Review Article

Emerging Treatment Of Rheumatoid Arthritis - Use of Biologic Agents

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Abstract

Until now there no curative treatment for Rheumatoid arthritis. As the pathogenesis of the disease is now greatly unveiled, and role of many immunologic key-molecules have been understood, new agents called 'biologic agents' are discovered, which are being used as therapeutic agents to target the key-molecules with great success. Remarkable results have been achieved (even cure in significant number of cases,when treatment started early) when some of these agents are used in combination with Methotrexate. Notable among these agents are anti-TNF agents, IL-1 and IL-6 inhibitors, B-cell antagonists (e.g. Rituximab), T-cell blocking agents, RANKL inhibitors (denosumab) etc. The main obstacle to their use is treir high cost, for which reason they out of reach of general people.

Key words : *Rheumatoid, Biologics, Anti-TNF.*

Introduction

Rheumatoid arthritis is a complex immune mediated disease for which there is no known cure. Both males and females suffer, 75% are women[1]. About 50% patients become disabled within 10 years, and survival is reduced[2]. Fortunately, in the last few years a shift of strategy of treatment towards early institution of DMARDS & recently, new classes of drugs known as "Biologics" or Biological agents have shown great promise in long term outcomes. Aspirin was the mainstay of therapy once. When Steroids were introduced in the treatment of the disease, it looked like a miraculous drug, but its use has been restricted because of multiple side-effects. Introduction of traditional DMARDs, specially Methotrexate (MTX) proved effective in reducing symptoms and disabilities, as well as slowing or halting radiographic changes[3-4]. But it has also limitations, quest for ideal drug continues.

Although the exact triggering agents have not been identified, over the past few years there have been great advances in understanding the role of auto-immunity , the relation between immune-system and Rh. Arthritis, the role of the Cytokines in the causation of Rheumatoid arthritis & mechanism of joint damage. These great advances in knowledge have led to the introduction of novel but very effective agents called the BIOLOGIC agents in the treatment of Rheumatoid arthritis.

The BIOLOGIC agents, also known as the ' Biologic response modifiers' are therapeutic agents that have the potential to inhibit the behavior of the cytokines, cellular activation and inflammatory gene transcription by various means[5]. They include monoclonal antibodies, soluble cytokine receptors and natural antagonists[6]. It was Maini et al who for the first time elucidated the key role of the TNF-alfa in the pathogenesis of the disease and led to the discovery of the anti-TNF agents[7]. Other key proinflammatory cytokines such as IL-1, IL-6 have been targetted with promising results. With these new targets of therapy treatment of Rh. Arthritis has been boosted with new promise.

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New targets of therapy:

Chronic and persistant inflammation of the synovial lining of the joint capsule due to complex immune mechanism is the cause of Rheumatoid arthritis. Over the past decade there has been great advancement in the understanding of the role of auto-immunity & the disease. Stated in a simple way, the current pathogenesis model involves - unidentified antigen interacting with antigen presenting cells (APCs) , such as mature CD20+ B-cells, which communicate with T-cells(CD4+). Through co-stimulatory signals, CD4+ T-cells become activated leading to stimulation of monocytes, macrophages and synovial fibroblasts to produce inflammatory mediators such as TNF-alfa, IL-1, IL-6 all of which are key cytokines of inflammatory process. These cytokines, specially TNF-alfa recruits other cells to proliferate and release destructive metallo-proteinases[8], further promoting inflammation. These actions lead to the destruction of connective tissues, also drive receptor activated NF-KappaB ligand (RANKL) expression & osteoclast activation, leading to bone and cartilage destruction[9]. Large quantities of of these cytokines exist in the synovial fluid and tissues of the

patients with Rheumatoid arthritis[10].

Considering this huge role of the CD4+ T-cells, CD20+B cells, co-stimulatory signal for T-cell-APC interaction, the key role of the cytokines TNF-alfa,IL-1, IL-6 researchers tried to find out agents which would target & which might antagonize or inactive them, thus halting the whole immunological process causing the initiation & persistence of the inflammatory process in Rheumatoid arthritis. These agents are together known as the BIOLOGIC agents. In fact, many studies have shown that many of these agents have very promising role in controlling Rheumatoid arthritis, although is does not constitute a permanent cure, as the disease returns after a variable period when treatment is stopped. They are much more effective than the traditional DMARDS. Patients with early disease respond much more than the patients with long standing disease, and in fact permanent remission has been achieved with anti-TNF agents in some patients11-12.

BIOLOGIC AGENTS (CURRENTLY USED & UPCOMING) :

IL-1 receptor antagonist :			
	Anakinra	-	available as KINERET
Anti- TNF alfa agents :			
	Infliximab	-	REMICADE
	Eternercept	-	ENBREL
	Adalimumab	-	HUMIRA
	Golimumab	-	Newly approved
	Certolizumab	-	Newly approved
IL- 6 inhibitor :			
	Tocilizumab	-	
B-Cell antagonists :			
	Rituximab	-	RITOXAN
	Ocrelizumab	-	Phase III developement
T-Cell co-stimulatory blocking agents :			
	Abatacept	-	ORENCIA
	RANKL	-	inhibitor
	Denosumab	-	Phase III development

To assess efficacy of Trials :

*ACR - American College Of Rheumatology Criteria[16]

There are many studies to asses the efficacy of the biologic agents as monotherapy, & as combination therapy with MTX,& as combination among the biologic agents agents. In clinical trials, outcome measures for disease are ACR 20,50,70. (American College of

medications, or to compare one trial to another trial18 & it has been widely used. ACR criteria measures improvement in tender joint counts and improvement in three of the following parameters:
- acute phase reactants
- patient assessment
- physical assessment
- pain scale
- disability/functional questionnaire.

Clinical trials report the percentage of study participants who achieve ACR20, ACR50, ACR70. for example, if a study reported that 55% of patients achieved ACR20. that means that 55% of patients in the study achieved a 20% improvement in tender or swollen joint counts as well as 20% improvement in three of the other five criteria. There are other ways to assess to measure efficacies of clinical trials - some trials use Disease Activity Score, (DAS score) which assesses disease activity by evaluating tender joints, swollen joints and patients own assessment on visual analogue scale. HAQ (Health assessment questionnaire) is used for measuring functional status one outcome- measure determines the extent of joint damage as assessed by X-rays. The most common scoring system is the Van der Heijde-modified Sharp score[17] which quantifies erosions and narrowing of joint space. There are also many other scores to measure the efficacies of trials.

Discussion about individual Agents :

IL- 1 antagonists :

This was the earliest approved biologic response modifier. a proinflammtory cytokine which has effects on cartilage degradation leading to damage as well as inhibiting repair, and it is a potent stimulus to osteoclast leading to bone erosion[18-19]. So, IL-1 inhibtors have significant role in altering course of RA when used alone or in combination with MTX. It is not commonly used since other agents show greater efficacy. However , it has better efficacy than the TNF- inhibitors in treatment of refractory adult-onset still's disease and systemic-onset juvenile R. arthritis[20-21].

Mechanism of action :

IL-1 is a17-kd protein mostly produced by monocytes and macrophages. IL-1 family consists of 3 structurally related proteins IL-1a, IL-1b & IL-1ra(receptor antagonist). IL-1a/1b acts on cell surface receptors type-I, & act as pro-inflammatory cytokines having effect on cartilage degradation leading to damage as well as inhibit repair, and it is a potent stimulus to osteoclasts leading to bone erosion, while IL-1ra act on same receptors but without signals-- thus it helps as an anti-inflammatory agent. So, inhibition of IL-1 inhibitors can singnificantly alter the course of RA when used alone or in combination with MTX.

Tumour necrosis factor Inhibitors :

TNF - alfa, cytokine central to the inflammatory cascade in RA - activates lymphocytes and leucocytes, stimulates elaboration of other cytokines, and is always found elevated in rheumatoid synovium.

Three agents are in use : ETANERCEPT, INFLIXIMAB, & ADALIMUMAB. Among the TNF -blocking agents, the first to be introduced was INFLIXIMAB (Remicade), followed by ETANERCEPT (Enbrel) and ADALIMUMAB (Humira). Infliximab (a chimeric monoclonal antibody) andAdalimumab (a fully human Anti-TNF antibody) are directed against TNF, while Etanercept is a construct of 2 TNF receptors (p 75) linked to the Fc portion of IgG 1, giving rise to an IgG-like molecule. Clinical trials have shown that all 3 agents have high efficacy in RA, where other agents including MTX has inadequate response. They can be used alone or in combination with MTX , but the combination has superior efficacy.[14-15] . After 12 months of Anti-TNF plus MTX compared to placebo plus Anti- TNF, all three agents show ACR* 20, 50, 70 responses in order of 60% versus 25%, 40% versus 10%, and 20% versus 10% respectively. Modified Sharp score are even more impressive,which means that these agents are vey effective in preventing joint damage as assessed by serial X-rays, out of proportions to their ability to reduce clinical signs and symptoms. Many other studies have shown that institution of these agents with MTX early in the course of treatment of RA has the highest efficacy, and far superior to treating with MTX alone.[11,12,22-24].

Newer anti-TNF agents :

Golimumab :

This is an newer anti-TNF agent approved by FDA (April 2009). It is found to be effective in cases of moderate RA, where other DMARDS including MTX have inadequate response[25] . It is also found to be effective where other TNF agents have failed. Patients who have discontinued previous anti-TNF therapy because of lack of effectiveness have significant response compared to placebo(39% versus 18%)[26]. Its is given in a convenient subcutaneous once a month dosing.

Certolizumab Pegol :

It is another anti-TNF agent, approved by FDA (May 2009). It is a humanised monoclonal antibody with a polyethylene glycol moiety that is thought to help limit complement or antibody-dependent cytotoxicity and allow for an extension of its half life. It is recommended to use as a monotherapy or combination therapy with DMARDS in severe RA. Studies have shown that they are very promising in the management RA and observed ACR benefit occurred as early as 1 week[27]. Side-effects were headache, hypertension, UTI, nasopharingitis, but tuberculosis and malignancy were not seen[28] .It comes in a prefilled syringe that should be protected from light.

Mechanism of action of the Anti-TNF Agents :

TNF-alfa is a soluble 17-kd trimeric protein that is produced mainly by monocytes and macrophages. It binds to TNF-alfa_receptors on a variety of target cells , setting up a signaling- cascade in that cell . there are two different types of TNF-receptors, the p75 and the p55, that are trans membrane proteins and activate different intracellular signal-transduction pathways. TNF receptor signaling occurs through two arms. One arm has death domain proteins which lead to apoptosis or programmed cell death, hence the name, tumor necrosis factor. The second and dominant signaling occurs through a series of kinases, leading to activation of nuclear-factor kappa B (NF-kB) that is a key trans- criptionfactor for activating genes involved in inflammation.[29] TNF-alfa tiggers production of other cytokines, induces endothelial adhesion molecules, stimulates collagenase and stromelysin, and stimulates osteoclast differentiation. That is why, blockade of TNF-alfa has a more global effects on inflammation than other cytokines.

Il-6 inhibitors (Tocilizumab):

Tocilizumab (ACTEMRA, Roche) is an important emerging treatment option in adult patients with moderate to severe form of RA. It is a recombinant humanized monoclonal antibody that acts as an IL-6 receptor antagonist..Intravanous Tocilizumab is effective and generally well tolerated as monotherapy or in combination with other DMARDS. Tocilizumab based therapy are consistantly more effective than placebo, MTX or other DMARDS.30-31 Notably, Tocilizumab is effective in long standing disease where anti-TNF therapy has failed. However, more data are needed to quantify its true effectiveness in case of moderate to severe RA. There was incidence of increased plasma Cholesterol level, decrease in absolute neutrophil counts and platelet counts in some cases as well as increase incidence of infections[31] .

B-Cell Antagonists:

Rituximab - B-cels are involved in multiple ways in immunological process. They serve as antigen presenting cells, can secret cytokines, and differentiate into antibody-forming plasmacells. Depleting or inhibiting B-cells has been shown to be effective in reducing symptoms & signs and halting progression of RA. One B-cell antagonist, RITUXIMAB, currently approved by FDA and in many countries, originally used for treatment of B-cell Lymphomas , has now been proved very effective in the treatment of RA, which are resistant to treatmet with MTX and the TNF-antaginists[32-33]. Although the therapeutic effects of the anti-TNF agents is promising there also still nonresponders. Many of these cases have been reported to respond to RITUXIMAB.

Ocrelizumab :

It is an humanized monoclonal antibody that is in early phaseIII trial[34]. It selectively targets CD+20 B-cells.

Mechanism of Action :

RITUXIMAB is a chimeric monoclonal antibody that binds to the CD+20 molecule on the surface of B-cells other than stem cells and pre-B lymphocytes, leading to removal of B cells from the circulation. This does not affect the plasma cells as they do not have CD+20 on their surface.

T-Cell Co-Stimulatory Blocked (Abatacept) (Orencia):

These agents interfere with the reactions between the antigen presenting cells and T-lymphocytes and thus affect early stages in the pathogenic cascade of events in RA. Abatacept is a fusion protein linking the extracellular domain of human cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) to the Fc portion of human IgG1. It works by competing for the binding between CD28 on T-lymphocytes and CD80/86 on antigen presenting cells. This is an important co-stimulatory signal that is important for T-cell activation. Blocking this activation by ABATACEPT results in turns down T-cell response. Additional effects are by decreasing the production of T-cell derived proinflammatory cytokines such as TNF.

It effective and recommended for use in patients who have inadequate response to either MTX or one or more of the TNF-antagonists[35-36].

Rankl Inhibitor : Denosumab

Thgisis a monoclonal antibody that binds to RANKL and thus prevents osteoclast development, activation and survival. It is in phase- III trial for treatment of osteoporosis. Trials are also underway for treatment of RA.[37]

Side-Effects of the Biologic Agents :

Because the biologic agents interfere with one or other component the immune system of the body, there is increased chance of infections.there is chance of reactivation of tuberculosis.[38-39] So, screening for TB may be justified before start of therapy with the TNF-agents. There are also some documentation of infections like atypical mycobacteria, histoplasma, nocardia, listeria, pneumacystis, candida, aspergillus, cytomegalovirus etc. As shown by different studies, Prolonged suppression of immunity may facilitate re-activation of slow virus infection like PML (progressive multifocal leucoencephalopathy)

There are occurrences of other demyelinating diseases with anti-TNF agents, all of them improved with discontinuation of therapy[40] . Cases of Lymphoma have been reported with TNF-agents[41] , but unlikely with Rituximab, as it is originally used to treat lymphomas. Exacerbation of chronic hepatitis B have been reported [42], although anti-TNF agents are safe in patients undergoing treatmet with interferon and ribavirin. Cases of drug induced Lupus have been reported.[43] Anti-TNF agents are reported to increase severity of Congestive heart failure and are not recommendedfor use.[44]

Other observed side-effects are local dermatologic reactions (injection site reactions),which is the commonest side-effect specially with self administered drugs.[43] Infusion reactions are also reported in asignificant number of patients.Rare cases of bone-marrow aplasia have also been reported with Infliximab[45]

So, side effects are relative ly rare and can be further reduced with more vigilant use of theagents. There seems to be some beneficiary side effects of the biologic agents. Evidences suggest that they may reduce risks of cardiovascular diseases[46] & strokes. They also reduce death from RA. Infliximab and etanercept have been shown to reduce insulin resistance[47] .

Future Trends & Conclusion :

With the advent of the Biologic DMARDS, significant progress has been made in the management of moderate to severe cases of RA where traditional treatment with the NSAIDS, DMARDS, Steroids etc have inadequate or failed response. As mechanism of causation RA is not driven a single factor or a single cytokine, it is highly unlikely that it could be cured by a miracle drug. However,there are numerous other biologic agents are under study and at different stages of evaluation. Many of them include newer version of existing targets, many new molecule. They include TNF-a converting enzyme, new recombinant IL-1 agents (IL_1RII, IL-1Trap, inhibitor of IL-1 converting enzyme, monoclonal antibody to IL-6 receptor, IL-15(HuMax-IL-15) , CD2 receptor. Other targets includeCD22, CD40-CD40L, CD28-CTLA4-B7, anti-BLyS (B-lymphocyte stimulator), And many others are under study.

An important issue for the patients of the third world countries and even for some patients of the developed countries is the high costs of these exellent agents. So, for the patients who can not afford,the choice is the use of the traditional DMADRS, if needed , combination them, titrating their use to get optimum response. For those who can afford , early institution of new Biologic agents, preferably in combination with MTX may even cure the disease.

Bibilography :

01. Ruderman E, Siddharth T. Rheumatoid Arthritis fact sheet. American College of Rheumatology; 2008.

02. Pincus T, Brooks RH, Callahan LF. Prediction of long term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. Ann. Intern. Med 1994;120:26-34

03. Young A, Koduri G, Batley M, Gough A et al. Mortality in Rheumatoid Arthritis Increased in early course of disease, inischemic heart disease and pulmonary fibrosis. Rheumatology (Oxford) 2007; 46: 350-7.

04. Madhok R, Capels H. Outstanding issues in the use of diseases modifying agents in Rheumatoid Arthritis. Lancet 1999; 353 : 257-258.

05. Shanker S, Handa H. Biological agentg in Rheumatoid arthritis. J post-graduate Med 2004; 50:293-9.

06. Shanahan JC,Moreland LW, Carter RH. Upcoming biologic agents for the treatment of rheumatic diseases. Curr Opin Rheumatol 2003; 15: 226-36.

07. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, et al. Therapeutic efficacy of multiple intravenous infusion ofanti-tumor necrosis factor alfa monoclonal antibody cobined with low dose weekly Methitrexate in rheumatoid arthritis. Arthritis Rheum 1998; 343:1594-602.

08. Shinju M, Nagai Y, Isayama T,Naono T, Nobunaga M, Nagai Y.The effects of cytokines on metalloproteinase inhibitors(TIMP) and collagenase production by human chondrocytes and TIMP production by synovial cells and endothelialcells. Clin Exp Immunol 1993; 94: 145-9.

09. Choi EH, Panai GS, Cytokine pathways andjoint inflammation in Rheumatiod arthritis. N Engl J Med2001;344:907-16.

10. Chikanza IC. Kingsley G, Panayi GS. Perioheral blood and synovial fluid monocyte expression of interleukin 1a during active rheumatoid arthritis Rheumatol1995;22:600-6.

11.Genovese MC, Bathon JM, martin RW, Fleishman RM, Tesser Jr, Schiff MH,etal. Etenercept versus Methotrexate in patients with early rheumatoid arthritis: two year radiographic and clinical outcomes. Arthritis Rheumm 2002;46:1443-50.

12. Gold blatt F, Isenberg DA. New therapy for Rheumatoid arthritis. Clin exp Immunol. 2005;140(2):195-204

13. Lipsky Pe, Van der Heijde DM, St clair EW, Furst DE, Breedveld FC, Kalden JR, et al.Anti-tumor necrosis factor trial in Rh Arthritis with concomitant therapy study group. Infliximab and Methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor Trial in Rh Arthritis with concomitant study group. N Engl J Med 2000;343:1594-602.

14. Klareskog L,van der heijde d, de jager JP, Gough A , Kalden J, Malaise M, et al. TEMPO(Trial of Etenercept and methotrexate with radiographic patient outcomes) study investigators. Therapeuticeffect of the combination of etenercept and methotrexate compared woth each treatment alone in patients with Rheumatoid arthritis; doble blind randomized contolled trial. Lancet2004;363:675-81.

15. Genovese MC, Kremer JM.Treatment of rheumatoid Arthritis with Etenercept. Rheum Dis Cli North Am2004;30:311-28.

16. 7.Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, et al. Therapeutic efficacy of multiple intravenous infusion ofanti-tumor necrosis factor alfa monoclonal antibody cobined with low dose weekly Methitrexate in rheumatoid arthritis. Arthritis Rheum 1998; 343:1594-602

17. Felson DT,Anderson JJ, Boers M, bombardier C, Furst D, Goldsmith C, et al.American College of Rheumatology-Preliminary definition of improvement in Rh Arthritis. Arthritis rheum1995;38:727-35.

18. Van der heijde Dm, Van,t Hof M, van Rief PZ, van de putte Lb. development of disease activity scoring basedon judgement in clinical practice by rheumatologists. J Rheumatol 1993;20:579-81

19. BresnihanB, NewmarkR,Robbins.S, GenantHK. Effects ofAnakinra monotherapy on joint damage in patients with Rh Arthritis. Extension of a 24 week randomized placebo - controlled trial. J Rheumatol 2004; 31: 1103-11

20. Tesser J et al. Anakinra, arecombinant human IL-1 receptor antagonist (r-metHuIL-1ra) in patients with Rheumatoid A ; alarge international , multicentre placebo-controlled trial. Arthritis Rheuml 2003.;48: 927-34.

21. Fitzgerald AA, Leclarq SA, Yan A, Homic JE, Dinarello CA. Rapid response in patients with refractory adult-onset still,s disease. Arthritis Rheumatol 2005;52:1794-803.

22. Verbsky Jr, White AJ,. Effective use of recombinant IL-1 receptor-antagonist anakinra in therapy resistant systemic onset juvenile rheumatoid arthritis. J Rheumatol 2004;31 2071-5.

23. Felson DT,Anderson JJ, Boers M, bombardier C, Furst D, Goldsmith C, et al.American College of Rheumatology-Preliminary definition of improvement in Rh Arthritis. Arthritis rheum1995;38:727-35.

24. Van der heijde Dm, Van,t Hof M, van Rief PZ, van de putte Lb. development of disease activity scoring basedon judgement in clinical practice by rheumatologists. J Rheumatol 1993;20:579-81

25. Moreland LW, Schiff MH, baumgartener SW, Tindall EA, Fleishmann RM, Bulpitt KJ, et al. Etanercept therapy in Rheumatoid arthritis:A randomized controlled trial. Ann Intern Me4d1999; 130:478-86.

26. Van de putte LB, Atkins C, Malaise M, Sany J, Russel As, Van Riel PL,et al.Efficacy and safety of adalimumab as monotherapy in patients with Rheumatoid arthritis for whom previous disease modifying antireumatic drug therapy has failed. Ann rheum dis2004,63:508-16.

27. Smolen JS, Han C, Bala M, Maini RN, kalden JR, van der Heijde DM,et al.Evidence of radiographic benefit of treatment with infliximab plus methoptrexate in Rheumatoid arthritis patients who had no clinical improvement: adetailed sub analysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis Rheum2005;52:1020-30

28. Keystone EC, Genovese MC, klareskog L,et al. GO-FORWARD study. Golimumab, ahuman antibody to tumor necrosis factor-alfa given by monthly sub-cutaneous injections, in rheumatoid arthritis despite methotrexate therap[y:THE GO-FORWARD study. Ann Rheum Dis2009;68(6):789-796.

29. Smolen JS, kay J, doyle MK, et al.: GO-AFTER Study investigators. Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor alfa inhibitors (GO-AFTER Study): amulticentre, randomized, double-blind, placebo-contolled, phase iii trial. Lancet2009;374(9685):210-221

30. Keystone E, Heijde D, Mason D Jr, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexaqte in active rheumatoid arthritis : findings of a , fifty two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group study. Arthritis Rheum. 2008;58(11): 3319-3329.

31. Smolen J, Landew RB, Mease P et al. Efficacy and safety of Certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2study. A randomized controlled trial. Ann Rheum dis. 2009; 68(6): 797-804.

32. Bazzoni F, Beutler B. The tumor necrosis factor ligand and receptor families. N Eng J Med1996;334:1717-25.

33. Smolen Js, Beaulieu A, Rubbert-Roth A, et al.OPTION investigators. Effect of interleukin-6 receptor inhibition with Tocilizumab in patients with Rheumatoid arthtitis(OPTION study) : a double-blind, placebo-controlled, randomized trial. Lancet 2008;371(9617):987-997.

34. Genovese MC Mckay JD, Nosonov EL, et al. Interleukin-6 inhibition with Tocilizumab reduces disease activity in rheumatoid arthritis with inadequqte response to disease modifying antirheumatic drugs : tocilizumab in conbina with the traditional disease-modifying anti-rheumatic drug therapy study. Arthritis rheum 2008;58(10): 1968-2980.

35. Keystone E, Burmester GR, Furie R, Loveless JE, Emery P, cravets MW, et al Improved quality of life with Rituximab plus methotrexate in patients with active arheumatoid arthritis who experienced inadequate response to one or more anti-TNF alpha therapies. Arthritis Rheum2005;52:287.

36. Edward JC, Szczepanski L,Szechinski J,Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell targeted therapy with Rituximab in patients with rheumatoid arthritis. N Eng J Med2004;350:2572-81.

37. Genovese MC, Kaine JL, Lowenstein MB, et al; ACTION study group. Ocrelizumab. A humanized anti-CD20 monoclonal antibody, in the treatment of patients with Rheumatoid arthritis: Phase I/II randomized , blinded,placebo-controlled, dose-ranging study. Arthritis Rheum. 2008; 58(9): 2652-2661.

38. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, kremer J, et al.Abatacept for Rheumatoid arthritis refractoty to tumor necrisis factor inhibition. N Eng J Med 2005; 353: 1114-23..

39. Kremer JM, Westhovens R, leon M, Di Georgio E, Alten R, Steinfeld S, et al. treatment of Rheumatoid arthritis by selective inhibition of T-cell activation

40. Cohen SB, Dore RK, Lane NE, et al; Denosumab Rheumatoid Arthritis Study Group. Denosumab treatment effects on structural dsmsge, bone-mineral density, and bone turn over in rheumatoid arthritis: atwelve- month, multicenter, drandomised, double-blind, placebo-controlled, phase II clinical trial. Arthritis rheum. 2008;58(5): 1299-309.

41. Mohan AK, Cote , Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following use of Etanercept, a tumor necrosis factor inhibitor. Clin Infect. disease 2004;39: 295-9

42. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J,Schwieterman WD, et al. tuberculosis associated with infliximab, atumor necrosis factor alfa-neutralising agent. N Eng J Med 2001;345:1098-104.

43. Mohan N, Edwards ET, Cupps TR, Oliverio PJ, Sandberg G , Crayton H, etal.Demyelination occurring during anti-tumor necrosis factor alfa therapy for treatment of inflammatory arthritidis. Arthritis Rheum 2001;44:2862-9.

44. Ekstrom K, Hjalgrim H,brandt T, baeklund E, Klareskog L, ekbom A, et al. risk malignant lymphomas in patients with rheumatoid arthritis and their first degree realatives. Arthritis Rheum. 2003;48 :963-70.

45. Esteve M, Saro C, Gonzales- huix F, Suarez F, Forne M, Viver JM. Chr. Hepatitis B reactivation followinging infliximab therapy in Crohn<s disease patients: need for primaqry prophylaxis. Gut;2004; 53: 1363-5.

46. Devos SA, Van den Bossche N, De Vos M,Naeyaert JM. Adverse skin reaction toanti-TNF-alfa monoclonal antibody therapy. Dermatology 2003;206:388-90.

47. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. (Anti-tumor necrosis factor Therapy Against Congestive heart Failure Investigators) Randomised,double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis-alfa, in patients with modeate to severe heart failure: results of anti-TNF therapy Against Congestive Heart Failute (ATTACH) trial. Circulation 2003;107:3133-40.

48. Vdal F, FontanaR, Richart C, severe neutropenia and thrombocytopenia associated with infliximab. Ann Intern Med 2003;139: W-W63.

49. Jacobsson LT, Turesson C, Gulfe A, et al. Treatment with tumor necrosis fator inhibitors is associated with a lower incidence of first cardiovascular events in patients with Rheumatoid arthritis. J rheumatol 2005;32:1213-8.

50. Gonzales-Gay MA, De Matias JM, Garcia-Porrua C, Martin J, et al.Anti-tumor necrosis factor alfa blockade improves insulin resistance in patients with Rheumatoid arthritis. Clin Exp Rheumatol