin, and differentiation antigens, such as CD20 and CD22. They differentiate into plasma cells that secrete autoantibodies to IgG (rheumatoid factor), cyclic citrullinated peptides (which in turn predicts severe RA). Activated B cells also serve as APCs and their survival and activation, including production of specific immunoglobulin isotypes, is mediated by T-cell help and co-stimulation. Rituximab is a monoclonal antibody against CD20 that targets and depletes B cells.

Many cytokines are activated in the synovium by various cell populations, several of them secreted by macrophage-like cells. From among these inflammatory mediators TNF- $\alpha$  and interleukin-1 is found abundantly in the rheumatoid joint. TNF- $\alpha$  is a very important therapeutic target and the monoclonal antibodies to TNF are widely used in rheumatology clinical practice. IL-6 is another cytokine target which is over-expressed in synovial tissue in patients with RA. IL-6 affects the functions of neutrophils, T cells, B cells, monocytes and osteoclasts and it is a major inducer

of the hepatic acute-phase response. The effects of IL-6 are mediated by binding to the IL-6 receptor, which is expressed on the cell surface and as a soluble form. Tocilizumab is a monoclonal antibody to the IL-6 receptor, which binds both soluble and membrane-expressed receptor. Table-I shows the biologics that are currently available for treatment of RA.

## EFFICACY OF BIOLOGICS IN RA

### TNF-inhibitors

The TNF inhibitors infliximab, etanercept, adalimumab are the most commonly used biologics in the treatment of RA in clinical practice. More recently golimumab and certolizumab have undergone phase III clinical trials. The TNF inhibitors have been evaluated in a series of RCTs, with methotrexate (MTX) as the gold standard for comparison.

**1) Infliximab:** The clinical and radiological efficacy of infliximab has been evaluated in a series of RCTs, but the Anti-TNF Trial in RA with Concomitant Therapy (ATTRACT) will be highlighted here<sup>3</sup>. The study enrolled 428 subjects with active RA (mean disease duration 9-12 years). These patients were randomly assigned placebo (n=88) or one of four regimens of infliximab at 0, 2 and 6 weeks followed

by infusions every four or eight weeks. The MTX dose was stable (median 15mg/week). Patients were assessed every 4 weeks for 30 weeks. Infliximab treatment was efficacious at all doses compared to placebo +MTX. At week 30 the ACR20 response was achieved by 50-60% of patients receiving 3mg/kg every 4 or 8 weeks or 10mg/kg every 4 or 8 weeks compared with 20% patients receiving placebo +MTX. Significantly more patients in the infliximab group achieved ACR50 and ACR70 responses than the group in the placebo + MTX group.

Since treatment with infliximab incurs a huge economic burden, every patient on treatment often asks the question as to when to stop the therapy? Studies on infliximab therapy in patient with early RA show that infliximab can just be given as induction therapy to induce remission. Followup study of the group 4 of the BeST study who received infliximab 3mg/kg in combination with MTX 25mg/week showed that 56% patients had persistent low disease activity (DAS  $\leq$  2.4) for at least 6 months and infliximab was tapered and discontinued. In these patients low disease activity was maintained while the MTX dosage was tapered to 10mg/week. The response with a MTX median dose of 10mg/week

*Table I. Biologics for the treatment of RA*

<b>Biologic</b>	<b>Mechanism of action</b>	<b>Molecule</b>	<b>Route and Dose of administration</b>
Infliximab	TNF inhibitor	Chimeric (human-murine) IgG1 anti-TNF- $\alpha$ antibody	Intravenous infusion 3mg/kg at 0, 2 and 6 weeks. Then after every 8 weeks.
Etanercept	TNF inhibitor	Recombinant soluble p75 TNF receptor: Fc fusion protein	Subcutaneous injection 50mg every week
Adalimumab	TNF inhibitor	Recombinant humanized monoclonal anti-TNF- $\alpha$ antibody	Subcutaneous injection 40mg every week
Golimumab	TNF inhibitor	Recombinant humanized monoclonal anti-TNF- $\alpha$ antibody	Subcutaneous injection 50mg every month
Certolizumab	TNF inhibitor	Recombinant pegylated humanized monoclonal anti-TNF- $\alpha$ antibody	Subcutaneous injection 200-400mg every 2-4 weeks
Anakinra	IL-1 receptor antagonist	Synthetic form of the human IL-1 receptor antagonist	Subcutaneous injection 100mg/day
Tocilizumab	IL-6 receptor antagonist	Human monoclonal antibody to IL-6 receptor	Intravenous infusion 4-8mg/kg every 4 weeks
Rituximab	Anti-CD20	monoclonal antibody against CD20	Intravenous infusion 1000mg at 0 and 2 weeks
Abatacept	Selective co-stimulation modulator	Recombinant fusion protein of CTLA 4, is used therapeutically to block CD80-mediated or CD86-mediated co-stimulation and activation of T cells	Intravenous infusion 500-1000mg at 0, 2 and 4 weeks, followed by maintenance every 4 weeks

was evident even after 2 years.

Serum antibodies to infliximab called human antichimeric antibody (HACA) were detected in 17% of all infliximab treated patients. However higher doses of infliximab and concomitant MTX treatment can lead to lower incidences of serum antibodies to infliximab.

**2) Etanercept:** The efficacy of etanercept has been documented in two RCTs, the TEMPO trial and ERA trial with improvements in clinical disease activity and laboratory parameters. The Early Rheumatoid Arthritis (ERA) clinical trial is a landmark study in the treatment of RA<sup>4</sup>. It provided proof that biologic monotherapy specifically targeted to inhibit a single cytokine and introduced early in disease could profoundly interrupt the natural history of this disease. Etanercept treatment was associated with a nearly ten-fold reduction in the rate of anticipated radiographic progression over twelve months by comparing the actual to the calculated baseline rate of progression. At 24 months, 72% patients receiving 25mg etanercept met ACR20 response compared to 59% receiving MTX.

The Trial of Etanercept and Methotrexate with Radiographic and Patient Outcomes (TEMPO study) is a 3-year double-blind study that compares the combination of etanercept and MTX with either etanercept monotherapy or MTX monotherapy in patients with active RA in whom previous treatment with a DMARD other than MTX had failed<sup>5</sup>. Patients with RA were treated with etanercept (25 mg subcutaneously twice weekly), oral MTX (up to 20 mg weekly), or combination therapy with etanercept plus MTX through a second year, in a double-blinded manner. A total of 503 of 686 patients continued into year 2 of the study. The ACR20, ACR50, and ACR70 responses and the remission rates were significantly higher with combination therapy than with either monotherapy.

**3) Adalimumab:** This is the first fully humanized monoclonal antibody to TNF- $\alpha$ . It has also been found to inhibit the progression of structural joint damage, reducing signs and symptoms and also improves physical function of patients with active RA<sup>6</sup>.

**4) Certolizumab:** This molecule a humanized, pegylated TNF- $\alpha$  antibody fragment has a long half-life, rapid onset of action. It has a potential advantage over the other TNF- $\alpha$  inhibitors because it is shown to yield similar ACR20 responses as other TNF inhibitors but demonstrate

a more rapid acquisition of ACR 50 and 70 responses<sup>7</sup>. In keeping with other TNF inhibitors, certolizumab inhibited radiographic progression at 52 weeks by 86% using a lyophilized formulation. Studies show that radiographic inhibition was achieved as early as in 1 week in patients not having achieved an ACR20 response.

**5) Golimumab:** Golimumab is a fully human monoclonal antibody to TNF, approved by the US FDA for the treatment of RA in April 2009. Being a fully human monoclonal antibody directed against TNF, golimumab resembles adalimumab. The efficacy and safety of golimumab in RA were evaluated in four RCTs. The ACR responses were achieved by significantly higher number of patients on golimumab and MTX than on MTX alone. Golimumab has been found to be efficacious in MTX-naïve patients with early active RA, in patients with active RA despite MTX therapy and it reduced the signs and symptoms of RA in patients with active disease who had previously received one or more TNF $\alpha$  inhibitors<sup>8</sup>.

#### B cell depletion therapy

**Rituximab:** is a chimeric human/mouse monoclonal antibody directed at the CD20 antigen expressed on mature-B and pre-B cells. It specifically depletes CD20+ B cells via several mechanisms. The rationale for use of rituximab in treatment of this disease comes from the fact that B cells have several functions in disease pathogenesis, including antigen presentation, autoantibody and cytokine production.

Rituximab is indicated in patients who had previously failed to previous TNF inhibitor therapy. In the phase IIb (DANCER) and phase III (REFLEX) trials rituximab has shown efficacy in both clinical and laboratory parameters<sup>9,10</sup>. It is used in a dosage of 1000mg on day 1 and day 15, premedicated with 100mg of methylprednisolone. Remission of disease activity has been found as long as 18 months with very few patients requiring additional therapy. Rituximab depleted peripheral CD20+ B cells without decreasing the mean immunoglobulin levels. In all trials, B cell depletion happened rapidly and completely, as assessed by CD19+ cell counts. But disease activity has been seen to recur after B cell repopulation, thus necessitating retreatment.

#### Selective co-stimulation modulator

**Abatacept:** a selective costimulation modulator, inhibits T cell activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a costimulatory signal necessary for full activation of T cells.

Activated T cells are implicated in the pathogenesis of RA and are found in abundance in the rheumatoid synovium.

Clinical trials of abatacept in patients with active RA, has shown that it is effective in inducing major clinical response, inhibiting radiological progression and improving physical function in patients with active RA who have had inadequate response to DMARDs or failure to another TNF inhibitor<sup>11</sup>. Abatacept has also been compared to infliximab. At 6 months similar clinical responses were noted and fewer adverse events were noted with abatacept. Abatacept may be used as monotherapy or concomitantly with MTX. Combination of abatacept with another biologic is not recommended.

### Interleukin -6 receptor blocker

**Tocilizumab:** is a humanized monoclonal antibody that targets the IL-6 receptor. Clinical studies have shown that tocilizumab not only has beneficial effects on joint inflammation but also on the systemic manifestations of RA like fatigue and anemia and rapid decreases of acute phase proteins like CRP, ESR and serum amyloid A. In the AMBITION trial it was shown that 70% patients with active RA on tocilizumab monotherapy achieved ACR20 responses at 24 weeks compared to 53% on MTX monotherapy. Remission (DAS-28 <2.6) was achieved by 34% patients on tocilizumab monotherapy compared to 12% patients on MTX. Tocilizumab can also prevent progression of radiological damage.

In a systematic review tocilizumab was found beneficial in decreasing RA disease activity and improving function<sup>12</sup>. Eight RCTs were included in this systematic review with 3334 participants; 2233 treated with tocilizumab and 1101 controls. Of the 2233, 1561 were treated with tocilizumab 8 mg/kg every four weeks. In patients taking concomitant MTX, compared to placebo, tocilizumab-treated patients were four times more likely to achieve ACR50, 11 times more likely to achieve remission, 1.8 times more likely to achieve clinically meaningful decrease in health assessment questionnaire scores. There were no statistically significant differences in serious adverse events. A significant increase in total, HDL and LDL cholesterol and triglyceride level was seen in the tocilizumab treated patients.

### Impact of biologics on clinical management of RA

Although there is evidence to show that biologics are effective in DMARD-naïve active early RA, biologics are typically initiated once a patient fails to respond to conventional DMARDs like MTX, sulfasalazine, hydroxychloroquine or leflunamide, because of the huge cost involved. The BeST

study clearly demonstrated that infliximab given early can impact the disease on the long term<sup>13</sup>. But because of their high cost not everybody can afford biologics. Thorough control of disease activity using combination DMARDs with a goal towards remission should be commenced once a patient is diagnosed. The COBRA trial showed that combination therapy begun early is superior over monotherapy<sup>14</sup>. If patients continue to show moderate to high disease on DMARDs then a switch to biologic (usually a TNF inhibitor) should be considered. If active disease prevails despite TNF inhibitor therapy, rituximab or abatacept could be considered. Recommendations from professional bodies are available to guide clinicians to choose the best therapy for their patients<sup>15</sup>.

1. Patients with RA who are DMARD-naïve, having poor prognostic factors (which includes functional limitation, extraarticular disease, RF positivity, positive anti-cyclic citrullinated peptide antibodies, or bony erosions by radiography) with moderate to high disease activity should be started with combination DMARD, irrespective of the duration of the disease
2. TNF inhibitor is recommended in early RA, if high disease activity was present for 3 months (on DMARD) with features of both a poor prognosis and an absence of barrier related to treatment cost
3. In intermediate-duration and longer-duration RA, use of the TNF inhibitors is recommended in patients with moderate disease activity and features of a poor prognosis, for whom prior MTX monotherapy led to an inadequate response, and for patients with high disease activity, irrespective of prognostic features
4. The TNF inhibitors or rituximab or abatacept is also recommended in patients for whom prior combination therapy with MTX, or if sequential administration of other nonbiologic DMARDs led to an inadequate response with at least moderate disease activity irrespective of prognostic features.

Overall there is no data to suggest superiority of one biologic over another in RA. The TNF inhibitors (infliximab, etanercept and adalimumab) are the most commonly used in clinical practice. Etanercept and adalimumab offers the advantage of self administered subcutaneous injection. The TNF inhibitors, rituximab, abatacept and tocilizumab all give better results when used in combination with MTX.

### Adverse effects

Infections are serious potential side effects of any drug that modifies the immune response. The TNF inhibitors are

particularly associated with reactivation of tuberculosis. Prior to initiating biologics all patients should be screened for latent tuberculosis. The current practice is to get a tuberculin test and a chest radiograph. A positive tuberculin skin test warrants antituberculosis prophylaxis. Patient with suspicious chest radiograph should undergo a CT chest.

Patients should also be evaluated for other preexisting infections like chronic hepatitis B and chronic hepatitis C. TNF inhibitors should be avoided in the presence of chronic infections. Since most patients are on concurrent MTX, blood counts and LFT should be monitored from time to time.

Based on experience from hematology practice rituximab does not appear to increase risk of tuberculosis. Prolonged suppression of the immune system may allow for reactivation of slow viruses such as the JC virus. Cases of progressive multifocal encephalopathy have been reported in patients with SLE treated with rituximab. The risk of lymphoma in patients receiving biologics cannot be ascertained since there is a known association between lymphoma and severe

RA. These agents are best avoided in patients with a known history of malignant disease. Infliximab is associated with excess mortality when used to treat patients with heart failure. Therefore infliximab is a contraindication in heart failure.

## CONCLUSIONS

Biologics agents are important advancement in treatment of various Rheumatic diseases including Rheumatoid Arthritis. These are the most effective drugs available today for treatment of this painful, chronic disabling disease. Many Biologics agents have been developed to act on particular arm of Immune inflammation, but in this country, maximum experience are available with Anti TNF agents -Infliximab, Etanercept & Anti B cell agent Rituximab. Tocilizumab & Abatacept are relatively new agents. Although these agents are most effective molecules for treatment of Rheumatoid Arthritis, the prohibitive cost remains the matter of concern. Author has long experience of using these agents since 2002.

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