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MANAGEMENT OF REFRACTORY RHEUMATOID ARTHRITIS [BIOLOGICALS IN RHEUMATOID ARTHRITIS (RA)]

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ABSTRACT
Rheumatoid arthritis is complex immune disorder and chronic systemic inflammatory disease that results in joint destruction and disability with multisystem involvement. Although with the advent of different DMARDS treatment of this disease is possible to some extent, but prolonged treatment course and adverse effects of the DMARDS are becoming its drawbacks and imposing to switch to other modalities of treatment. Treatment involving Biologicals have revolutionized the approach to this disease. These are found to target the pathologically involved cytokines such as tumour necrosis factor (TNF) and immune cells like B cells. New cytokine directed therapies target important proinflammatory mediators such as GM-CSF, new members of the IL-1 family, IL-6 and its receptor, IL-17, IL-20, IL-21, IL-23 as well as synovium-specific targets. Biologics are known to reduce the joint inflammation, limit erosions, decrease disability and improve quality of life. Although infections and cost effectiveness of drug are limiting its wide use, their use in conjunct with DMARDS (METHOTEXTRATE) has proven beneficial and is now the new mode of novel approach to the patient with Rheumatoid Arthritis.

Keywords: Tumour Necrosis Factor (TNF-α), Interleukins (IL-6), synovium, Monoclonal antibodies.

INTRODUCTION
Rheumatoid arthritis (RA) is a disease of unknown aetiology that is characterized by changes in the synovial tissue, prompted by unknown initiating events, potentially involving infections and tissue injury. The subsequent inflammatory process is reflected by joint pain and swelling as well as systemic manifestations, caused by metabolites of arachidonic acid and various inflammatory cytokines. Abnormalities in the cellular and humoral immune response lead to the occurrence of autoantibodies (rheumatoid factors [RF] and antibodies against citrullinated peptides/proteins [ACPA]) as well as the immigration of T cells and B cells into the synovium. In the effector phase, cartilage is destroyed by invading fibroblasts and the juxta-articular bone by activated osteoclasts.[1]

Biological agents that target a specific molecule provide an effective means for therapeutic management of RA due to their specificity and powerful functional capabilities, and this approach has resulted in a paradigm shift in the treatment strategy for this disease.Of the multiple events in the inflamed synovium of RA patients, one of the upstream events, an indispensable factor, is demonstrated to be the enhanced release of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin-1, and interleukin-6. Also, it has been postulated that T and B cells play important roles in autoimmune-mediated processes for perpetuating inflammation.[2]

Pathogenesis or Target molecules in RA

RA is characterized by several stages: initial activation of the (auto)immune system leading to the inflammatory cascade (initiation phase); establishment of chronic pathology (sometimes referred to as 'chronification') with perpetuation of inflammatory processes in joints and certain extra-articular sites (transformation phase); and, finally, the destruction of the target tissues resulting in irreversible organ damage (effector phase) (Figure 1). Emerging therapies in RA address molecular and cellular targets in all of these phases. These new approaches are necessary, as despite the remarkable success of modern targeted therapy in RA, a considerable need for new treatment modalities remains.[5]

Clinical assessments

Impact of biologics treatment is assessed in several ways which includes overall impacts of RA using combined indices, core clinical measures, erosive damage, and quality of life. [3]

Combined indices

These include different individual assessments. Those used in clinical trials, American college of Rheumatology (ACR) criteria, Disease Activity Score 28 (DAS 28), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI).

Core Measures

These involve Physician based assessments, laboratory tests which include ESR, CRP and Pateint based assessment for pain, global assessment and disability.

Erosive damage

Juxta-articular erosions characterize progressive, established RA and are usually irreversible. They are most readily detected in X-rays of the hands and feet. Extensive erosive and other radiological damage suggests the presence of inadequately controlled RA. Rapid progression of joint damage requires intensive treatment. Several radiological scoring systems record the extent of damage seen on X-rays. The scoring systems of Larsen and of Sharp, both of which have been substantially modified, are widely used.[4]

Quality of Life

The assessment of disability using HAQ is widely used as an indicator of the ways in which RA reduces quality of life.

Biologics in RA

Currently there are five different groups of Biologics available for treatment of RA.
These include

1. TNF-α INHIBITORS.
2. Interleukin- 1 receptor antagonists.
3. B- cell inhibition.
4. T- cell co stimulation inhibition.

5. Interleukin-6 inhibition.
6. Small molecule inhibitor.

INDICATIONS OF BIOLOGICALS

- Established severe active RA.
- Persistent symptoms and signs of poorly controlled and active disease defined as 6 or more swollen and tender joints, or 4 non-hand joints, or a DAS 28 score >=3.2.
- Failed adequate therapy with 2 standard DMARDs of which MTX must have been one. DMARDs including MTX should have been given for at least 3-6 months with at least 2 months at standard target dose (eg. MTX 20-25mgs per week) unless limited by toxicity or intolerance.

TNF- α INHIBITORS

This class includes five drugs used in RA, which can be divide into

- First generation : includes Etanercept, infliximab and adalimumab.
- Second generation : includes certolizumab and golimumab.

Infliximab

Infliximab is a chimeric immunoglobulin 1 (IgG1) anti-TNF-α antibody with the antigen-binding region derived from a mouse antibody and the constant region from a human antibody. It binds to soluble and membrane-bound TNF-α with high affinity, thereby impairing the binding of TNF-α to its receptor. Infliximab also kills cells that express TNF-α, through antibody-dependent and complement-dependent cytotoxicity. There are considerable interpatient differences in the pharmacokinetics of infliximab. Trough concentrations, seen at 8 weeks after intravenous administration of 3 mg/kg of infliximab, vary considerably among patients. For increasing the trough levels, shortening the interval between doses may be more effective than increasing the dose. Most patients show response to a dose of 3 mg/kg once every 8 weeks. Some patients need higher doses or shorter intervals between doses.[6]

Etanercept

Etanercept is a soluble TNF-receptor fusion protein. It has two dimers, each with an extracellular, ligand-binding portion of the higher-affinity type 2 TNF-receptor (p75) linked to the Fc portion of human IgG1. This fusion protein binds to both TNF-α and TNF-β. It prevents them from interacting with their receptors. Etanercept is administered as a subcutaneous injection of 25 mg twice a week or 50 mg once a week. These dosages are based on its half-life, which is ~4 days.

Adalimumab

This is a recombinant human IgG1 monoclonal antibody. It binds to human TNF-α with high affinity and, as a consequence, it inhibits the cytokine from binding to its receptors. It also lyses cells that express TNF-α on their surface. It is administered by subcutaneous injection and is absorbed slowly. Although there are wide variations in the pharmacokinetics of this biologic among patients, it is generally administered once every 2 weeks.

Certolizumab

Certolizumabpegol is a recombinant humanized Fab' fragment (the antigen-binding domain) of a TNFantibody coupled to an ~40 kDa polyethylene glycol to enhance its plasma half-life to ~2 weeks. It binds and neutralizes membrane-bound and soluble human TNF-α. In contrast to the other TNF inhibitors, it lacks an Fc region. It is given by subcutaneous injection, with 80% bioavailability. It has an initial loading dose of 400 mg every 2 weeks for 6 weeks, followed by 200 mg every 2 weeks.

Golimumab

Golimumab is a human IgG1 monoclonal antibody specific for TNF-α and is produced in a transgenic mouse. It targets and neutralizes both soluble and membrane-bound TNF-α; it has a half-life of 7–20 days. Golimumab is administered as a subcutaneous injection at an initial dose of 50 mg a month, to be increased to 100 mg a month if there is no response after 4 doses (provided the body weight of the patient is >100 kg).

Interleukin-6 inhibition: (Tocilizumab)

IL-6 is an important pro-inflammatory cytokine in RA. It promotes inflammation through the expansion and activation of T cells, differentiation of B cells, and induction of acute-phase reactants by hepatocytes. IL-6 signal transduction is mediated by membrane-bound and soluble receptors. Currently, tocilizumab is the only available IL-6 inhibitor for the treatment of inflammatory arthritis. It is a recombinant humanized antihuman IL-6 receptor monoclonal antibody of the IgG1 subclass.[7] It binds to both membrane-bound and soluble IL-6 receptors, preventing their activation by Il-6.

B- cell inhibition

Role of B- cells in RA

The possible mechanisms are as following,

- B-cells may function as antigen-presenting cells and provide important costimulatory signals required for CD4+ T cell clone expansion and effector functions.
- T-cell activation is a key component of the pathogenesis of RA. Recent evidences indicates that this activation is critically dependent in the presence of B cells.[8] B cells in RA synovial membrane may also secret pro-inflammatory cytokines such as TNF-α and chemokines.
- The RA synovial membrane contains an abundance of B cells that produce the rheumatoid factor (RF) antibody. RF-positive RA is associated with more aggressive disease with higher prevalence of extra articular manifestations and increased morbidityand mortality.[9] RF may also be self-perpetuating stimulus for B cells that leads to activation and antigen presentation to T-cell, which may be responsible for further RF production. Thus, the RF immune-complex mediated complement activation in conjunction with binding of the Fcγ receptor, collectively contribute to the progression of inflammatory cascade.[10,11.]

Rituximab is a genetically engineered chimeric monoclonal antibody. It depletes the B-cell population by targeting cells bearing the CD20 surface marker.This binding interferes with the activation and differentiation of B cells. It was introduced for the treatment of lymphomas but was subsequently found to be effective in RA. The efficacy of rituximab is superior in patients with RA who also have the rheumatoid factor (termed “seropositive” disease). Its clinical effects appear to be associated with rheumatoid factor levels; these levels fall when clinical responses are seen. Many experts are therefore of the opinion that rituximab exerts its effects in RA through reducing B-cell-driven autoantibody production alongside B-cell-related T-cell activation.

Current Direct and Indirect surface and extra cellular B-cell targets in RA are summarized in Figure 2 & Table 1.

Selective T-cell Costimulation Modulator (Abatacept)

One of the initial steps in T-cell activation is antigen recognition through the T-cell receptor. Following antigen recognition, T cells require costimulation to become fully activated. One of the best-characterized costimulatory pathways is the engagement of CD80/ CD86 on antigen-presenting cells (APCs) with CD28 on T cells. This produces a positive costimulatory signal and promotes full T-cell activation. There are several other pathways involved in T-cell activation,

some of which optimize T-cell activity and some of which cause down regulation. CTLA-4 is a well-defined downregulator of T-cell activation and has a much higher binding avidity with CD80/CD86 than does CD28.

Abatacept (CTLA-4 Ig) is a soluble recombinant fusion protein comprising the extracellular domain of human CTLA-4 and a fragment of the Fc domain of human IgG1, which has been modified to prevent complement fixation. Abatacept employs the high binding avidity of CTLA-4 for CD80/CD86 on APCs to competitively bind CD80/CD86. This prevents these molecules from engaging CD28 on T cells and selectively modulates this costimulatory pathway, preventing full T-cell activation.

Small molecule inhibitor: (Tofacitinib)

This is found to inhibit JAK1 and JAK3, which mediates the signalling of the common γ-chain related cytokines, also IFN-γ and IL-6, which in turn are involved in T and B cell activation for inflammation.

Emerging cytokine targets in RA:

In addition to well-known cytokine targets such as TNF or IL-6, other soluble proinflammatory mediators might have relevant roles in disease pathogenesis. One such mediator is granulocyte-macrophage colony-stimulating factor (GM-CSF), which is mainly involved in the generation, survival, and activation of cells from the myeloid compartment.83 In fact, this cytokine especially regulates the function of neutrophils, eosinophils, and macrophages, and thus, is clearly part of the pro-inflammatory network in RA, which is characterized by intensive activation of the mononuclear phagocyte system. Thus, it was shown that GM-CSF and its receptor are detectable within synovial fluid and synovial tissue of patients with RA.[12.]and therefore, GM-CSF signalling was identified as a promising target in RA.

Another GM-CSF neutralizing compound is MOR103, a fully human mAb, which is also in clinical development. Three different dosages (0.3, 1.0 and 1.5 mg/kg intravenously) have been tested against placebo for the treatment of RA in a phase Ib/IIa clinical trial in Europe;[13] however, results have not yet been published.

IL-17, a highly inflammatory cytokine with pleiotropic effects, acts on several cell types that express the IL-17 receptor (IL-17R), including immune cells, epithelial cells and fibroblasts. IL-17A and IL-17F have been found to be up-regulated especially in inflammatory conditions as well as in activated T cells, and these isoforms are therefore the most promising candidate targets in RA. IL-17R activation induces the production of inflammatory cytokines (such as IL-6, IL-1β, TNF and GM-CSF) and the secretion of chemokines (such as CXCchemokine ligand 8, CC-chemokine ligand (CCL) 3 and CCL2), thus initiating the recruitment and activation of neutrophils, lymphocytes and macrophages, leading to local inflammation and tissue damage (reviewed elsewhere in 2008[14]). In addition, IL-17 can directly induce tissue injury by upregulating the expression of matrix metalloproteinases. IL-17-producing cells—type 17 T helper (TH17) cells—have been shown to infiltrate the RA synovium.[15.]The most advanced anti-IL-17 compound for treatment of RA is secukinumab, a fully human anti-IL-17A mAb.Another humanized anti-IL-17A mAb, ixekizumab (LY2439821, IgG4 subclass), has been investigated in RA and chronic plaque psoriasis.[16.]the other target molecules are summarized in the following table. (Table 2)

Adverse Reactions/ Toxicity

In an overview of the toxicity of biologics, Khraishi[17] divided them into risks of infection, infusion/injection reactions, malignancy, and a range of other concerns including lupus-like syndromes, demyelinating syndromes, and the development of blocking antibodies. There are concerns about the use of biologics in patients with congestive heart failure. Some biologics have idiosyncratic effects on lipid metabolism. Other unusual adverse effects include the triggering of

interstitial lung disease and psoriasis. The toxicity of biologics has been evaluated in clinical trials and extension studies and in large national registries. Many of the studies produce conflicting results about the frequency of each of the reactions.

Infections

The main problem associated with the use of biologics is the occurrence of infections. RA itself increases the risk of infections, and this risk is heightened by biologics, particularly TNF inhibitors.Trials and registries all show an increased risk of tuberculosis in patients receiving TNF inhibitors.

Many other infections are associated with the use of biologics. There are concerns that patients receiving biologics have greater risks of contracting viral infections, including herpes zoster.[18]There are similar anxieties about viral hepatitis. Patients should be screened for hepatitis B and C before being started on TNF inhibitors because the long-term safety of these biologics in patients with chronic viral hepatitis is not known. A particular concern with rituximab treatment is the risk of progressive multifocal leukoencephalopathy due to activation of the JC polyomavirus. There have been only a few reports of this fatal progressive brain disease in RA patients treated with rituximab, and it is difficult to be certain about the risks involved.[19]Although the risks are small, the clinical consequences of progressive multifocal leukoencephalopathy are severe.

Cancer

There have been concerns that biologics might be associated with an increased risk of developing cancer. However, there are complexities in assessing the frequency of cancers, particularly lymphomas, in patients treated with biologics. This is because the incidence of lymphoma is in any case higher in patients with RA, with the risk being highest in patients with active disease, the same patients who are also most likely to be receiving biologics. There is some evidence that there may be a higher rate of some solid tumours, particularly skin cancer, in patients receiving biologics. However, a recent systematic review by Solomon et.al[20] who evaluated 11 studies of cancer risk associated with TNF inhibitors and assessed the data from an appropriate epidemiologic perspective, found little or no cancer risk associated with TNF inhibitors. The balance of recent evidence suggests that there is currently no convincing evidence of an increased cancer risk associated with the use of biologics; however, continuing caution is needed.

Starting or resuming rituximab is recommended only for the following patients with RA[21]:

- Those with either a previously treated solid malignancy or a previously treated nonmelan oma skin cancer within the past 5 years.
- Those with a previously treated melanoma skin cancer.
- Those with a previously treated lymphoproliferative malignancy

The ACR panel indicates that there are limited data regarding the effects of biologic agents in patients with RA and a history of a solid cancer within the past 5 years.[21]

BIOLOGICALS IN EXTRA-ARTICULAR MANIFESTATIONS OF RA

It is not clear what role anti-TNF therapies and other biologics, such as B-cell-directed therapies, play. On the basis of the pathophysiology of RA, theoretically, it seems likely that anti-TNF therapies and anti-B-cell therapies should reduce the incidence of and treat the extra-articular manifestations of RA. In RA patients, both anti-TNF therapies and anti-B-cell-directed therapy (rituximab) are associated with reduction in RF and cytokine levels.[27,28]There are no controlled trials investigating the role of anti-TNF therapies or rituximab for treating extra-articular manifestations of RA. However, uncontrolled studies have suggested that these biologic therapies may be effective for treating cardiovascular disease,[29,30]anemia of chronic disease,[31] vasculitis,[32] osteoporosis,[33,34] amyloidosis (Tocilizumab)[35,36]and ocular manifestations[37] that

accompany RA. Nonetheless, anti-TNF therapy should be used with caution in some RA patients with extra-articular manifestations on the basis of multiple case reports describing the development of interstitial lung disease and leukocytoclastic vasculitis following treatment with anti-TNF therapies.[38]

GUIDANCE FOR USE OF BIOLOGICALS IN RA

There is evidence (of varying strengths) that biologics are effective in four clinical situations:

- Prevention of RA.
- As first-line treatment for early active RA.
- When methotrexate and other DMARDs fail to control RA.
- When patients fail to respond to initial treatment with biologics, particularly TNF inhibitors.

Many guidelines have been devised to ensure that biologics are used in the most effective and cost-effective manner in RA. These include North American guidance, continental European guidance, and English guidance based on reviews by the National Institute for Health and Clinical Excellence (NICE).[22-24]The general ethos of this guidance is similar, although it differs in points of detail.

The common points shared by most guidelines are that:

- Biologics should be reserved for use in patients with active disease who have failed to respond to methotrexate and, potentially, to other DMARDs.
- It is preferable to give biologics in combination with methotrexate and, potentially, with other DMARDs.
- It is advisable to start with the most established biologics, which are usually the TNF inhibitors.
- If patients have active disease despite TNF inhibitors,alternative biologics should be administered until disease control is achieved or until the patient has failed to respond to all appropriate biologics.

The key issues about the place of conventional therapy and biologics in RA treatment are summarized in figure-3.

2012 ACR updated guideline for the use of Biologics in Patients of RA with Hepatitis, Congestive heart failure and malignancy is summarized in Table-3.

CONCLUSION

With all the improved and growing understanding knowledge of immune and inflammatory pathways in RA, newer treatments are a promising tool for effective disease control. Despite the remarkable success of such approaches in a proportion of patients in RA,many individuals do not derive sufficient benefit from these treatment modalities and new approaches are still necessary. Promising immediate targets are proinflammatory cytokines, as we have learned much about how to tackle them with existing tools—mostly mAbs or receptor-fusion proteins—that can now be specifically designed and produced in nearly unlimited amounts with excellent quality. Novel B-cell targets can also be bound by such agents. Developmental therapies also include chemokine-blocking approaches[25] and—at quite an early stage in development—RNA-based agents that interfere with gene expression and regulation.[26] In the future, other potential cytokine and synovium-specific targets include IL-23, IL-36, IL-37 and IL-38 as well as the hope to directly modulate synovial fibroblasts and various secreted proteases that are involved in the joint-destructive process in RA. Future challenges will be to identify patients as early as possible in the disease course, and presumably on the basis of biomarkers, tailor the best possible treatment approach to each individual patient as well as enhancing the proportion of patients achieving remission.

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FIGURE-1: Stepwise development of arthritis in RA.

a | Induction phase: initial activation of the (auto)immune system leads to an inflammatory cascade. Possible triggers are injuries, infections and exposures to toxic substances (smoking). These events, which involve APCs and the citrullination of relevant proteins, might occur outside of the joints as well as within them. Along with monocyte/macrophage infiltration into the synovium, local synovial cells, notably fibroblasts and macrophages, are activated leading to the secretion of proinflammatory cytokines of both the innate and adaptive immune systems.

b | Inflammation phase: self antigens, notably citrullinated proteins, are presented in the context of HLA class II molecules that are characteristic of RA. This presentation leads to polyclonal activation of T cells and B cells, and the formation of germinal like centres in the synovial tissue. This process is insufficiently controlled by TREG cells.

c | Self perpetuation: cartilage autoantigens, which are not normally accessible to the immune system, become exposed by damage and are presented, activating the immune system against cartilage tissue with further infiltration of pannus into the joints resulting in further destruction.

d | Destruction phase: synovial fibroblasts and osteoclasts are activated by proinflammatory cytokines such as TNF and IL 6. Destruction of bone and cartilage ensues. Abbreviations: APC, antigen presenting cell; GM CSF, granulocyte macrophage colony stimulating factor; RA, rheumatoid arthritis; TEFF, effector T (cell); TH, helper T (cell); TH1, type 1 helper T (cell); TH17, type 17 helper T (cell); TREG, regulatory T (cell).

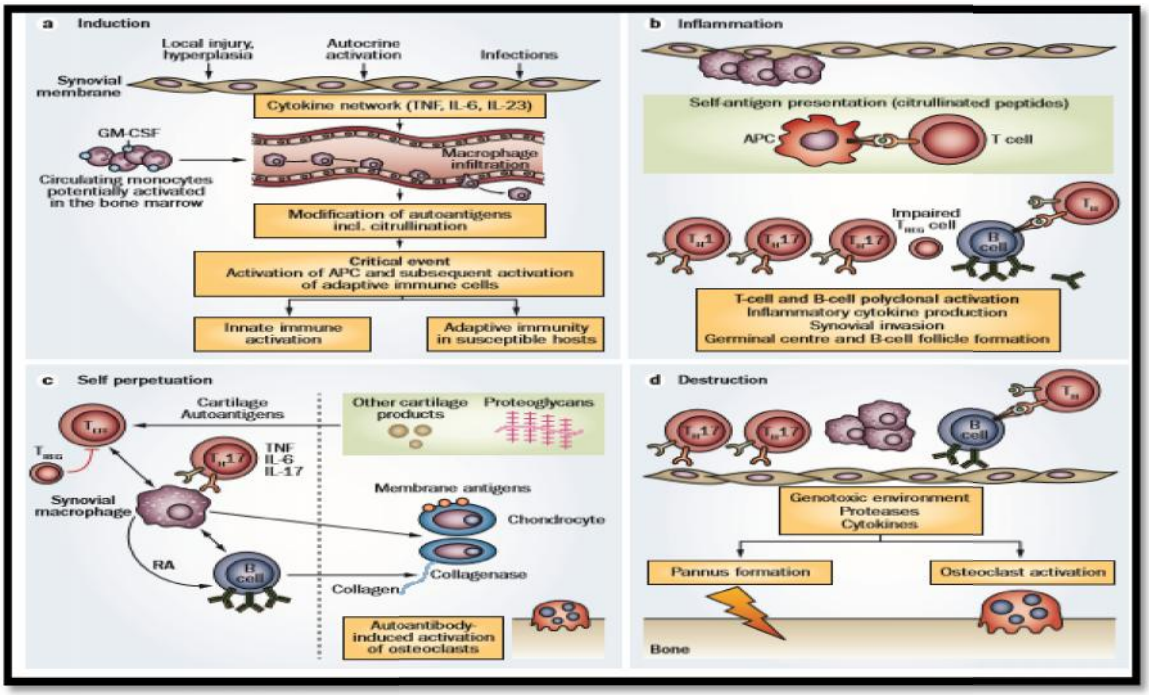

FIGURE-2

Potential interventions using TREG cells in RA. IL 2 treatment might directly restore and/or initiate the growth and/or function of CD25 positive TREG cells in vivo. TREG cells might be expanded in vitro and potentially be modified through genetic manipulation to target antigens present in the inflamed joint. These cells could then be transferred back to the patient. Another approach would be to specifically activate TREG cells using the anti CD4 monoclonal antibody tregalizumab. Finally, Tregitopes—peptides derived from human IgG—might be used to specifically activate TREG cells, dampening an autoimmune response. Abbreviations: DC, dendritic cell; IDO, indolamin 2,3 dioxygenase; RA, rheumatoid arthritis; TCR, T cell receptor; TREG, regulatory T (cell).

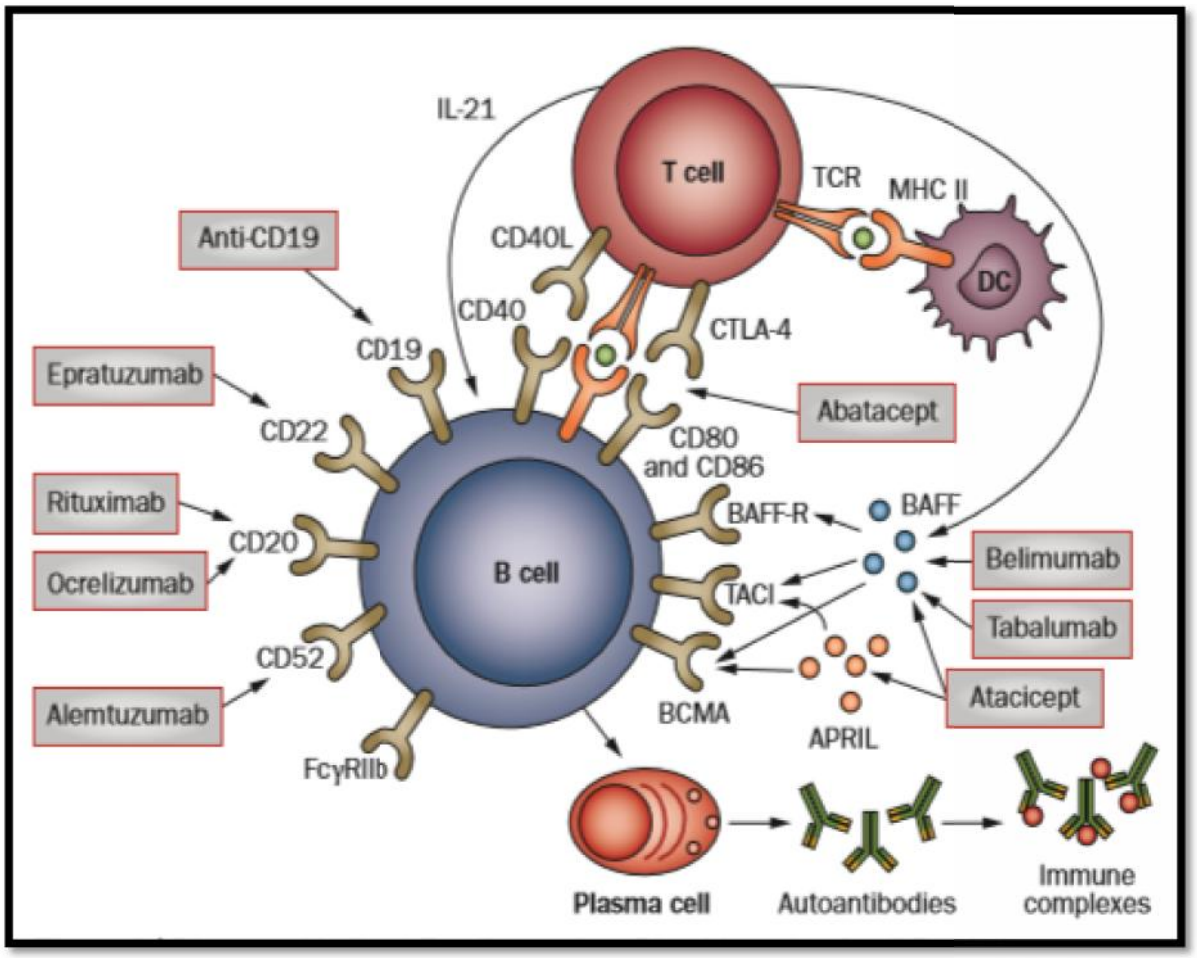

FIGURE- 3: Conventional Therapy and Biologics use overview.

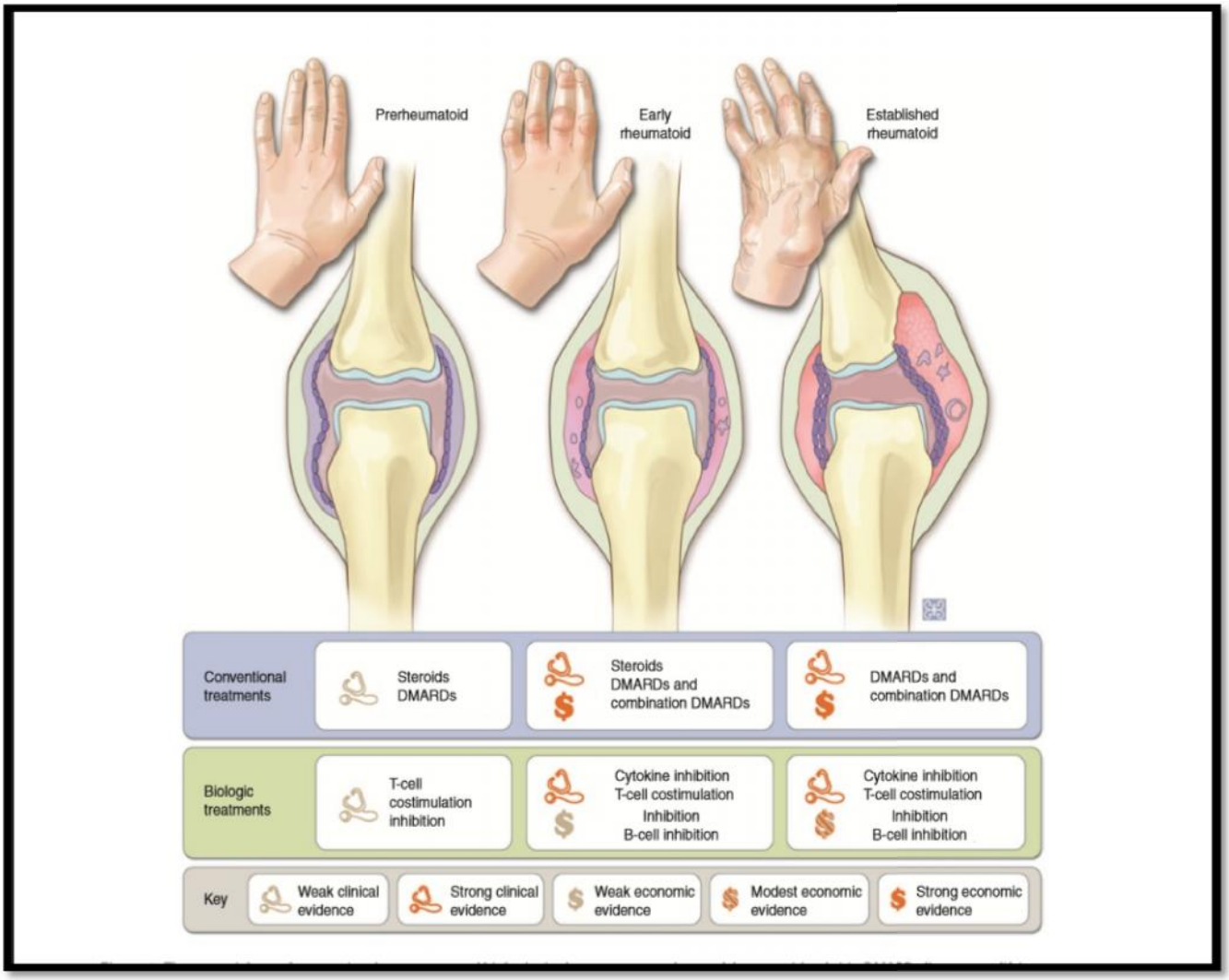

TABLE 1
Direct targeting of B-cell in Rheumatic Diseases:

Target: putative and/or intended mechanism of action	Agent	Developmental Status*
CD19; B cell depletion	MDX 1342 (anti CD19 fully human mAb)	Phase I trial in patients with RA (of single i.v. dose in combination with methotrexate) completed; no results posted.
CD20 type I; B cell depletion	Rituximab (chimeric anti CD20 mAb)	Approved for use in RA48,49,66 and ANCA associated vasculitis
	Ocrelizumab (humanized anti CD20 mAb)	Discontinued for RA and SLE
	Veltuzumab (humanized anti CD20 mAb)	Phase II study in patients with RA terminated ("trial re design; no safety issues identified"); no results posted
	Ofatumumab (fully human anti CD20 mAb)	Phase I/II reported69 Phase II trial in patients with RA ongoing; but currently not recruiting (support progression to phase III
CD22; peripheral reduction of B cells, inhibition of B cell activation (BCR via phosphorylation of SYK and PLCγ2) and proliferation	Epratuzumab (humanized anti CD22 mAb)	Phase III trials in patients with SLE ongoing and recruiting124,125 Phase II data reported.
CD52; depletion of T cells and B cells	Alemtuzumab (humanized anti CD52 mAb)	Phase I/II in RA, no further studies.

TABLE 2: Emerging cytokine targets in RA:

TARGET	AGENT	DEVELOPMENTAL STATUS
GM-CSF	Mavrilimumab (human anti GM CSFR α antibody)	Phase II trials in patients with RA ongoing; phase I/II results published, Phase II trial versus golimumab (anti TNF agent) in patients with RA recruiting
	MOR103 (human anti GM CSF mAb)	Phase Ib/IIa trial in patients with RA completed; no results posted
IL-17	Secukinumab (human anti IL 17A mAb)	Phase III trials in patients with RA recruiting
	Ixekizumab (anti IL17 mAb)	Phase II trial in patients with RA completed; no results posted (however, abstract presented).
IL-20	NNC0109 0012 (human anti IL 20 mAb)	Phase II trials in patients with RA and inadequate responses to methotrexate133 or anti TNF agents recruiting.
IL-21	NNC114 0005 (anti IL 21 mAb)	Phase I trial in patients with RA completed; no results posted.

TABLE -3: 2012 ACR updated guidelines for the use of Biologics in Patients of RA with Hepatitis, Congestive heart failure and malignancy:

Comorbidity/clinical circumstance	Recommended	Not recommended	Level of evidence
Hepatitis			
• Hepatitis C	Etanercept		C
• Untreated chronic hepatitis B or with treated chronic hepatitis B with Child-Pugh class B and higher†		Any Biological Agent	C
Malignancy			
• Treated solid malignancy >5 years ago or treated nonmelanoma skin cancer >5 years ago.	Any biological agent		C
• Treated solid malignancy within the last 5 years or treated nonmelanoma skin cancer within the last 5 years‡	Rituximab		C
• Treated skin melanoma‡			
• Treated lymphoproliferative malignancy	Rituximab Rituximab		C C
Congestive heart failure			
• NYHA class III/IV and with an ejection fraction of 50%§		Anti TNF Biologic	C

* For definitions and key terms, please refer to Table 2. NYHA New York Heart Association; anti-TNF anti–tumor necrosis factor.

† Therapydefinedasanantiviralregimendeemedappropriatebyanexpertinliverdiseases. TheChild-Pughclassificationliverdiseasescoringsystem is based on the presence of albumin, ascites, total bilirubin, prothrombin time, and encephalopathy. Patients with a score of 10 or more (in the class C category) have a prognosis with 1-year survival being 50%. Patients with class A or B have a better prognosis of 5 years, with a survival rate of 70–80%.

‡ Little is known about the effects of biologic therapy on solid cancers treated within the past 5 years, due to exclusion of these patients from most randomized controlled trials.

§ NYHA class III patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain. NYHA class IV patients with cardiac disease resulting in inability to carry out anyphysicalactivitywithoutdiscomfort.Symptomsofcardiacinsufficiencyorof angina syndromemaybepresentevenatrest.Ifanyphysicalactivity is undertaken, discomfort is increased