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BIOLOGICS: ROLE IN RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis is an autoimmune disease which is chronic in nature and the exact etiology is unknown. Genetic and environmental factors disrupt the immune system which causes interaction between the T-cells and antigen presenting cells (APC). Biologic disease-modifying antirheumatic drugs (DMARDs) are biologic response modifiers that target a particular protein that contributes to rheumatoid arthritis (RA). Biological agents are anti-TNF agents, abatacept, rituximab, tofacitinib citrate, anakinra, tocilizumab and some under trial drugs. Various studies have shown that efficacy of biological DMARD+ conventional synthetic DMARD combination is more effective than only biological DMARD treatment. Various adverse effects are seen with biologics caused due to suppression of the immune system. Biologics are given according to 2013 EULAR (EUROPEAN LEAGUE AGAINST RHEUMATISM). The use of biologics is determined by measuring the disease activity with certain tools like Simplified Disease Activity index (SDAI) and Clinical Disease Activity Index (CDAI).

KEYWORDS: anakinra, anti-TNF agents, CDAI, EULAR, infusion reaction, SDAI, tocilizumab.

INTRODUCTION

Rheumatoid arthritis is an inflammatory disease which is chronic in nature and the exact etiology is unknown. The incidence of this disease increases from 25 to 55 years and plateaus till 75 years. In India 0.1-0.4 percent of population suffer from this disease. It is a systemic disease where both articular and extra articular manifestations are seen. The articular manifestations are characterized by inflammation of joints (small joints of hands and feet),

tendons and bursa. There is also early morning stiffness seen lasting for more than one hour. The common joints involved are wrists, proximal interphalangeal joints (PIP) and metacarpophalangeal joints (MCP). The extra articular manifestations are fever, fatigue, weight loss, nodules, anemia, pleuritis, pericarditis, myocarditis, interstitial nephritis, episcleritis, xerostomia, myositis, and osteoporosis. Various genetic factors proposed to cause rheumatoid arthritis (RA) are HLA-DRB1, HLA-DR4, PTPN-22, PAD 14, STAT4, CD244. Allelic variations of HLA-DRB1 gene which codes for MHC II molecule is most commonly responsible in RA. Mutation of the PTPN22 gene causes abnormal selection of T and B cells. PAD14 gene is responsible for causing rheumatoid arthritis among the Asian population. Some environmental factors responsible for triggering the disease are tobacco smoke, infections(Epstein Barr virus parovirus and mycoplasma) and periodontal disease (Porphyromonas gingivalis)[1,2].

IMMUNOPATHOGENESIS

Genetic and environmental factors disrupt the immune system which causes the interaction between the T-cells and antigen presenting cells (APC). The T-cells get involved due to loss of self-tolerance or due to self-reactivity (abnormal central selection). The APC cells are basically the MHC-II in nature which have toll like receptors and recognise microbial infections. The first interaction is between the T-cell receptor (TCR) and the MHC-II molecule which causes activation of T-cell but a single activation is not enough. A second signal for activation is delivered after the interaction of CD28 and CD80. Activation of T-cells results in three fate lines i.e the T-helper cells, T-effector cells and T-17 cells. The T-helper cells interact with the B-cells and plasma cells through the CD-40 ligand and release autoantibodies like rheumatoid factor and anti-CCP(anti cyclic citrulline peptides) autoantibodies. These autoantibodies cause increase bone, joint and cartilage destruction. Most specific is anti-CCP (cyclic citrulline peptides) antibodies. Citrulline is a post translational modification that occurs on arginine residues which is seen on proteins and peptides. Citrullation is a normal physiological process but however in RA, autoimmune response develops against citrullated peptides which form anticitrullated peptide antibodies and they are detected by anti-CCP antibodies. T-effector cells release IFN-γ, IL-17 which stimulates the macrophages and release various mediators like TNF-α, IL-1, IL-17, IL-18. TNF-α plays various roles in the bone destruction by upregulating adhesion molecules on endothelial cells, promoting influx of leucocytes, activating synovial fibroblast, stimulating angiogenesis, promote pain receptor pathways and activation of osteoclast. Expression of

wnt causes bone formation through activation of osteoprogenator (OPG) cells. TNF-α causes increases expression of dickkof-1(DKK1) which inhibits wnt pathway and as a result osteoblastic activity is inhibited. It also activates pre-osteoclasts cells which acquires RANK-L ligand from stromal cells and forms mature osteoclast. The osteoclast finally releases cathepsin which causes joint destruction. Fibroblast which also releases matrix metalloproteases(MMP) causing articular cartilage damage. The pathological changes seen in the joint space of rheumatoid arthritis are synovial lining hyperplasia, pannus formation and various cells are detected like the T-cells, B-cells, dendritic cells, mast cells and granulocytes. There is also structural damage of mineralized cartilage and subchondral bone[1,2,3].

Biologic disease-modifying antirheumatic drugs (DMARDs) are biologic response modifiers that target a particular protein that contributes to rheumatoid arthritis (RA). The various biological agents are tumor necrosis factor inhibitors which includes etanercept, infliximab, adalimumab, golimumab, certolizumab. Other biologics are anakinra, tocilizumab, abatacept , rituximab. Some of the newer drugs under trial are saralimumab, fostamatinib, sekukinamab, barcitinib and revamilast. Various studies have shown that efficacy of biological DMARD+ conventional synthetic DMARD combination is more effective than only biological DMARD treatment[4].

TNF-α Inhibitors

These were the first drugs to get approved for treatment of RA. The FDA approved drugs for monotherapy are etanercept, adalimumab and certolizumab pegol[5]. Combination therapy of the above class of drugs with methotrexate has shown better results[3,6]. They are most commonly used in moderate to severe case of RA. Its effect starts in 2-4 weeks and full effect is seen in 3-6 months.

Etanercept is a fusion protein produced by recombinant DNA. The protein consists of TNF receptor (which binds to TNF-α) soluble in nature and human end of Fc end of immunoglobulin (IgG) which is linked together. First chimeric monoclonal antibody against TNF-α. It functions as a decoy receptor that binds to TNF and due to fusion protein it has greater half-life. It is used in a dose of 25mg twice a week or 50mg once a week subcutaneously[2, 3, 5]. It is obtained in a lyophilized powder which must be reconstituted with a diluent and then injected subcutaneously. A single use of 50mg prefilled syringe or auto injector pen is also available. Infliximab, a chimeral monoclonal antibody neutralizes the biological activity of TNF-α by binding with TNF-α which is found freely soluble in blood

and on the outermembrane of T-cells and immune cells. As a result it prevents the binding of TNF-α to its receptors. They have the capability of lysing cells involved in the inflammatory process. As a result they prevent the action of TNF with its receptors. The preparation available is in the form of sterile white lyophilized powder and it must be reconstituted in hospital setting. It is given at a dose of 3mg/kg i.v at weeks 0, 2, 6 and then every 8 weeks. Its dose can be increased every 4 weeks up to 10mg/kg[2,3,5].

Adalimumab binds to TNF-α and prevents the activation of TNF receptors. It is a full human monoclonal antibody with extracellular domain of human p75 receptor connected with the fc portion human IgG and is given subcutaneously. It is available as 0.8ml vials preloaded in 0.8 ml syringes and also available in the form of preloaded pen devices.

Certolizumab is obtained in pegylated form which blocks the action of TNF. The dose given is 400mg initially and then at week 2 and week 4. It is then followed by 200 mg every week for maintenance dosing or 400 mg every 4 weeks can also be given.[2,3,5,7].

Golimumab is also full human monoclonal antibody which blocks the action of TNF. It is given at a dose of 50 mg subcutaneously every month[2,3,5,8]. Its combination with methotrexate has shown better results.

Abatacept

Abatacept is a protein formed by the fusion of the extracellular domain of the CTLA4 (CD154) molecule with the Fc portion of human immunoglobulin. Abatacept binds at the CD80/86 molecule on the APC cells and competitively inhibits the binding CD28 with CD80/86. As a result the second stimulation required for activation of T-cells is not possible and activation of inflammatory mediators and cytokines are prevented. The route of administration is either subcutaneously or intravenously. It is given as weight based- i.v. dose i.e. less than 60 kg: 500 mg; 60–100 kg: 750 mg; more than 100 kg: 1000 mg[2,5]. The i.v. dose is given at week 0, 2 and 4 then every 4 weeks. The subcutaneous dose- 125 mg s.c weekly and is indicated in patients inadequately respond to TNF inhibitors[2,3].

Rituximab

B-cells are important inflammatory cells which on interaction with T-cells form plasma cells and release antibodies. Rituximab, a chimeral monoclonal antibody which binds over the CD20 molecule on the surface of B-cell leading to removal of B-cells from systemic

circulation. It is effective in reducing the symptoms and signs and also slows the radiographic activity in RA. It is used in patients who do not respond to TNF inhibitors and other DMARD therapies. A single dose of rituximab 1000 mg i.v. over 3- 4 hours apart and then 2 doses 2 weeks apart[2,3,5]. Intravenous steroid to be given 30 minutes prior infusion so as to prevent infusion reaction. The effect of the drug lasts for 6 months to 2 years.

Anakinra

IL-1 has an inflammatory response which causes bone resorption and cartilage degradation due to loss of proteoglycans. It is a human recombinant IL-1 receptor antagonist which blocks the activity of IL-1 by acting specifically on IL-1R type 1 It is used either as single drug treatment or combined with other non-biological DMARDS. It is given as 100mg subcutaneously per day and the usual time of effect is 2- 4wks[2].

Tocilizumab

The synovial and endothelial cells which produces IL-6 causes T-cell activation. Tocilizumab is the first approved drug for IL-6 inhibitor. It acts on both soluble and membrane bound IL-6 receptors and it inhibits IL-6 mediated signaling through these receptors[3]. It reduces the signs and symptoms of RA and slows the activity of RA. It is used in patients who failed to respond to anti-TNF agents. It can be used as monotherapy in treatment of RA or in patients whom methotrexate intolerant/ ineffective/inappropriate. Studies have shown that the above drug is quite effective as monotherapy and do not require methotrexate to improve their performance[5]. Studies reveal that better efficacy of only tocilizumab treatment in rheumatoid arthritis especially in DMARD-naïve patients and TNF failure cases [9]. It is used in a dose of 4- 8mg/kg i.v monthly and the effect is seen in 4- 8 weeks.

Tofacitinib Citrate

It is a selective inhibitor of JAK kinase enzyme and it is the oral kinase inhibitors approved by FDA. JAK enzymes activate various cytokines through their surface receptors which are solely responsible for inflammation of RA. JAK enzyme (1and 3) are involved in signal transduction which results in transcription and gene expression intracellularly. Tofacitinib citrate prevents signaling of JAK enzymes and causes interruption of the signal transduction which is responsible for the immune response in RA[10]. It is given at a dose of 5mg orally twice a day[5]. It is used in moderate to severe cases of RA. It can be used in patients who are inadequate or intolerant to methotrexate. It is used as monotherapy which showed better results than in combination with methotrexate[5,6].

Newer Biological DMARDs Under Trial.

Saralimumab is a human monoclonal antibody against IL-6 receptor. Fostamatinib is a pro-drug of the active compound tamatinib which is a inhibitor of the enzyme spleen tyrosine kinase (syk). This syk activates B-cells and causes increase in inflammatory activity. Sekukinamab is a human monoclonal antibody for IL-17. Barcitinib is an oral JAK kinase inhibitor (JAK 1&3). Revamilast is a selective inhibitor of phosphodiesterase 4(PDE4) which causes TNF inhibition (93%)[11].

ADVERSE EFFECTS[1, 2, 3]

Drug	Adverse effects
1. ANTI- TNF AGENTS	Infections, reactivation of TB and hepatitis-B, lymphomas and non-melanoma skin cancers, transient neutropenia and other blood abnormalities
2. ABATACEPT	Infections,malignancies,infusion reaction
3. RITUXIMAB	Infusion reactions(most common), reactivation of viral infection, progressive multifocal encephalopathy, decrease in IgG and IgM levels
4.ANAKINRA	injection site reaction, reactivation of infection, neutropenia
5.TOCILIZUMAB	Reinfection, decrease platelet count,LFT abnormalities and abnormal lipid levels(most common)
6.TOFACITINIB CITRATE	Opportunistic infections, increase risk of herpes zoster infections, neutropenia, lymphopenia, anemia, elevated cholesterol and triglyceride level, elevated liver transaminases

Patients on TNF inhibitors had a higher risk of tuberculosis and herpes zoster compared to malignancies like lymphoma and non-melanoma skin cancers, but rate of risk of melanoma is high[12].

When To Use Biologics

According to 2013 EULAR (EUROPEAN LEAGUE AGAINST RHEUMATISM) biologics are used in the following cases[13]

1. Patients responding inadequately to methotrexate and other conventional synthetic DMARDS with or without addition of glucocorticoids, biological DMARDS like TNF inhibitors,abatacept, tocilizumab are added to the regimen and in special cases rituximab is added to methotrexate.

2. If a first biological DMARD has failed during treatment then patient has to be started with another biological DMARD. If the first TNF inhibitor has failed he should be started with an another TNF inhibitor or another biological agent with another mode of action.

3. Tofacitinib can be used if biological agents fail [13].
4. The use of biologics is determined by measuring the disease activity with certain tools like SDAI(simplified disease activity index) and CDAI(clinical disease activity index)[14].

SDAI- TJC+SJC+PGA+EGA+CRP

CDAI- TJC+SJC+PGA+EGA

TJC- no. of tender joints using a 28 joint count

SJC- no. of swollen joint using a 28 joint count

PGA - patient global assessment (0-100mm)

EGA- evaluator global assessment (0-100mm)

CRP- C- reactive protein

Disease Activity Cut-Off/Absolute Disease Activity Level[14]:

Disease activity	SDAI	CDAI
REMISSION	<or = 3.3	<or=2.8
LOW	<or = 11	<or = 10
MODERATE	<or=26	<or=22
HIGH	>or=26	>or=22

When the patient is diagnosed as rheumatoid arthritis he is started with methotrexate (first line DMARD). If his response is not adequate then he is added other non-biological DMARDS like hydroxychloroquine, sulfasalazine etc. He is initially kept on these drugs for 3 months and later his response is checked post 3-months. If his SDAI>26(CDAI>22) post 3month treatment but less than six months he is categorized as high disease activity and he is added a TNF inhibitor. For six month to one year follow up period if his SDAI>26 and CDAI>22 he is categorized as high disease activity and he is either added/switched to TNF inhibitor. Other drugs like abatacept, rituximab and tocilizumab can be added instead of TNF-inhibitor. Beyond one year of follow up if SDAI>11 or CDAI>10 then it is considered as high disease activity where all biological and non-biological agents are discontinued and patient is started with sufasalazine and hydroxychloroquine with addition of biological agents like abatacept, tocilizumab, rituximab and anakinra[14].

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