MONOCLONAL ANTIBODY THERAPY IN RHEUMATOID ARTHRITIS

Tania Rosen
T.Y.BTech
Pharmaceutical Sciences & Technology

ABSTRACT:

Rheumatoid Arthritis (RA) is a systemic autoimmune syndrome in which chronic inflammation of the joints is believed to be initiated by autoantibodies and maintained by cellular inflammatory mechanisms. The inflammation and damage is being caused by various pro-inflammatory cytokines, primarily, TNF-a (Tumor Necrosis Factor – alpha). Other such cytokines include IL-1 (interleukin), IL-6, IL-8 and GM-CSF (granulocyte monocyte colony stimulating factor). Monoclonal Antibodies are biological response modifiers which aid in immunosuppression in RA. They block or bind to these cytokines, thereby reducing inflammation, joint damage, and pain. They are less toxic than conventional drugs used. This paper is a review of the studies on the mechanism of action of various monoclonal antibodies against certain cytokines i.e. TNF – alpha, IL-1, IL-6, and inflammatory cells such as B cells and T cells. We have focused on TNF antagonists, such as Infliximab, as TNF–alpha is a major pro-inflammatory cytokine in RA.

Keywords: Rheumatoid Arthritis, Monoclonal antibodies, Tumor Necrosis Factor-alpha.

1. INTRODUCTION:

Rheumatoid Arthritis is a systemic autoimmune syndrome, in which chronic inflammation of the joint is believed to be initiated by autoantibodies and maintained by cellular inflammatory mechanisms. In rheumatoid arthritis (RA), an unknown immunological trigger begins an inflammatory process that ultimately manifests clinically by typical signs and symptoms of disease, such as joint swelling and tenderness. Inflammation is also responsible for stimulating destructive mechanisms in the joint which lead to structural damage and subsequently to functional declines and disability.[1]

The rheumatoid joint contains numerous cell types that are involved in these inflammatory and destructive processes. As seen in Figure 1, the inflamed synovial membrane contains synovial macrophages and fibroblasts (synoviocytes), whereas plasma cells, dendritic cells, T lymphocytes, and mast cells are found in the subsynovial layer. The composition of the synovial fluid varies, but is principally composed of neutrophils.

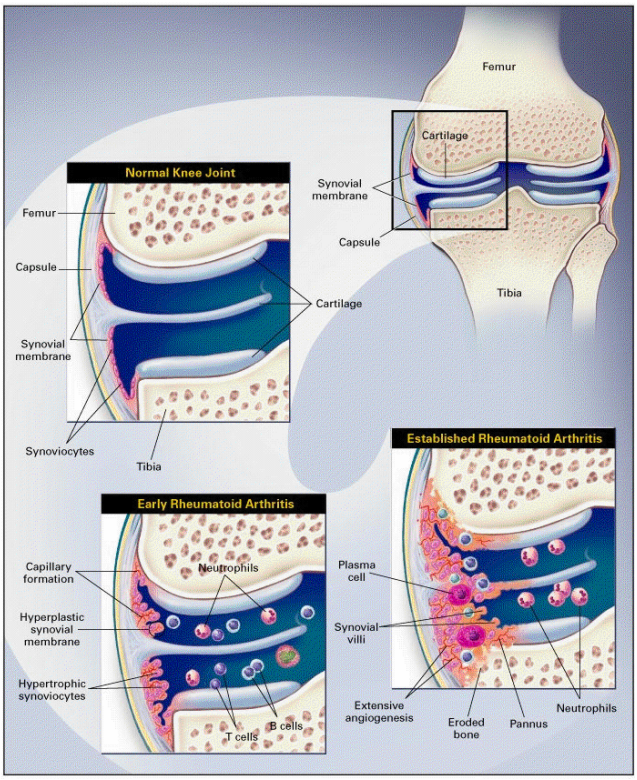


figure 1

This figure presents a schematic of normal and inflamed rheumatoid joints. A fibrous capsule encloses the joint within which the synovial membrane encloses synovial fluid in the synovial space. Cartilage covers the surface of each bone, acting to stop bones clashing and as a shock absorber. A rheumatoid joint has a very different appearance. Most obvious is the greatly

increased size of the joint. The synovial membrane, which normally is just a few cell layers thick, becomes vastly enlarged and is infiltrated with leukocytes, in particular T-cells (which direct the fate and extent of immune reactions) and macrophages (which engulf pathogens). The inflamed synovial membrane becomes a tissue described as a pannus. This structure invades the synovial space and begins to destroy the structure of the joint by degrading cartilage and inducing bone destruction.

Source: Dr. Mesecar-Lecture 2, PHAR 408, Spring (2007)

The formation of immune complexes in the joint spaces leads to the activation of the complement system, which further leads to destructive inflammation. CD4+ T cells, B cells and monocytes-macrophages migrate into and remain in the synovial interstitium, presumably as a result of specific chemotactic stimuli and interaction of cellular adhesion molecules with counter ligands expressed on extracellular matrix molecules.[26]

This acute inflammatory phase may be followed by delayed-type hypersensitivity (DTH) chronic inflammation, which is macrophages driven. A majority of the pro-inflammatory cytokines in the synovium are macrophage derived such as IL-1, TNF-alpha, IL-6, GM-CSF (granulocyte monocyte colony stimulating factor). According to the alternative theory (the "macrophage-fibroblast theory") of RA, the macrophages and fibroblasts seem to be responsible for creating a self-perpetuating state of chronic inflammation in which T cell participation may no longer be crucial. Thus the pathogenesis of RA involves interplay between immune complexes, cytokines and DTH reactions.[14, 26]

1.1 Inflammatory mediators in RA

The rheumatoid joint contains a variety of proinflammatory cytokines besides IL-1 and TNF-alpha which include IL-6, IL-8, IL-15, IL-16, IL-17, IL-18, IFN-gamma, granulocyte macrophage-colony stimulating factor and chemokines such as IL-8, macrophage inflammatory protein-1alpha and monocyte chemoattractant protein-1. Under normal physiologic conditions, the actions of these proinflammatory cytokines are maintained in balance by anti-inflammatory cytokines, such as IL-4, IL-10, IL-11, and IL-13, and by natural cytokine antagonists, including IL-1 receptor antagonist (IL-1ra), soluble

type 2 IL-1 receptor, soluble TNF receptor (sTNF-RI), and IL-18 binding protein. In the rheumatoid joint, however, the balance swings in favor of the proinflammatory cytokines.[8,10,26]

IL-1 and TNF-alpha have numerous functions throughout the body, many of which are important in RA. Both IL-1 and TNF activate a variety of cell types found in the rheumatoid joint, including macrophages, fibroblast-like synoviocytes, chondrocytes, and osteoclasts, resulting in the release of other proinflammatory mediators and enzymes.

TNF-α triggers production of other cytokines, induces endothelial adhesion molecules, stimulates collagenase and stromelysin and stimulates osteoclast differentiation. Hence, the blockade of TNF-α has a more global effect on inflammation than the blockade of other cytokines.[8]

2. RHEUMATOID ARTHRITIS TREATMENT

Rheumatoid arthritis is a chronic disorder for which there is no known cure. The current goal of treatment aims toward achieving the lowest possible level of the disease activity and remission if possible, the minimization of joint damage, and enhancing physical function and quality of life.

The management of RA was revolutionized with the advent of corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs) as the disease course could now be modified favorably. Conventional DMARDs, however, have several limitations like slow onset of action, induction of partial remission and modest 5-year retention rates. [15]

Some drugs used include NSAIDS, Corticosteroids, DMARDs - Methotrexate, Hydroxychloroquine, Sulfasalazine, Leflunomide, Intramuscular Gold, Azathioprine, Cyclophosphamide, etc, Tumor Necrosis Factor Inhibitors – Etanercept, Adalimumab, Infliximab, T-cell Co-stimulatory Blocking agents – Abatacept, B-Cell Depleting Agents – Rituximab, Interleukin-1 Receptor Antagonist therapy – Anakinra.

A better understanding of the pathophysiology of RA has enabled scientists to develop designer drugs termed ′Biologicals′ that tackle the key inflammatory cytokines like TNF-α.

′Biologicals′ or ′biological response modifiers′ are therapeutic agents that have the potential to inhibit the behaviour of cytokine, cellular activation, and inflammatory gene transcription by various means. These include monoclonal

antibodies, soluble cytokine receptors and natural antagonists. The first two biologicals developed for the treatment of RA were the TNF-α inhibiting agents, namely, Etanercept and Infliximab. Thereafter newer agents were developed, including Anakinra, a recombinant form of the naturally occurring IL-1 receptor antagonist, and Adalimumab, a fully human monoclonal antibody against TNF-α.

3. MONOCLONAL ANTIBODIES – "The Magic Bullets"

It has long been established that certain antibodies can be used to suppress the immune system. Recent advances in biotechnology have improved significantly on the conventional antiserums of the past. It is now possible to produce virtually unlimited quantities of specific homogeneous antibodies called "monoclonal antibodies". These antibodies have invariably added to our ability to identify and selectively bind distinct cells of the immune system, unlike the conventional antiserums which elicited non-specific responses.

As a result, monoclonal antibodies can be used to manipulate the immune system in ways that were not previously possible.

3.1 Production

The idea of using antibodies to focus therapy on cells with specific surface antigens is not new. Paul Ehrlich first conceived of the idea almost a century ago when he considered using antibodies as "magic bullets" that might be effective not only against bacterial cells but also against cancer cells. Until recently, it was impossible to achieve this goal because normal B lymphocytes, with the capacity to produce specific antibodies, would not survive long term in culture. Only malignant cells such as multiple myeloma cells could be maintained perpetually in vitro as cultured cells.

In 1975, however, George Kohler and Cesar Milstein developed techniques through which they could generate cells that possessed the specific antibody-producing characteristics of a normal lymphocyte and the "immortal" characteristics of a myeloma cell. Individual clones derived from these unique cells could survive in culture and produce large quantities of identical (monoclonal) antibodies.[5]

First, a mouse is immunized with the antigen(s) against which a monoclonal antibody is desired. As a consequence, lymphocytes capable of producing antibodies to the antigen(s) proliferate in its spleen. The spleen cells are

subsequently removed and incubated with myeloma cells in the presence of an agent that facilitates fusion of cell membranes. Some of these cells fuse with each other, producing hybrid cells that may retain the antibody-producing capacity of the spleen cell and the immortal quality of the myeloma cell. Clones derived from such hybrid cells are referred to as "hybridomas." Selected hybridomas can then be grown in cell culture to produce monoclonal antibodies or frozen as a permanent source of specific antibody-producing cells.[5, 6]

3.2 Advantages

Conventional antiserums are heterogeneous in nature, composed of many structurally and functionally distinct antibody molecules that react with many different antigenic determinants. They are not reproducible but their composition varies depending on their source and the particular point in time when they are obtained.

In contrast, monoclonal antibodies are homogeneous, reproducible agents that can be characterized precisely and that have a highly restricted pattern of reactivity. The homogeneity and specificity of monoclonal antibodies that are produced from hybridomas makes them particularly suitable for *in vivo* administration for therapeutic purposes. The most important advantage of monoclonal antibodies over the antiserum is the ability to produce pure antibody without a pure antigen. That is, it is possible to use a preparation containing many different antigens-such as a suspension of lymphocytes-to produce a panel of monoclonal antibodies, each of which will react with specifically one antigenic determinant.

As a result, it is possible to generate monoclonal antibodies that will identify subsets of cells that might otherwise be difficult to distinguish, such as helper or suppressor T cells, pathogenic or nonpathogenic organisms, benign or malignant cells, etc. [5]

Clinical studies using mouse monoclonal antibodies have been disappointing because the human immune system recognizes them as ‘foreign’. This results in their rapid clearance from circulation and in some cases, can lead to the induction of a severe allergic reaction to the mouse antibodies – an effect known as the human anti-mouse antibody (HAMA) response.

3.3 Chimaeric monoclonal antibodies (mAbs)

To reduce the potential for HAMA responses, the variable regions of the mouse antibody genes can be recombined

with constant regions from human antibody genes. The recombinant gene encodes a chimaeric mouse–human antibody that has antigenic specificity derived from the mouse, but is a human isotype. Hence, the resultant protein has human effector functions and fewer mouse antigenic determinants, and is therefore less likely to be immunogenic in humans. Mouse variable regions are also known to cause an immune response in humans, and chimaeric antibodies containing only mouse complementarity determining regions (CDRs) have subsequently been developed. CDRs are the region of the antibody molecule that are largely responsible for antibody–antigen binding and using only these elements rather than the full variable region of the antibody, further reduces the risk of immunogenicity. Replacing some mouse CDR sequences with human sequences aids in further humanizing antibodies; mouse residues are minimized but retained at the key binding regions, to maintain affinity. [6,10]

One of the earliest successful applications of mAbs in therapy involved rheumatoid arthritis (RA), and this is currently the disease with the largest number of patients treated with mAbs. In RA, cytokines, which are important regulators of immune and inflammatory responses, are linked in a network or cascade with tumor necrosis factor α (TNFα) at its apex.

3.4 Mechanism of Action

Monoclonal Antibodies function as immunosuppressive agents in various autoimmune disorders. They block the pro-inflammatory cytokines released during RA. Studies in short-term cultures of rheumatoid synovial membranes demonstrated that inhibition of TNFα by anti-TNFα mAbs inhibited the production of interleukin (IL)-1, IL-6, IL-8 and GM-CSF (granulocyte macrophage colony stimulating factor) cytokines produced locally in all of the rheumatoid synovial membrane samples, regardless of the duration of disease or its treatment.

These biological-response modifiers include inhibitors of Tumor necrosis factor-alpha (TNF-α) (Adalimumab, Etanercept, and Infliximab), a recombinant inhibitor of interleukin (IL)-1 (Anakinra), a chimaeric anti-CD20 monoclonal antibody (Rituximab), and a co-stimulation blocker (Abatacept). Additional therapies for RA under current investigation include new TNF-α inhibitors, anti-IL-6-receptor monoclonal antibodies, and antibodies targeting proteins involved in B-cell function and survival.

Figure 2

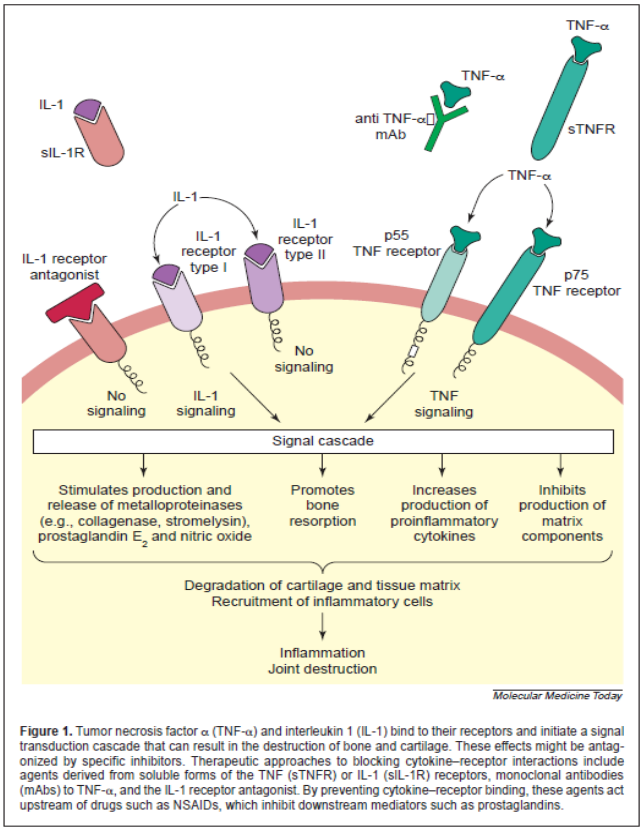


Figure 1. Tumor necrosis factor α (TNF-α) and interleukin 1 (IL-1) bind to their receptors and initiate a signal transduction cascade that can result in the destruction of bone and cartilage. These effects might be antagonized by specific inhibitors. Therapeutic approaches to blocking cytokine–receptor interactions include agents derived from soluble forms of the TNF (sTNFR) or IL-1 (sIL-1R) receptors, monoclonal antibodies (mAbs) to TNF-α, and the IL-1 receptor antagonist. By preventing cytokine–receptor binding, these agents act upstream of drugs such as NSAIDs, which inhibit downstream mediators such as prostaglandins.

Source: Carteron N. L., Cytokines In Rheumatoid Arthritis: Trials and Tribulations, *Molecular Medicine Today* (Aug 2000), Vol 6

3.4.1 Antibodies directed against TNF-alpha:

Two biological agents have been licensed for clinical use. The first is Infliximab (RemicadeTM), a chimaeric anti-TNF mAb comprising a human IgG1k antibody

with a mouse Fv of high affinity and neutralizing capacity. Fv is the variable fragment of an antibody molecule that specifically binds an antigen; IgG1k is an immunoglobulin of IgG1 class with a kappa light chain; and Fc is the constant fragment of the immunoglobulin molecule. The second agent is Etanercept (EnbrelTM), an engineered p75 TNF receptor dimer linked to the Fc portion of human IgG1. Both agents act as competitive inhibitors of TNF binding to its receptors.

Other anti-TNF agents with proven clinical efficacy include CDP571, a humanized murine complementarity-determining region-3 engrafted mAb; D2E7 (Adalimumab), a 'human' antibody produced by phage display Celltech/Pharmacia's PEGylated (linked to polyethylene glycol) CDP870 anti-TNF antibody; and Amgen's PEGylated anti-TNF receptor antibody.

3.4.1.1 Infliximab:

Infliximab, a chimaeric (25% mouse Fv1, 75% human IgG1) monoclonal antibody, specifically binds to both membrane-bound and soluble TNFα with high affinity to form stable immune complexes. The binding of Infliximab to TNFα prevents the binding of TNFα to its receptors and blocks the initiation of the intracellular signaling that leads to gene transcription and subsequent inflammation.[8]

3.4.1.2 Pharmacokinetics and clinical response

Therapeutic response to Infliximab correlates with the pharmacokinetics of Infliximab and basal expression of TNFα in synovial tissue. Measurements of Infliximab blood levels and TNFα expression in joints suggest that TNFα blockade at the site of production is the key to its mode of action. Infliximab given repeatedly at a high dose of 1 mg/kg was associated with a rapid loss of response and accelerated clearance from the blood. However, the synergy of Infliximab was observed when combined with MTX, which can be explained by a lowered incidence of anti-Infliximab antibodies observed with combination therapy. [3]

3.4.1.3 Infliximab regulates the cytokine network

It was noted in one of the first trials that, following the administration of Infliximab, simultaneous reductions in CRP and IL-6 concentrations were observed in the blood. In a subsequent study, a rapid reduction in serum IL-6 concentrations in Infliximab-treated patients was observed, but not in patients receiving placebo. As CRP production by hepatocytes is regulated primarily by IL-6, this data is consistent with the conclusion that downregulation of IL-6 production in RA joints was as a result of TNFα blockade.

A reduction of IL-1 synthesis in synovial tissue by an anti-TNFα antibody *in vitro* was a crucial observation that led investigators to suspect the involvement of a cytokine cascade in RA; however, it has been difficult to verify these observations *in vivo*. Following Infliximab therapy, a reduction in serum concentration of IL-1ra (IL-1 receptor antagonist) and soluble TNF receptors has proved that two major anticytokines are regulated by TNFα. The simultaneous reduction in pro-inflammatory and anti-inflammatory molecules indicates the dominance of TNFα in the cytokine network and a probable explanation for why anti-TNFα therapy does not restore a long-lasting remission but instead perpetuates the cytokine imbalance, and hence there is relapse of disease upon withdrawal of therapy.[3, 21]

3.4.1.4 Infliximab regulates cell recruitment

The marked reduction in the swelling and tenderness of joints following Infliximab treatment was associated with a reduction in the cellularity of the synovium of RA patients. In a detailed analysis of serial biopsies before and after Infliximab, it was observed that a reduction in CD3+ and CD68+ cells was accompanied by a reduction in IL-8, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and E-selectin.[3]

3.4.1.5 Infliximab regulates a major angiogenic factor (VEGF) and angiogenesis

From the early stages of disease, rheumatoid synovial inflammation is observed to be accompanied by angiogenesis. The increase in blood vessel density provides a conduit for the increased trafficking of inflammatory cells into joints. This further leads to the formation of vascular pannus tissue that invades and destroys cartilage and bone in the minimum area of the attachment of synovium to subchondral bone. The cytokine vascular endothelial growth

factor (VEGF) induces new blood vessel formation and is in higher amounts in the joints and blood of RA patients. Infliximab therapy reduces circulating VEGF levels and the density of neovasculature in the synovium. [3]

3.4.1.6 Infliximab prevents cartilage catabolism and bone erosion

Infliximab was seen to preserve of chondrocytes and cartilage matrix. The lack of pannus invasion of the bone was a notable feature in response to treatment with Infliximab. In RA patients, protection of cartilage and bone was observed — possibly with healing — as judged by comparison of baseline and 54-week radiographs of hands and feet in patients treated with Infliximab. This finding supports the conclusion that mechanisms of tissue destruction in RA are TNFα-dependent. A reduction in matrix metalloproteinases following Infliximab treatment has been documented and this implies that this therapy induces a downregulation of matrix-degrading enzymes.[3]

3.4.1.7 Adverse Effects (of anti-TNF therapy):

TNF antagonists are generally safe; however, there have been concerns over increased risks of acute infusion-related reactions, lymphoma, delayed hypersensitivity reactions, atypical and opportunistic infections. From a public health standpoint, the development of active Tuberculosis in some patients who received TNF-alpha inhibitor therapy is a matter of serious concern. Clinicians should be vigilant for tuberculosis (or its latent form) in patients being treated with TNF antagonists because tuberculosis often presents itself as an extrapulmonary or disseminated disease. [4, 11, 24]

Therefore, before beginning therapy, the patient must be assessed for the presence of tuberculosis in its latent form. The patient is asked to start anti-TB drugs while undergoing Infliximab treatment.

The frequency of non-lymphoid malignancies in patients who have participated in anti-TNFα studies is similar to the expected frequency in the age-matched population, as assessed by using Cancer databases. Similarly, although cases of lymphoma have been reported in long term follow-up studies of Infliximab-treated RA patients, the observed incidence appears to be within the expected range. However, longer-term follow-up of a larger number of patients is required before it is possible to definitively exclude (or confirm) any association.[12, 16]

3.4.2 Antibodies directed against other cytokines:

IL-1 is another pro-inflammatory cytokine abundantly expressed in RA synovium. It stimulates resorption of cartilage and bone through activation of osteoclasts and inhibits synthesis of proteoglycan and articular collagen. IL-1 blockade has been established with daily, subcutaneous administration of IL-1 receptor antagonist (Anakinra, KineretTM), a naturally occurring inhibitor of IL-1.

Anakinra (Kinaret) is a recombinant form of IL-1Ra that competes with IL-1 for binding to cell surface-bound IL-1 receptor, but does not induce intracellular signaling. A significant drawback is its short half-life (6 hours) in plasma, which necessitates daily treatment with high doses required to maintain a significant therapeutic effect. The combination of Anakinra and Methotrexate is well-tolerated and provides significantly greater clinical benefit than Methotrexate alone. [10, 11]

IL-6, stimulated by TNF-alpha and IL-1, present in fair amounts in the synovial fluid, regulates the production of acute phase proteins by hepatocytes, and activates bone absorption by osteoclasts. The therapeutic potential of a humanized anti-IL-6 receptor mAb is currently being assessed in randomized trials in Europe and Japan. The response onset time seems to be longer than that for TNF blockade, with diarrhoea being one of the most commonly reported side effects.[11]

Its receptor, the IL-6Ra chain, employs an accessory molecule, gp130, for signal transduction and cell activation.Gp130 can be activated by both the transmembrane IL-6Ra and its soluble form via trans-signaling. Employment of a humanized antibody to the IL-6Ra chain targets both the membrane-bound and the soluble IL-6Ra. Moreover, monotherapy with Tocilizumab had good inhibitory effects on progression of joint destruction. Interestingly, IL-6 inhibition with Tocilizumab is also highly efficacious in the treatment of systemic-onset juvenile arthritis. Tocilizumab might become approved in Europe in the near future.[14]

Other potential cytokine targets for antibody-based biological therapies in RA include IL-8, IL-15, IL-17 and IL-18, and the results of clinical trials are awaited.

3.4.3 Antibodies directed against inflammatory cells:

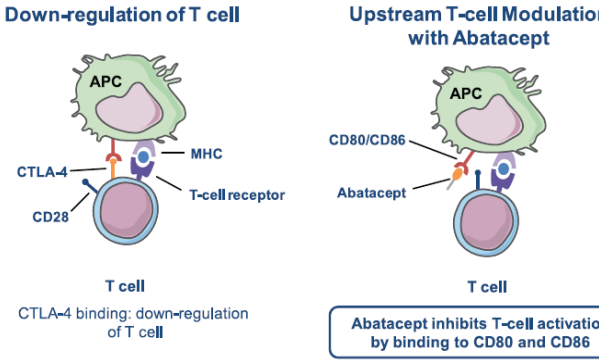
3.4.3.1 Targeting T cells

Inhibition of T cell activation with a co-stimulation inhibitor, Abatacept, consisting of cytotoxic T lymphocyte antigen-4 (CTLA-4) fused to an Fc portion of an immunologobulin G molecule (CTLA-4-Ig) is also an effective and approved

treatment option for RA. This molecule binds to the co-stimulatory molecules CD80 and CD86 on Antigen Presenting Cells and thus prevents their interaction with their receptor on T cells, CD28, thereby interfering with T cell activation.[7,13]

Based on their patterns of expression during the immune response, it appears that CD86 is the primary co-stimulatory ligand involved in early T-cell activation, whereas CD80 is the functionally predominant co-stimulatory ligand in established responses. In chronic RA, CD80-specific inhibitors would be the preferred agents, leaving primary T-cell responses to recently encountered foreign pathogens relatively unaffected. This suggests that there might be advantages in CD80 monotherapy or selective blockade of CD80 for the treatment of established RA. [14]

Figure 3



Source: Solomon G. E., T-Cell Agents in the Treatment of Rheumatoid Arthritis, *Bulletin of NYU Hospital for Joint Diseases* (2010), Vol 68, Issue 3, 162-5

Safety: The safety profile of Abatacept is reassuring with low rates of both serious adverse events and major infections. In the 2-year extension data from conducted trials, the rates of significant adverse events was similar to the rates seen in the placebo group and fell well within the ranges reported for patients receiving anti-TNF therapies.[7]

3.4.3.2 Targeting B cells

The potential of **B lymphocyte depletion** as an approach to therapy is under investigation using an anti-CD20 mAb, Rituximab. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids with a molecular weight of 145 kD. An improved clinical response was observed in the combination therapy groups.

Mechanism of action of Rituximab: It may be acting by eliminating circulating B cells. B cells are very efficient antigen-presenting cells, particularly after they have been activated. Thus loss of B-cells would result in less stimulation of T-cells and also lesser production of autoantibodies. [9]

4. Conclusion

Where do we stand today?

Currently, we can achieve stringent remissions of symptoms, i.e., no evidence of active disease. However, cure is not yet in sight. Although cure will ultimately require knowing the cause of this disorder, interference with the vicious cycle of the inflammatory occurrences in the very early stages of the disease process may reverse the events usually destined to become chronic in predisposed individuals. Such a window of opportunity is addressed by currently ongoing clinical trials, and it is yet to be seen if this supposition can be realized.

The future of Biological Response Modifiers (BRMs)

BRMs hold the promise of providing both important clinical benefits and key insights into the pathophysiology of RA. Because BRMs target one specific molecule, they might be less likely to cause the adverse effects associated with older DMARDs, which typically interact with multiple receptors. Many of the most effective DMARDs, including Methotrexate, Leflunomide, gold, and Penicillamine, can cause severe, sometimes irreversible, toxic effects. Most non-steroidal anti-inflammatory drugs (NSAIDS) can result in significant gastrointestinal toxicity, abdominal pain, nausea, indigestion and ulcers. Corticosteroids, such as prednisone, are highly effective at relieving pain but can cause weight gain, and, in some patients, can contribute to the development of osteoporosis. The favorable safety profiles of some BRMS might make them well-suited for early RA therapy.

The high cost of these antibodies may be a prohibitive factor. The cost varies from around Rs 50,000 to around a lakh rupees, depending on which mAb is under consideration. So, inspite of its effectiveness in immunosuppression and remission of the symptoms of RA, with relatively less toxicity than most DMARDS, it is definitely not within the reach of the common man.

It is therefore suggested that the government take steps to subsidize the cost of these mAbs so that the drug will be a more accessible to the public at affordable rates. With advances in technology, newer methods can be developed, which can bring down the cost of production of mAbs, while possibly enhancing its effectiveness and duration of action.

A complete understanding of the pathophysiology of RA could fuel the search for more and better treatments or even, perhaps, a vaccine or other ‘cure.’

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