Drug Update

Biologics in the Management of Rheumatoid Arthritis

Vivek M Bhalerao*

Abstract:

Improved understanding of pathogenesis of Rheumatoid Arthritis(RA), better imaging techniques like MRI and newer modalities of treatment like Disease modifying anti rheumatic drugs(DMARD) and now the management of the disease by the biologics has vastly improved the outcome of the disease as compared to the prebiologics era. From 1990s various biologics have been use either alone or in combination with DMARDs. Although biologics have shown to be clearly beneficial in the treatment of Rheumatoid arthritis, the need for careful monitoring and infections cannot be overlooked. Biologics can be used safely in patients who are not responding to DMARDs or cannot tolerate DMARDs. But till date clinical trials have shown combination of Methotrexate (MTX) with biologics is clearly more effective than monotherapy. Only Tocilizumab has been shown to be more effective as a monotherapy than Methotrexate in certain population with RA.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic multisystem, autoimmune, inflammatory disorder which is characterized by synovial inflammation, cartilage damage, bony erosions which finally leads to joint destruction and considerable morbidity. It is important to diagnose and treat the condition at an early stage before bony erosions occur. The main stay of the treatment remains the use of NSAID, steroids, DMARDs and physiotherapy. From 1990 biologics have been used in the management of RA.Biologics are the therapeutic agents that inhibit the action of various cytokines, cellular activation and inflammatory gene transcription by various mechanisms. They are produced by the use of biotechnology[1,2].

The most common hypothesis postulated for RA is some unidentified antigen probably infection or other stimulus binds with the dendritic cells and macrophages which then migrate to lymph nodes and stimulate CD4 +T lymphocytes. These cells migrate to joints. They produce inflammatory mediators, which stimulate macrophages, monocytes, fibroblasts and chondrocytes. Activated cells release various cytokines like Tumor necrosis factor alpha(TNF alpha) ,lnterluekin 6 (IL- 6) ,IL-15 and IL-18 which in turn stimulate B cells and nutrophils .B cells secrete auto antibodies like Rheumatoid factor and CCP.All this results in marked inflammation ,synovitis, bony erosions and cartilage damage.

Mechanism of action

Biologics are therapeutic agents that act by inhibiting the cytokines, cellular activation and inflammatory gene transcription by various ways. Biologics target the various parts of immune system. Most of the biologics act by inhibiting the mechanism of TNF-alpha e.g. Etarnacept, Infliximab, Adalimumab, Golimumab & Certolizumab. Ankinara act by blocking the action of IL-1 whereas Tolizumab act as IL-6 receptor antagonist. Rituximab act by depleting CD20 + B cells by various mechanisms. Abatacept causes blockage of CD80 or CD86 mediated Co stimulation and activation of T-cells. Therefore all the biological agent act by blocking at some stage of inflammation and causes reduction of joint inflammation and reduces the morbidity in RA[3,4,]. They also reduce the levels of inflammatory markers such as ESR & CRP.

Biologics used in RA- In late 1990s biologics changed the expectations for patients with RA. Patients with RA related pain and inflammation had a new and better way to control the condition. The TNF alpha inhibitors Etanercept, Infliximab and Adalimumab are used most commonly[5,6]. Recently Golimumab and Certolizumab have also been approved for use.

TNF alpha Inhibitors

Infliximab- It is chimeric (human murine) IgG 1 anti TNF alpha antibody which is used in combination with methotrexate in RA. The efficacy was proved in ATTRACT trial.

Dose- IV infusion 3mg/kg at 0, 2 and 6 weeks and then every 8 weeks.

Adverse Reactions - Anaphylactic reaction, Bacterial infection like pneumonia, Reactivation of latent TB or fungal infections & optic neuritis can occur. There may be worsening of heart failure.

Eternacept- It is a dimeric fusion protein consisting of

* Consulting Physician,Nagpur
Address for correspondence
V. M. Bhalerao
email: vivek_bhalerao@yahoo.com

soluble P-75 THF receptor type 2 and Fc portion of human IgG 1. It has a half life of 4-8 days. It causes reduction in joint swelling, reduces ESR & CRP[8].

Dose- It is given subcutaneously 50mg weekly.

Adalimumab- It is recombinant humanized monoclonal anti TNF antibody. It is given as a subcutaneous injection 40mg weekly. Side effects include injection site reaction and risk of infections.

Golimumab- It is an anti TNF alpha monoclonal antibody indicated in moderate to severe RA approved by FDA. The dose is 50 mg subcutaneous injection once a month. Side effects include Upper Respiratory Tract Infection & injection site reactions were often seen. Golimumab has an important role in patients who have failed to respond to other anti TNF alpha blocking agents and can be given once a month with less side effects.

Certolizumab Pegol(CGP)- FDA approved this drug on April 13th 2009. It is a humanized monoclonal antibody with polyethylene glycol moiety. Dose is 400 mg subcutaneously followed by 400 mg at week 2 and 4 then 400 mg every month.

IL-1 Antagonists

Ankinara- It is recombinant form of naturally occurring IL-1 receptor antagonist. It has mild clinical efficacy. However it is used most commonly in neonatal inflammatory disease.

Dose- It is given as subcutaneous injection 100mg daily.

IL-6 Antagonists

Tocilizumab- It is a humanized anti interleukin IL-6 antibody that specifically inhibits the action of IL-6. It also causes bone resorption by osteoclast activation. It is given as an IV infusion 4-8 mg/kg every 4 weeks. It is shown to increase the LDL levels. It can also raise the liver enzymes.

Selective Co Stimulation Modulator

Abatacept- It is recombinant protein made by fusing the fragment of Fc domain of IgG with extracellular domain of T-cell inhibiting receptor CTAL4. It blocks the CD80 or CD86 mediated co stimulation of t cells.

Dose- It is given iv infusion 500-1000 mg at 0-2 and 4 weeks followed by maintenance dose every month.

B cell Targeted Therapy for RA

Rituximab- It is a humanized mouse monoclonal antibody directed against CD20 antigen on B cells. It depletes the B cells. It is advocated by FDA for use in RA not responding to other biologics and DMRADs.

Dose- It is given in RA as 1000mg infusion at 2 weeks interval and repeated every 16-24 weeks.

Adverse Reaction- Allergic reactions common during 1st infusion. Patient may complain of dizziness, headache, chest pain, breathlessness. Patient should be monitored carefully. It is safe to give iv methyl prednisolone and antihistaminic before infusion.

Late reactions include pancytopenia, reactivation of hepatitis B, sepsis and worsening of heart failure.

Recommendation for treatment with Rituximab

1) Patient should have active disease, defined as DAS 28>3.2 OR SDAI>11 (simplified disease activity index).
2) Patient is not responding to TNF alpha and DMARDs.
3) Screening for hepatitis B is mandatory.
4) It is contraindicated in patients who have allergy or heart failure.

Indication of Biologics in RA

1) Established severe RA.
2) Persistent symptoms and signs of poorly controlled active disease defined as 6 or more tender or swollen joints or DAS 28 score more than or equal to 3.2.
3) Failed adequate therapy with two standard DMARDs of which MTX is one. DMARDs including methotrexate should have been given 3-6 months with at least 2 months of standard target dose of methotrexate (25mg per week).

It has been recommended to combine TNF alpha inhibitors with methtrexate for superior efficacy and improved radiological outcome[9,10,11].

Side Effects

1) The risk of infection increases with biologics. Reactivation of latent TB has been observed in many patients. Tuberculin skin testing should be done before starting the therapy.
2) Biologics increases the risk of opportunistic and fungal infections.
3) Lymphoma has been assosciated in some cases.
4) Demyelination disorders and injection site reactions can occur.
5) Worsening of heart failure has been noted in some cases.

Laboratory Monitoring

Before starting the therapy following tests should be done.

1) ESR, CRP, CBC, LFT and KFT.
2) Tuberculin Test
3) Hepatitis B and C serology

4) HIV screening
5) X-ray chest
6) ANA , anti ds DNA, anti CCP and RF (rheumatoid factor)

These tests can be checked every 3 months after initiation of the therapy.

Newer Biologics in Future[12]

1) Ocrelizumab- It is a newer anti CD20 monoclonal antibody currently in phase 3 trials.
2) Denosumab- It inhibits RANKL causing decrease osteoclast activity currently in early phase 2 trials.
3) Tofacitinib- It is a new oral biologic which is a inhibitor of janus kinase enzyme. It has been approved by FDA in dose of 5mg twice daily in RA[7].

Conclusion

Although the cause of RA is still not known improved understanding of pathogenesis has opened doors for innovative therapy. TNF alpha blocking agents, IL-1 and IL-6 blocking agents have proved to be as effective as DMARDs. By targeting the special molecules involved in the pathogenesis they may be more beneficial and less toxic in the long term management[13]. However the major deterrent is cost and risk of infections. In future patients with RA will see more and more use of biologics.

References-

1) Shankar S ,Honda R.Biologic agents in RA J.of post graduate medicine 2004,50,293-9.
2] Weaver et al Impact of new biologics in the treatment of RA. Rheumatology Oxford june 2004, 43.
3] Ved chaturvedi ,Molly thabab, Biologics in RA JAPI india.org medicine update 2011/50.
4] S.P.Venkatraman,S.Sidhu.\,P.Pandhi, Malhotra Efficacy of biological in the treatment of RA ,Pharmacology 2009,83, 1-95
5] Sharma PK,Hota D,Pandhi P Biologics in RA JAPI ,2004 , March 52,231-6 ,
6] Singh j.a.,Christanan R,Wells g.Biologics for RA, an overview of Cochrane reviews , Cochrane database sept.rev2009
7] NEJM, Placebo controlled trial of Tofacitinib monotherapy in RA ,2012,367.495-507
8] John bathon Comparison of etarnacept and mtx in patients with early RA.,NEJM,2000,nov.1586-1593 .
9] L.Sizova Approach to treatment of early RA,British j.of clinical pharmacology 66,aug 2008.
10] Choy E.H,Panaryl G.S Cytokine pathway and joint inflammation, NEJM,2001,344 [12]907-916.
11] Ruderman E, Siddhartha T, RA fact sheet, American college of Rhuematology 2008.
12] Maini R.L.,Taylor P.C. Anti Cytokine therapy for RA , annu.rev.medicine 2000,207-29.
13] Keyston E.C,Genovese M.C.Goforward study,Ann.of rhuematology diseases,2009, 68 [6] 789-796.