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TARGETED THERAPIES FOR RHEUMATOID ARTHRITIS: A REVIEW

Anju Lama* and Hiteswar Saikia

Department of Pharmacology, Melmaruvathur Adhiparasakthi Institute of Medical Science & Research, Melmaruvathur, India

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Correspondence to Author:

Dr. Anju Lama

Asst. Prof., Department of Pharmacology, Melmaruvathur Adhiparasakthi Institute of Medical Science & Research, Melmaruvathur, India

ABSTRACT

Rheumatoid arthritis (RA) is an aggressive disease that needs to be treated effectively if subsequent deformity and disability are to be reduced. A recent advance in the management of RA is the use of biological agents which block certain key molecules involved in the pathogenesis of the illness. They include tumor necrosis factor (TNF-α) - blocking agents, Anti-Interleukin-1receptor (IL-1) antagonist, anti-CD-20 agents, CTLA-4 Ig, anti IL-6 etc. These newer agents proved to be useful for alleviating symptoms and slowing the disease progression in the patients with RA who have failed to respond to conventional disease modifying anti-rheumatic drugs (DMARDs). DMARDs are nonspecific immunomodulators, each of which has substantial drawbacks in terms of effectiveness or adverse effects (AEs). The development of biologic agents has provided more effective therapeutic options. The terms biologic therapies and biologics have emerged to describe agents with biologic properties, including monoclonal antibodies and soluble cytokine receptors etc. The advent of effective biological agents has certainly been a major advance in the treatment of inflammatory arthritis, heralding a new era for rheumatology. In this review the focus is only on pathophysiology of the disease process as well as the recent advances with Biological response modifiers (BRMs) and its impact on current clinical practice in the treatment of RA.

INTRODUCTION: Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown cause. Although there are varieties of systemic manifestations, the characteristic feature of established RA is persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. The potential of the synovial inflammation to cause cartilage damage and bone erosion and subsequent changes in joint integrity is the hallmark of the disease. Despite its destructive potential, the course of RA can be quite variable. Some patients may experience only a mild oligoarticular illness of brief duration with minimal joint damage, but most will have a relentless progressive polyarthritis with marked functional impairment [1].

The prevalence of RA is relatively constant in many populations, at 0.5-1.0%. However, a high prevalence of RA has been reported in the Pima Indians (5.3%) and in the Chippewa Indians (6.8%) [2]. The concept that drugs should be used to slow down the damage caused by the disease rather than simply to control symptoms, which were initially called SAARDS or "*slow acting antirheumatic drugs*". These includes intramuscular or oral gold salts, D-penicillamine, antimalarial agents, sulphasalazine and methotrexate (MTX). The term SAARD was replaced with DMARDs and currently MTX is the most commonly used DMARDs in several rheumatic diseases. Other commonly used DMARDs include sulphasalazine (SSZ), hydroxychloroquine and leflunomide [3].

Non-steroidal anti-inflammatory drugs (NSAIDs) and Cox-2 selective inhibitors are associated with cardiovascular, gastrointestinal and renal risk [4]. The current goals of RA management are to relieve pain and inflammation, prevent joint destruction, preserve or improve functional ability, and maintain a patient's normal lifestyle. Although literature is constantly changing, there is still a role for traditional DMARDs in the treatment of RA but this will require the skills of a clinician to balance efficacy, toxicity, and cost [5]. "Cure" in RA is not possible with our currently available RA therapies; we do not yet have the capability to achieve "remission" in RA [6]. Clearly, therapies that regulate arthritic inflammation by controlling synoviocyte activation, suppressing immune cell cytokine release and inhibiting degradative enzyme expression would be valuable in controlling RA progression. The role of inflammatory mediators for pathogenesis of RA is being investigated tremendously to develop safer and more effective drugs. The development of BRMs has dramatically changed the present scenario of the therapeutic approach to RA as well as the other inflammatory diseases in general within the last few years.

Etiology and Pathogenesis of the Disease: The cause of RA remains unknown. It has been suggested that RA might be a manifestation of the response to an infectious agent in a genetically susceptible host. Because of the world wise distribution of RA, it has been hypothesized that if an infectious agent is involved, the organism must be ubiquitous. A number of possible causative agents have been suggested, including *Mycoplasma*, *Epstein-Barr* virus, *cytomegalovirus*, *Parvovirus*, and *Rubella virus*, but convincing evidence that these or other infectious agents cause RA has not emerged [1].

The pathogenesis of RA is complex and involves the collaboration of many cells of the immune system. Although there has been argument regarding the relative importance of the various cell types and processes found in rheumatoid synovium, it is generally agreed that the disease process involves abnormal presentation of self antigen by antigen presenting cells (APC), leading to activation of auto reactive T- lymphocytes, and that this autoimmunity is a fundamental element in the disease generation [7].

Molecular studies have shown that individuals bearing the HLA- DR4 (HLA- DR1 in some populations) haplotype with specific HLA- DQ and HLA- DP alleles are more likely to develop severe RA. Individuals with RA also have decreased numbers of $CD\text{-}4^{+}$ $2H^{+}$ suppressor- inducer cells in the synovium and thus may

be unable to contain ongoing articular inflammation. The concordance of RA in identical twins, however, is only about 30%, indicating that environmental factors are necessary to induce the disease [8]. A number of non-HLA loci that have shown evidence ($p < 0.05$) for linkage with RA have been previously identified. A rational basis for pursuing high-density linkage and association studies of RA in several regions outside of the HLA region, particularly on chromosomes 1p, 1q, and 18q [9].

The viability of population screening for RA and identifies several high-risk genetic combinations. However, given the population incidence of RA, genetic screening based on these loci alone is neither sufficiently sensitive nor specific at the current time. Combinations of RA susceptibility factors increase risk of disease above any one factor alone. Genetics alone cannot currently accurately predict an individual's risk of disease. Genetic screening for RA is not currently viable, although it may be in the future [10].

The joint destruction is promoted by degenerative enzymes from polymorphonuclear leukocytic, synovial cytokines and chrondrocyte-derived degradative enzymes such as collagenase and stromelysin. IL-6 released in response to IL-1 production has been shown to inhibit matrix synthesis by chondrocytes. Bone destruction is also promoted by release of IL-1 and other cytokines such as TNF-α, TNF-β, and colony-stimulating factors (CSF). The majority of the lymphocytes in the synovium in RA are activated T-cells, many of which have acquired reactivity against native chondrocyte membranes, and so local cytotoxic effects are also possible. The persistent inflammatory response produces the characteristic pathologic stigmas of RA [8].

Polymorphic alleles in candidate genes for osteoporosis, such as the *VDR (vitamin D receptor) TaqI t* and *BsmI B*, are associated with accelerated generalized bone loss in RA. Polymorphisms in *VDR* and inflammatory response genes IL6, TNF receptor type 2 may serve as genetic markers of systemic bone loss in RA [11]. The role for vitamin D in the pathogenesis of autoimmune and inflammatory diseases is emerging. Inadequate levels of serum 25-hydroxyvitamin D are not only detrimental to musculoskeletal health and calcium homeostasis but may also have a role in immunopathology. Recently, M. Mouyis *et al,* found that, Hypovitaminosis D is common among rheumatology patients, particularly low levels are seen in inflammatory arthritis and chronic pain /fibromyalgia [12].

There has recently been renewed interest in the link between cigarette smoking and RA and suggestive of an increased risk [13]. Britt-Marie NW *et al* showed that high disease activity and disability in the first two years are risk factors for severe extra-articular RA. Current smoking, high disease activity at RA onset and rheumatoid factor (RF) seropositivity also increase the risk [14]. Apart from these causative factors, the involvement of hypoxia and oxidative stress is also involved in the pathogenesis of RA [15].

Cytokines in the pathogenesis of rheumatoid arthritis: Cytokines regulate a broad range of inflammatory processes that are implicated in the pathogenesis of RA. In rheumatoid joints, it is well known that an imbalance between pro- and anti-inflammatory cytokine activities favors the induction of autoimmunity, chronic inflammation and thereby joint damage [16]. Cytokines are the small peptides with potent short-range biological actions, appear to play a key role in the process of joint inflammation; it would appear that this complex process includes several interdependent interactions between pro-inflammatory and anti-inflammatory mechanisms.

They have been shown to be important mediators of several fundamental biological processes that include inflammation, tissue repair, cell growth, fibrosis, angiogenesis and immune response. The major pro-inflammatory cytokines are TNF-α, IL-1, IL-8, INF-α, IL-6, IL-12 and IL-2. The major anti-inflammatory

cytokines are IL-4, IL-10, IL-13, IL-5, IL-1 receptor antagonist, soluble TNF receptor and they block the action of pro-inflammatory cytokines, proteolytic enzymes (that are involved in the cartilage damage), and up regulate the IL-1 receptor antagonist (IL-1Ra), a major anti-inflammatory cytokine. So, pro-inflammatory cytokines could be the major targets for therapeutic manipulation in RA [17]. IL-17A also shows a weak association with RA [18], T cells secreting IL-17 may have an important role in autoimmune disease. Th17 cells have been shown to be enriched in juvenile arthritis and adult seronegative arthritis [19].

Considerable evidence accumulated over the past decade has clarified some of the mechanisms of cell-cell interactions in rheumatoid synovitis and the important roles of IL-1 and TNF-α in inflammation and tissue destruction. These advances in knowledge have led to the development of novel anti-cytokine therapies for RA. However, in spite of these successes, disagreement remains concerning the relative roles of T cell- dependent versus T cell- independent mechanisms and of IL-1 versus TNF-α in the initiation and perpetuation of rheumatoid synovitis [20]. In actively inflamed rheumatoid synovium, activation of T cells, B cells, macrophages, fibroblasts, endothelial cells and plasma cells can be identified.

Pro-inflammatory cytokines are spontaneously produced. Specifically, IL-1, TNFα, lymphotoxin, IL-6 and a range of chemokines have been identified. To counter this enormous load of pro-inflammatory cytokines, a number of anti-inflammatory mediators are up-regulated. The anti-inflammatory cytokines and receptors are insufficient to block the action of the pro-inflammatory cytokines and this leads to fatigue, fever, elevation of acute phase proteins, angiogenesis, bone marrow suppression, increase in adhesion molecules on endothelium, activation of macrophages, and induction of metalloproteinases and Leukotrienes. All of these effects contribute to active RA [21]. A case-control study was performed by Kokkonen *et al* in 2009 [22], to identify whether cytokines, cytokine related factors, and chemokines are up-regulated prior to the development of RA or not. Finally they concluded that, individuals before the onset of symptoms of RA have elevated concentrations of pro-inflammatory cytokines, cytokine-related factors, and chemokines, indicating activation of the immune system. In that study, such activation occurred before any symptoms of joint involvement. These findings present an opportunity for a better prediction of the risk of developing RA and, therefore, possibly preventing disease progression.

Treatment Approach: Pharmacotherapy for RA generally involves NSAIDs for control of pain, with selective use of low-dose oral or intra-articular (IA) glucocorticoids, and initiation of DMARDs. In past decades, pharmacologic treatment of RA was managed using a pyramid approach: symptom-alleviating treatment was started at diagnosis, and only with progression of symptoms were dosages changed or additional medications added. However, a “reverse pyramid” approach now is favored, in which DMARDs are initiated quickly to slow disease progression as early as possible. A number of additional, non-pharmacologic treatments for RA have been tried.

Therapeutic fasting, dietary supplementation of essential fatty acids, and journaling have shown benefit, as have spa therapies and exercise. Patient education and a multidisciplinary approach to patient care provide at least short-term benefits. Evidence is inconclusive regarding herbal medications, acupuncture, and splinting. Surgery should be considered when pain is unacceptable, loss of motion is significant, or functional impairment is severe [23]. To initiate treatment of very early RA with symptomatic therapy, DMARDs, or BRMs, it is a very important question for a general practitioner. Axel Finckh *et al.,* showed that therapeutic strategies involving early conventional DMARDs or early BRMs are preferred, but the additional costs of early BRMs may not be justified for all patients. The most rational use of resources is prompt initiation of conventional DMARD

therapy for patients with very early RA [24]. Despite tremendous advances in therapy, RA remains a cause of substantial morbidity and increased mortality. To treat patients with newly diagnosed RA, James R. O'Dell *et al.,* recently enumerated some points. First, with the ever-increasing complexity, expense, and toxicity of modern therapy, a rheumatologist should be actively involved in the care of all patients with RA in conjunction with the primary care physician. Second, all patients should receive a DMARD (in most cases MTX) as soon as possible. Finally, rheumatologists should adjust therapy in a timely fashion (increasing doses or adding other DMARDs) until patients have achieved low levels of disease activity (or are in remission) [25].

As for example, Prednisone 10 mg/day, provides clinical benefit, particularly in the first 6 months, and substantially inhibits progression of radiologic joint damage in patients with early active RA and no previous treatment with DMARDs. Because of their limited disease modifying effects, glucocorticoids should be combined with DMARDs in patients with RA. Glucocorticoid-induced osteoporosis is a major side effect [26]. Though medium- to long-term glucocorticoid therapy in RA is associated with toxicity compared to placebo, long-term- low-dose glucocorticoid therapy is not considered a substitute for aggressive therapy for early RA [27]. On the other hand Lydia G. Schipper *et al.,* found that, addition of MTX to SSZ is a therapeutic option in SSZ failures. Combination of MTX and SSZ in DMARD-naive patients has no added value unless combined with glucocorticosteroids [28]. Increased disease severity, corticosteroid use and co morbidities are associated with an increased infection risk. Low-dose MTX does not appear to increase infection risk in RA patients [29].

Biological response modifiers: The term "*biological response modifiers*" or '*Biologicals*' (BRMs) may be used to refer to those agents or approaches that modify the host's response to pathogens and have beneficial effects on disease. BRMs have the potential to inhibit the behavior of cytokine, cellular activation, and inflammatory gene transcription by various means. These include monoclonal antibodies (mAb), soluble cytokine receptors and natural antagonists. The first two biologicals developed for the treatment of RA were the TNF-α inhibiting agent, 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. These biologicals represent a major advance in the treatment of RA [30].

TNF-α inhibitors: TNF-α is a proinflammatory cytokine that has a complex role in the pathogenesis of RA. TNF-α induces deleterious effects in several inflammatory diseases through the binding with two different receptors (called types I and II), which are expressed in all cell types except erythrocytes [31]. Its precursor form, Transmembrane TNF-α, is also involved in the inflammatory response. Transmembrane TNF-α exerts its biological function in a cell-to-cell contact fashion, which is distinct from the feature of soluble TNF-α, which acts at sites remote from the TNF-α producing cells [32]. The development of anti-TNF-α therapy has been a milestone in the treatment of RA and is proving equally important in other inflammatory-mediated conditions [33].

These drugs can be effective in patients who have failed to respond to DMARD therapy; however, some fail to show an improvement, partially respond or develop side-effects necessitating discontinuation of therapy. In one retrospective cohort study shows, 57% of patients who remained on therapy despite failing the 3 month assessment attained a response by 6 months [34]. These agents can be divided into two groups. The first one is constituted from antibody to TNF-α (Infliximab, Adalimumab, Golimumab, and Certolizumab pegol), and the second one is constituted from TNF-α receptors linked to Fc domains (Etanercept) [35]. These drugs are also being used or studied for use in non rheumatic diseases, including

asthma, inflammatory eye disease, psoriasis, lymphoma, and sarcoidosis [36]. Chung ES *et al.,* noted one important concern about the safety of using anti-TNF-α (especially at high doses) for the treatment of non-cardiac disorders in patients who also have moderate-to-severe heart failure, was associated with an increased risk of worsening heart failure [37].

Anti-TNF-α agents significantly improve disability in patients with persistent disease activity despite standard DMARDs [38]. It may also exert some beneficial effects on bone metabolism in RA patients [39]. On the other hand, there is also known risks of infection with intracellular organisms such as *Salmonella, Listeria, Histoplasma, Mycobacteria and Toxoplasma.* Individual reports of patients with viral infections, sepsis, thrombosis, heart failure, liver failure, lymphoma and worsening of multiple sclerosis also suggest caution in using TNF-α inhibitors [21].

Etanercept: Etanercept, a genetically engineered fusion protein consisting of two identical chains of the recombinant human TNF-receptor *p*75 monomer fused with the Fc domain of human IgG1 binds and inactivates TNF [40]. The fusion protein binds to circulating TNF and reduces the amount of inflammatory cytokines available for membrane receptor binding. The Fc portion of the immunoglobulin increases the proteins half-life. It has a half life of 4-5 days [41]. It is the first BRM approved for use in the treatment of RA and juvenile RA. It acts as a molecular sponge to mop up excess TNF, has been demonstrated to be highly effective in patients who have failed conventional therapy and can be used in combination with MTX [42].

Genovese *et al.,* compared the clinical and radiographic outcomes in patients with RA who received monotherapy with either etanercept or MTX for 2 years and to assess the safety of this therapy and concluded that, etanercept and MTX had excellent profiles for initial treatment of patients with active, erosive RA. The benefits of 25-mg etanercept as monotherapy were shown to be superior to those of MTX at 2 years, and improvements in clinical, radiographic, and disability end points were maintained with sustained therapy [43]. On the other hand, Moreland LW *et al.*, sought to define further the clinical activity of Etanercept over a longer treatment period and to establish a simplified dosing schema and found that, Etanercept was well tolerated and effective in reducing disease activity in patients with active RA who had an inadequate response to DMARDs therapy.

They studied in patients with long-standing RA (mean duration, 12 years), and 90% had previously been treated with MTX. Clinical response to etanercept was rapid, beginning as early as 2 weeks after initiation of therapy, and was maintained throughout the 6-month study. They concluded that, twice-weekly SC (25-mg) administration of etanercept resulted in significant improvement in disease activity and quality of life with minimal toxicity in patients with active RA [44]. Misra R *et al.*, also studied the open label phase IIIb for the safety and efficacy of Etanercept in Indian patients with RA, and concluded that Etanercept 25 mg SC, twice weekly was very well tolerated. There was one SAE, diabetes mellitus that was severe and probably related to Etanercept [45]. Although etanercept is a very effective therapy, greatest concern is about its undesired and potential side effects.

The adverse effects of etanercept are as follows: Injection site reactions (ISR), Increased risk of serious infections, Opportunistic infections have been reported as the commonest AE, Exacerbation of previously quiescent multiple sclerosis, Aplastic anemia, Interstitial lung disease. Lupus like syndrome, Hepatotoxicity, reactivation of prior tuberculosis, Optic neuritis (rare), and an increased risk of lymphoma has also been reported. Therefore it should be used cautiously in patients with history of malignancy [46]. Baumgartner *et al.,* compared etanercept- induced improvement in disability of patients with recent onset of RA to that of patients with established RA and finally they concluded that, Etanercept therapy improves

disability in patients with early and long-standing RA, with greater benefit conferred on patients with early disease. Early intervention provides an opportunity to achieve and maintain greater physical function in patients with RA [47]. Kremer *et al.,* observed the long-term safety and efficacy of combination therapy with etanercept and MTX in patients with RA, whether the addition of etanercept allowed reductions in MTX or corticosteroid dosages while maintaining a clinical response or not. They found that the addition of etanercept therapy in patients receiving background MTX provides sustained clinical benefit and continues to be well tolerated with extended use [48].

On the other hand Vollenhoven *et al.,* found that the combination of etanercept plus MTX was clinically more efficacious than etanercept alone. In patients who have an insufficient clinical response to MTX, the addition of etanercept to MTX may give better efficacy than instituting etanercept as monotherapy (i.e. switching from the one drug to the other). They also suggest that, in patients receiving etanercept as monotherapy with only partially satisfactory responses, the addition of MTX might give additional clinical benefit. It could play a role of some importance in guiding physicians' decision-making processes [49].

Blumenauer *et al.,* assessed the efficacy and safety of etanercept for the treatment of RA from electronic databases, searched from 1966 to February 2003 without language restriction. This study suggests etanercept is well tolerated and safe. The most common side effect was ISR. However, there are concerns with increased incidence of infections (particularly tuberculosis) and possibly increased malignancy risks, so the long-term efficacy and safety need to be further evaluated [50]. Gerd Horneff *et al.*, evaluated safety and efficacy of etanercept once weekly 0.8 mg/kg up to 50mg SC for the treatment of resistant polyarticular JIA in a 3 month open label trial. They found that JIA patients can effectively be treated with etanercept once weekly 0.8 mg/kg. During this short study period there was no serious AEs [51].

Infliximab: Infliximab, a chimeric monoclonal antibody (75% human, 25% mouse protein) which targets both soluble and membrane-bound forms of TNF-α by binding with high avidity and specificity. Thus, infliximab neutralizes the effect of this cytokine and its ability to induce other downstream biological mediators associated with chronic inflammatory diseases [39]. Infliximab is given in a dose of 3mg/kg as an IV infusion at '0', '2', '6'weeks repeated every 2 months thereafter. It has a half-life of 8-12 days. It is useful in the treatment of RA, Seronegative Spondylarthropathy (SSA), Crohn's disease, systemic inflammatory diseases including various vasculitides and adult onset Still's Disease (AOSD). Infliximab is effective in controlling ocular and mucocutaneous inflammation in Behçet syndrome [41].

U. Lange *et al.,* demonstrated the beneficial effects of infliximab in RA therapy are accompanied by a significant amelioration of different parameters of bone metabolism, suggesting a profound effect- similar to the findings in patients with spondyloarthropathies- on osteoprotective pathways [39]. Lipsky PE *et al.,* suggested that the combination of infliximab and MTX improves the symptoms and signs of inflammation, physical function, and the quality of life and prevents radiographic evidence of progressive joint damage in a majority of patients with RA who have no response to MTX alone [52].

The rate of tuberculosis (TB) is not increased in RA patients generally. Among infliximab-treated patients, the rate is 52.5 cases per 100,000 patient-years of exposure. A thorough medical history regarding TB, as well as tuberculin testing and radiographic examination (if indicated), should be an essential component of anti- TNF-α therapy [53]. Therefore, clinicians should be aware of the risk for TB and the need to appropriately screen patients for TB (pulmonary as well as extrapulmonary) risk factors before and during starting infliximab therapy, because patients may develop active TB even when their prescreening tuberculin skin test is negative [54].

Adalimumab: Adalimumab is developed through phage-display biotechnology and is the first human (100% human peptide sequences) anti-TNF-α monoclonal antibody to be investigated for the treatment of RA, structurally and functionally analogous to naturally occurring human IgG1. It has a terminal half-life comparable with that of human IgG1 (~14 days) and demonstrates a high specificity and affinity for TNF-α. Adalimumab exerts its therapeutic effects by blocking the interaction of TNF-α with the 'p-55' and 'p-75' TNF cell surface receptors. It controls the signs and symptoms of RA and has a positive effect on the long-term radiographic outcome [55]. It is administered as a single SC injection (20-80mg) every other week. Serious infections, neurological effects, and certain malignancies of the lymphoid system are the serious adverse effects associated with it [56].

Keystone *et al.,* investigated a randomized, Placebo-Controlled, 52-Week Trial for the ability of adalimumab, to inhibit the progression of structural joint damage, reduce the signs and symptoms, and improve physical function in patients with active RA receiving concomitant treatment with MTX. They concluded that addition of adalimumab (40 mg every other week or 20 mg weekly administered SC) to the MTX regimen in patients partially responsive to MTX provides additional benefit, with inhibition of the progression of structural joint damage, reduction in the signs and symptoms, and improvement in physical function and health-related quality of life [55].

Adalimumab is approved by the US FDA to treat RA and it is effective and safe in patients with previous biological failures, especially to infliximab [57]. The effectiveness and safety of adalimumab in treating patients with ankylosing spondylitis (AS) and advanced structural damage was investigated by *Martin Rudwaleit et al*. They found Adalimumab was effective in patients with advanced spinal ankylosis, including patients with bamboo spine [58]. On the other hand, Adalimumab induces remission more frequently than placebo in adult patients with moderate to severe Crohn's disease who cannot tolerate infliximab or who have symptoms despite receiving infliximab therapy [59].

Golimumab: Golimumab is a human mAb raised against TNF-α produced in immunized transgenic mouse with human TNF-α giving specific antibodies with human-derived variable and constant regions. It was approved for the treatment of adults, beginning from 18 years old, with moderate to- severely active RA after SC injection in a dose of 50 mg once a month. It is intended for use in combination with MTX for RA treatment and with/without MTX or other DMARDs and or NSAID for psoriatic arthritis (PA) and ankylosing spondylitis (AS). As majority of TNF-α blockers, Golimumab inhibits soluble and transmembrane forms of TNF-α binding to their specific receptors and blocking in consequence their bioactivity.

Furthermore, Golimumab neither bind nor inhibit other members of TNF-α as the lymphotoxin (TNF-β). Competing with TNF-α receptors, Golimumab regulates TNF-α pro-inflammatory cytokines essentially produced by activated macrophages. Golimumab has also the power to fix complement inducing cell lysis and to participate in immune responses implicating antibody-dependent cell cytotoxicity function [35].

Certolizumab: Certolizumab, like adalimumab, etanercept and infliximab, is a TNF-α inhibitor indicated for RA. It is a recombinant humanised antibody Fab' fragment which has been pegylated to extend its plasma half-life to that of the whole antibody. Peak plasma concentrations are reached between 54 and 171 hours after SC administration and its bioavailability is approximately 80%. The terminal elimination half-life is around 14 days. However, the presence of antibodies to certolizumab increases its clearance and appears to correlate with reduced patient responses. Giving MTX concomitantly with certolizumab reduces the formation of anti-certolizumab antibodies. Certolizumab is indicated for adults with moderate to severely active RA. It should

be combined with MTX in patients who have had an inadequate response to or are intolerant to other treatments with one or more DMARDs. Certolizumab should only be given on its own if MTX is contraindicated or not tolerated. This drug is contraindicated in patients with moderate to severe *congestive heart failure and pregnancy.* It should not be used in combination with anakinra or abatacept. Live or attenuated vaccines should not be given with certolizumab. Certolizumab offers an alternative to patients who have not responded to other RA treatments [60].

Strand V *et al* found Patients treated with certolizumab plus MTX reported significant (P <0.001), clinically meaningful improvements in health-related quality of life (HRQoL) at the first assessment (week 12); reductions in fatigue, disease activity and pain and improvements in physical function were reported at week 1. Certolizumab treated patients reported improvements, particularly in mental health. They concluded that, treatment with certolizumab plus MTX resulted in rapid and sustained improvements in all patient-reported outcomes, indicating that the benefits of certolizumab extend beyond clinical efficacy endpoints into areas that are more relevant and meaningful for patients on a daily basis [61].

Lanercept: This is another TNF-α inhibitor. The production of this soluble TNF-receptor p55 dimer was halted by its pharmaceutical sponsor despite initial clinical benefits and safety [62].

IL-1 receptor antagonist*:*

Anakinra: Anakinra, a recombinant interleukin-1 receptor antagonist (IL-1ra), specifically inhibits the proinflammatory and destructive pathophysiological effects of IL-1 [63], received regulatory approval from the US Food and Drug Administration late in 2001 and from the European Commission in 2002 for the treatment of patients with RA. The uses of anakinra as monotherapy in patients with moderate to- severe RA or as combination therapy in patients with active disease despite DMARD treatment. To date, anakinra has primarily been used in patients receiving concurrent DMARD therapy with ongoing active disease [64].

The structure of anakinra differs by only one amino acid from the structure of the naturally occurring human IL-1 receptor antagonist. This difference is to enable genetically engineered *Escherichia coli* to produce anakinra. Patients have to subcutaneously inject anakinra every day. The maximum plasma concentration is reached in 3-7 hours. Anakinra is probably cleared by the kidneys and has a half-life of 4–6 hours.

The most common adverse effect of anakinra was injection site reactions (ISRs). Serious infections such as pneumonia occurred more frequently. Anakinra does not appear to be more effective than etanercept or infliximab [65]. Anakinra is the first and only selective blocker of IL-1. The extensive safety analysis of anakinra in patients with RA has demonstrated that the agent is well tolerated, even in those with co-morbidities or receiving concomitant medications. Furthermore, the short half-life of anakinra (4-6 h) provides flexible control of therapy and may therefore have significant benefits with respect to the prevention and treatment of serious adverse events (SAEs).

Fleischmann RM *et al.,* summarized the over all safety of anakinra in patients with RA, from the analysis of five randomized, placebo-controlled trials involving a total of 2932 patients, that there were no significant differences between anakinra $\leq$100 mg/day and placebo with respect to the development of adverse effects. ISRs were the most common cause for withdrawal with any dose of anakinra- 7.3% of patients receiving anakinra 100 mg/day and 7.1% of patients receiving anakinra at doses >100 mg/day withdrew due to ISRs, compared with 1.3% of patients receiving placebo. In the anakinra 100 mg/day group, SAEs that occurred in >0.2% of patients included worsening of RA (0.7%), pneumonia (0.9%), abdominal pain (0.3%), abdominal hernia (0.2%) and dyspnoea (0.3%) [66].

Anakinra is an important addition to the rheumatology treatment armamentarium. B. Bresnihan and M. Cobby has found from large efficacy studies that treatment with anakinra results in significant improvements in the signs and symptoms of RA and has beneficial effects on functional status. The therapeutic effects occur early and are sustained throughout treatment. In addition, treatment with anakinra retards the rate of structural joint damage in RA and is beneficial in preserving and protecting bone and cartilage [63].

According to one meta-analysis performed on the basis of randomized placebo-controlled trials, rituximab, abatacept and anakinra seem to be safe as regards the risk of serious infections. Nevertheless, an increased risk was observed for high doses of anakinra (>100 mg) in patients with co-morbidity factors. Moreover, such clinical trials select patients who are not representative of all patients with RA in daily practice. Thus the use of these biological agents will require careful monitoring in daily practice especially in patients with co-morbidity conditions and with concomitant treatments, such as steroids [67].

The new therapeutic targets in rheumatoid arthritis: the IL-6 & IL-23 receptor: IL-6 is the most abundant cytokine in the serum and synovial fluid (SF) of patients with RA and levels correlate with both disease activity and joint destruction. IL-6 is a multitarget cytokine with activity relevant to RA at joint and systemic levels. At the joint, IL-6 has a pivotal role in the inflammatory process, in osteoclast-mediated bone resorption and in pannus development through increased VEGF expression. IL-6 is pro-inflammatory, induces acute-phase proteins (including CRP) and contributes to the systemic manifestations of RA though hepcidin production (anaemia), its potent action on the HPA axis (fatigue) and its impact on bone metabolism (osteoporosis). In addition, IL-6 may contribute to the induction and maintenance of the autoimmune process through B-cell modulation and Th17 cell differentiation. These findings make IL-6 activity a logical target for inhibition in patients with RA [68]. In another study, Philippa Hillyer *et al.,* concluded that there is small amounts of cell-associated IL-23 are found in RA synovial tissue (ST) and this IL-23 regulates endogenous IL-17 production in RA- ST Explants. So, IL-23 would be a potential therapeutic target in Rain near future [69].

Tocilizumab: Tocilizumab (TCZ) is a humanized anti-human IL-6 receptor antibody (IL-6Ra) that blocks the IL-6 signaling pathway. It was created by using complementarily determining region grafting techniques to humanize a mouse monoclonal antibody that neutralizes IL-6 function by binding to human IL-6R, and is manufactured in Chinese hamster ovary cells. TCZ is an IgG1 subclass antibody and is a κlight chain glycoprotein with a molecular weight of 148 kDa. TCZ inhibits the binding of IL-6 to IL-6R and thus blocks IL-6 signaling in cells. The serum IL-6 level is closely related to disease activity in RA patients, and many of the local and systemic symptoms and signs of RA can be attributed to the overproduction of IL-6 [70].

TCZ is used in the targeted therapy of RA as well as juvenile idiopathic arthritis (JIA). Within recent years, TCZ has been used for RA patients with treatment-resistant disease. The blockade of the biological functions of IL-6 may theoretically be available through a blockade of the gp130 receptor by neutralizing IL-6 or by the prevention of the IL-6/IL-6R complex formation. Since the *gp130* homodimer is shared among other receptors than for IL-6, the blockade of *gp130* may implicate a wide range of undesirable effects. TCZ, formerly myeloma receptor antibody (MRA), is a humanized anti-IL-6R mAb engrafted with a human IgG1 Fc to minimize potential immunogenic responses in humans. It has a high affinity to IL-6R and abrogates the IL-6 signaling by preventing the formation of the IL-6/IL-6R complex [71].

Atlizumab: This monoclonal antibody also acts on IL-6 receptor. Main drawback of this mAb is increased blood cholesterol level. It is given in the dose of 2-8 mg/kg body weight intravenously, every 2 weeks [62].

Anti-CD20 therapy in RA patients: Rituximab: Rituximab (RTX), a chimeric anti-CD-20 mAb was approved in 1997 for non-Hodgkin's lymphoma. RTX depletes B cells that have CD-20 on their surface (including pre-B cells through mature B cells; but not stem cells or plasma cells) by several effector mechanisms. B cells contribute to the pathophysiology of RA and other autoimmune conditions, providing the rationale for the study of RTX. RTX has been approved by the US FDA for use in adult patients with moderate to severe RA who have not responded adequately to the TNF-α antagonists [72]. It is hypothesized that, RA may be driven by auto-reactive B-lymphocytes and RTX tends to deplete B cells, thus diminishing the progression of the disease [73].

RTX 2×1000 mg in combination with MTX resulted in a significant clinical and radiographical benefit in patients with an inadequate response or intolerance to TNF-α inhibitors, and this dose or a lower dose of 2×500 mg resulted in significant improvements in disease activity in patients with an inadequate response to non-biological DMARDs. Andrea Rubbert-Roth *et al.,* evaluated the efficacy and safety of three dosing and repeat treatment regimens of RTX plus MTX in patients with active RA in a Phase III randomized study (MIRROR) and concluded that, RTX is effective and well tolerated in patients with an inadequate response to DMARDs irrespective of the earlier treatment with a TNF-α inhibitor and some efficacy outcomes suggest improved outcomes for RTX 2×1000 vs 2×500 mg.

The safety profile of RTX remained favorable, with no new safety signals becoming apparent with repeat courses [74]. Viruses may be part of the pathogenesis in RA. Also, susceptibility to viral infection may in fact increase in RA patients as a result of immunosuppressive therapy. EBV and parvovirus genomes are frequently found in bone marrow of RA patients. The presence of EBV genome was associated with a better clinical response to RTX. Thus, presence of EBV genome may predict clinical response to RTX. Mattias Magnusson *et al.,* found that the significant better effect of RTX therapy in EBV-positive patients as opposed to non-EBV patients indicates that B cells are part of the RA pathogenesis in RA patients infected with EBV, but less so in the pathogenesis of uninfected RA patients.

What defines these B cells, apart from being infected with EBV, remains to be determined [75]. RTX may be used in patients with active RF-positive RA, who have had an incomplete response or intolerance to an adequate course with TNF-α inhibitors and also can be used in patients with an inadequate response or intolerance to more than one conventional DMARD, who cannot receive TNF-α inhibitors. RF-negative patients also can be considered for RTX treatment if they fulfill the treatment failure criteria [76].

Taru A. Hallinen *et al.,* evaluated the cost–utility of different treatment strategies in severe RA after TNF-α inhibitor failure in Finland and concluded that, RTX is the most cost-effective treatment strategy in RA after failure of TNF-α inhibitors [77]. Ziswiler HR *et al* found that high-resolution ultrasound confirms reduced synovial hyperplasia following RTX treatment in RA. Grey-scale US provides evidence of reduced synovial hyperplasia and improved RA disease activity after RTX treatment [78].

Selective Inhibition of T-Cell Activation: Abatacept: Abatacept belongs to a new class of selective co-stimulation modulators. This agent may have novel mechanism of action at the level of the T cell [79]. A fusion protein- cytotoxic T-lymphocyte-associated antigen 4-IgG1 (CTLA4Ig) - is the first in a new class of drugs known as co-stimulation blockers being evaluated for the treatment of RA. CTLA4Ig binds to CD80 and CD86 on antigen-presenting cells, blocking the engagement of CD28 on T cells and preventing T-cell activation. CTLA4Ig was safe and well tolerated, and the rate of discontinuation because of adverse events was no higher than that in the placebo group. In addition, no clinically significant antibody response to

CTLA4Ig was detected in either active-treatment group. Further more, the combination of CTLA4Ig and MTX improved the signs and symptoms of disease, physical function, and quality of life in patients who had active RA despite ongoing MTX therapy [80].

Abatacept (CTLA-4Ig) is a recombinant fusion protein comprising the extra cellular domain of human CTLA-4 and an Fc domain of human IgG1 that has been modified to prevent complement fixation. Abatacept competitively binds with high avidity to CD80/CD86 preventing these molecules from engaging CD28 on T cells, and thereby prevents full T-cell activation. Abatacept has been approved by the US FDA for use in adult patients with moderate to severe RA who have not responded adequately either to oral DMARDS (such as MTX) or to the TNF-α antagonists [72].

Genovese MC *et al.*, conducted a randomized, double-blind, phase 3 trial to evaluate the efficacy and safety of abatacept, in patients with active RA and an inadequate response to at least three months of anti-TNF-α therapy and they had concluded that, abatacept is clinically efficacious and has an acceptable safety profile in patients with RA and an inadequate response to anti- TNF-α therapy. Abatacept may thus represent a potential new treatment for patients, including those who have had an inadequate response to anti– TNF-α therapy [79]. In patients with moderately to severely active RA and inadequate response to MTX, abatacept therapy is cost-effective by current standards of medical practice [81].

Nixon R *et al.*, conducted a meta-analysis and adjusted indirect comparisons between the efficacy of inhibiting TNF- α and IL-1 in patients with RA, finally they concluded that TNF- α antagonist treatment is more efficacious compared with the IL-1 antagonist anakinra and TNF- α antagonist as a class are no different from each other [82]. Abatacept has intrinsic activity in patients with RA who's MTX and TNF-α inhibitor therapies have failed [83]. In the absence of direct comparisons of biological agents in patients with RA, practitioners are faced with a dilemma when choosing these drugs, for patients who have failed traditional DMARDs. Based upon indirect comparisons, anakinra seemed less efficacious than etanercept, adalimumab and rituximab; and etanercept seemed to cause fewer withdrawals due to adverse events than adalimumab, anakinra and infliximab.

Significant heterogeneity in characteristics of trial populations imply that these finding must be interpreted with caution. These findings can inform physicians and patients regarding their choice of biologic for treatment of RA [84]. Abatacept is clinically efficacious and has an acceptable safety profile in patients with rheumatoid arthritis. It may represent a potential new treatment for patients with rheumatoid arthritis, including those who have had an inadequate response to anti– TNF-α therapy [79]. Abatacept should be given as a 30-minute intravenous infusion. The dose is dependent on the patient's body weight. The infusion should be repeated at two and four weeks and then every four weeks after that. Following multiple 10 mg/kg intravenous infusions of abatacept, the serum concentration reaches a steady state after 60 days. The mean half-life is approximately 13 days in patients with RA, and clearance increases with body weight.

A one-year, multicenter, randomized, double-blind, placebo controlled trial evaluated the effects of abatacept in patients with persistent, active RA despite MTX treatment, that the clinical benefits seen with the fixed dosage of abatacept encompassed clinical and radiographic efficacy, statistically significant and clinically meaningful improvements in patients' physical function and HRQoL, and a consistent safety profile. This study also demonstrates the slowing of radiographic progression as well as the safety and clinical findings that are expected to be extended with longer-term observations by abatacept. Overall, abatacept seems to be a rational and effective treatment strategy for RA who has an inadequate response to weekly MTX [85].

J. C. Cole *et al.,* concluded in their two double-blind, placebo-controlled, multicentre randomized clinical trials that, quality of life improvements seen in abatacept clinical trials for RA can be converted into other metrics, including medical expenditure and likelihood of job loss. Converted Quality of life results indicated that abatacept resulted in significantly lower medical expenditure over time compared with placebo. Converted Quality of life results also indicated that abatacept results in significantly lower likelihood of job loss compared with placebo [86].

RECENT ADVANCES:

Tyrosine kinases as new targets for Rheumatoid Arthritis: RA is characterized by leukocyte infiltration, synoviocyte hyperplasia and osteoclastogenesis, and tyrosine kinases have key roles in the signaling pathways that regulate these processes. Blocking signaling through Bruton's tyrosine kinase might reduce B-cell and T-cell activation. Imatinib, which inhibits several tyrosine kinases, and more-specific inhibitors of Janus kinases (JAK) and syk, have shown efficacy in the treatment of RA; however, toxicity remains an issue. TKIs (tyrosine kinase inhibitors) such as imatinib and dasatinib are pleiotropic inhibitors- they might additionally inhibit TK that are not involved in RA, and thus be more likely to cause unrelated tissue damage and limits their therapeutic use [87].

Protein tyrosine kinase inhibitor:

Masitinib: (AB1010), a potent and selective protein tyrosine kinase inhibitor of c-KIT, in the monotherapy treatment of DMARD-refractory RA. The results of a multicentre, open-label, dose-ranging, phase 2- a study showed that, treatment with masitinib improved DMARD refractory active RA. This study has indicated that masitinib is a generally well-tolerated (especially after the initial 12 weeks) and effective treatment for DMARD-refractory active RA. Given the selective antimastocyte mechanism of action of masitinib, the results of this study help to further establish the critical role of mast cells in the pathogenesis of active RA. More specifically, this study supports the viability of exploiting the stem cell factor/c-KIT pathway as a therapeutic target [88].

Syk Kinase Inhibitor: Spleen tyrosine kinase (Syk) is a cytoplasmic tyrosine kinase that is an important mediator of immunoreceptor signaling in a variety of cells, including mast cells, macrophages, neutrophils, and B cells. Increased levels of phosphorylated Syk have been seen in RA synovial tissue. Syk activation is important in TNF-α induced cytokine and metalloproteinase production in RA fibroblast-like synoviocytes. Interruption of Syk signaling with an inhibitor therefore may interrupt TNF-α and metalloproteinase production involved in the development of RA. R788 (fostamatinib disodium) is a prodrug that, following oral administration, is rapidly converted to R406. R406 is a potent inhibitor of Syk kinase with considerable selectivity. *Weinblatt et al.*, has found in a twelve-week, randomized, placebo-controlled trial that an inhibitor of Syk kinase produces significant clinical benefits at 12 weeks in a population of patients with active RA receiving MTX therapy. Syk kinase may be an important new therapeutic target in RA and related autoimmune conditions [89].

Radiosynovectomy in Rheumatoid Arthritis: Radiosynovectomy or radiosynoviorthesis is defined as the restoration of inflamed and damaged synovial membrane of the joints after application of radio nuclides (radioisotopes). The radio nuclides are used to effectively control the inflammatory process of the synovial membrane and are indicated as an alternative therapy to early surgical synovectomy [90]. Using Yittrium-90 (Y-90) for knee joints, Rhenium (Re-186) is used for middle sized joints; Erbium (Er-169) is used in small joints of the fingers has found very good results [91]. The availability of Holmium (Ho-166) in colloidal form and expected P-32 colloids to be made available by BRIT, this modality of treatment is poised to be economical [90]. There is no radiation risk and the procedure can be performed on an outpatient basis [91].

Prednisone Chronotherapy*:* Frank Buttgereit *et al.,* investigated the long-term safety and efficacy of prednisone chronotherapy with a novel modified-release (MR) prednisone for up to 12 months, a 9-month open-label extension of the Circadian Administration of Prednisone in RA Study (CAPRA 1). They suggest that low-dose MR prednisone chronotherapy offers significant benefits over immediate-release (IR) prednisone for the treatment of RA which is maintained for up to 12 months. Further studies are warranted to investigate the benefit of low-dose MR prednisone chronotherapy in both oral glucocorticoid-naive patients with early RA and those with other inflammatory conditions. Indeed, chronotherapy may well offer significant advantages over standard therapies in diseases such as polymyalgia rheumatica and also asthma [92].

Laser Irradiation: V.T. Timofeyev *et al.,* described another potential method for Immuno correction in rheumatoid arthritis is Laser irradiation. Intravenous laser irradiation of blood (ILIB) is a prospective method at least for short-term remission of RA, if patients are properly selected based on clinical features and laboratory data. Their study does not answer the question whether ILIB-therapy has a prolonged disease- modifying action. Further long-term studies of its clinical efficiency and mechanism of action are necessary to determine the place and significance of ILIB in rheumatology [93].

Synthetic Peroxisome Proliferator- Activated Receptor Gamma (PPAR-γ) Agonist: Sumariwalla PF *et al.,* evaluated the clinical efficacy of a novel synthetic PPAR-γ) agonist, CLX-090717, in several in vitro cell culture systems and murine CIA, an experimental model of RA. CLX-090717 significantly inhibited release of the pro-inflammatory cytokine TNF-α from both human and mouse mononuclear cells, and that this effect in human monocytes was in part modulated through nuclear factor-κB (NF-κB). Importantly, CLX-090717 markedly inhibited TNF-α release from human rheumatoid synovial membrane cells in culture, ameliorated arthritis in mice and conferred joint protection when used therapeutically. This novel synthetic compound CLX-090717 may be useful in the management of chronic inflammatory disorders such as RA. The compound CLX-090717 has potential as a small molecular weight therapeutic in RA [94].

Role of Statins in inhibition of C-reactive protein-induced chemokine secretion: CRP induces pro-inflammatory activities in human adherent monocytes through extracellular signal regulated kinase (ERK) ½ activation and inhibits CRP-mediated pro-inflammatory activities through the inhibition of HMG-CoA-ERK 1/2 pathway. HMG-CoA-ERK 1/2 pathway could represent a promising target to reduce CRP-mediated activities in human monocytes [95].

Role of kinin generation in rheumatoid arthritis: Cassim B *et al.,* recently assessed the expression of kallikreins, kininogens and kinin receptors in circulating and SF neutrophils, as well as ST of RA patients, and also assessed kinin generation in SF. Kallikrein- kinin proteins on neutrophils play an important role in kinin generation and the pathophysiology of RA. Finally they conclude that neutrophils generate kinins in SF of RA patients and kinin generation correlates with disease activity. Specific kallikrein and kinin receptor antagonists may have potential as intra-articular therapies for inflamed joints [96].

Imaging of bony pathology as early predictors of RA: Revealing new insights and aspects of bony alterations in early arthritis, a multi pinhole SPECT (MPH-SPECT) might be an important research tool in the near future [97]. Flexor tenosynovitis is a strong early predictor of RA in MRI of the hand. Combining this finding with positive serum anti-cyclic citrullinated peptides (anti-CCP) values or alternatively with positive RF values yields even stronger early predictors of RA [98].

Combination of BRM therapy in RA: Depletion of B cells and anti-TNF-α therapy target different pathways of inflammation and therefore probably act

synergistically. RTX treatment virtually depletes B cells in the circulation, but synovial B cells are only depleted in patients with RA who show a good response to RTX therapy. An inflammatory network with multiple cell types, cytokines and chemokines contributes to synovitis. Recently, Blank N *et al.,* has first reported that the combination of RTX + Etanercept and DMARDs might be safe and effective in patients with RA [99].

Stem cell transplantation: Another most exciting development in the management of RA and some of the other autoimmune diseases is the Stem cell transplantation. They might offer the ability to ablating the autoimmune disease completely in near future. Designing stem cell transplant protocols that minimize procedure-related morbidity and mortality may offer potentially curative therapy to patients with RA [100].

Gene therapy for arthritis: There is a great potential for gene therapy approaches in RA, not only for the site specific and long-lasting delivery of therapeutic proteins, but also for the specific targeting of disease processes that are characteristic and unique for RA[101]. The ability to deliver genes to local sites of inflammation decreases the possibility of systemic side effects, making arthritis a good candidate for gene therapy. Progress has been made in recent years is the gene therapy for arthritis. Future efforts will be focused on determining which genes are the most promising for therapy, which vectors are the best for delivering these genes, and ultimately how to regulate expression of the genes being delivered [102].

CONCLUSION: Although some BRMs have proved to be extremely successful in treating the symptoms as well as in slowing down the disease progression of RA, but they have not yet met the expectations of permanently silencing chronic (auto) immune inflammation. A greater understanding of the contributions of the innate and adaptive immune systems in RA may lead to the development of more specific and effective therapeutic approaches in the near future. An increasing range of BRMs are undergoing trials on the basis of expanding knowledge of the immune system, and these trials show great promises and the time is not too distant when we will attain a state of remission in the vast majority of our patients. We still have much more to learn about these drugs, let alone the principle of neutralizing selective cytokines therapeutically. These important issues will demand significant expertise, time and resource- but may result in the continuing improvement of therapies in the most cost effective manner. The economical weight of prescriptions of BRMs in a context of limitation of assigned resources makes necessary reflection on the impact of such treatments on costs of RA.

Despite making major progress in RA research, important work still lies ahead of us; new insights into the various molecular pathways have been used to develop new and very efficient treatment approaches for patients. However, we still need to find out how to best target these drugs to the right individuals at the right time. Some environmental risk factors for RA have been identified (i.e. - smoking), but we have not used this knowledge enough in clinical practice or worked sufficiently to identify and modify additional environmental and lifestyle factors that could affect onset and progression of the disease. Furthermore, we have not been able to change permanently the destructive behavior of the immune system. We, thus, have every reason to believe that we are only at the beginning of a process whereby the disorder we call RA will be subject to further change, treatment, cure, and prevention.

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REFERENCES:

1. Lipsky PE: Harrison's Principle of Internal Medicine. Mc Graw Hill Companies, Inc. New York, 17th edition, Vol 2, 2008:2083-2092.
2. Silman AJ and Pearson JE: Epidemiology and genetics of rheumatoid arthritis. Arthritis Res 2002, 4 (suppl 3):S265-S272.
3. Fan PT and Leong KH: The Use of Biological Agents in the Treatment of Rheumatoid Arthritis. Ann Acad Med Singapore 2007; 36:128-34.
4. Bijlsma JWJ: Patient benefit_risk in arthritis—a rheumatologist's perspective. Rheumatology 2010; 49:ii11–ii17.
5. Pittier A: Current Advances in Rheumatoid Arthritis Therapy. Trinity Student Medical Journal 2000; 1: 72-76.
6. Ranganath V K: Through the Looking Glass: "Remission" in Rheumatoid Arthritis Editorial. J Rheumatol 2010; 37:1371–3.
7. Thomas R, MacDonald KPA, Pettit AR, Cavanagh LL, Padmanabha J and Zehntner S: Dendritic cells and the pathogenesis of rheumatoid arthritis. J Leukoc Biol.1999; 66: 286–292.
8. Hough Jr AJ: Anderson's Pathology. Elsevier Inc, Indian Reprint, 10th edition, vol-2, 2009: 2630- 2634.
9. Jawaheer D, Seldin MF, Amos CI, Chen W V, Shigeta R, Etzel C et al: Screening the Genome for Rheumatoid Arthritis Susceptibility Genes: A Replication Study and Combined Analysis of 512 Multicase Families. Arthritis & Rheumatism 2003; 48 (4): 906–916.
10. McClure A, Lunt M, Eyre S, Xiayi Ke, Thomson W, Hinks A et al: Investigating the viability of genetic screening/testing for RA susceptibility using combinations of five confirmed risk loci. Rheumatology 2009; 48:1369–1374.
11. Ranganathan P: Genetics of bone loss in rheumatoid arthritis—role of vitamin D receptor polymorphisms. Rheumatology 2009; 48:342–346.
12. Mouyis M, Ostor AJK, Crisp AJ, Ginawi A, Halsall DJ, Shenker N, Poole KES: Hypovitaminosis-D among rheumatology outpatients in clinical practice. Rheumatology 2008; 47:1348–1351.
13. Baka Z, Buzás E and Nagy G: Rheumatoid arthritis and smoking: putting the pieces together. Arthritis Research & Therapy 2009, 11:238.
14. Nyhall-Wahlin BM, Petersson IF, Nilsson JA, Jacobsson LTH, Turesson C et al: High disease activity disability burden and smoking predict severe extra-articular manifestations in early rheumatoid arthritis. Rheumatology 2009; 48:416–420.
15. Al-Shukaili AK and Al- Jabri AA: Rheumatoid Arthritis, Cytokines and hypoxia: What is the link? Saudi Med J 2006; 27(11): 1642-1649.
16. McInnes IB and Schett G: Cytokines in the pathogenesis of rheumatoid arthritis. Nature Reviews: Immunology 2007; 7:429-442.
17. Malaviya AM: Cytokine Network and Its Manipulation in Rheumatoid Arthritis Supplement to Journal of the Association of Physicians of India 2006; 54: 15-18.
18. Nordang GBN, Viken MK, Hollis-Moffatt JH, Merriman TR, Forre OT, Helgetveit K et al: Association analysis of the interleukin 17A gene in Caucasian rheumatoid arthritis patients from Norway and New Zealand. Rheumatology 2009; 48:367–370.
19. Nistala K, Wedderburn LR: Th17 and regulatory T cells: rebalancing pro- and anti-inflammatory forces in autoimmune arthritis. Rheumatology 2009; 48:602–606.
20. Arend WP: Cytokines and cellular interactions in inflammatory synovitis. The Journal of Clinical Investigation 2001; 107(9): 1081-1082.
21. Sullivan KE: TNF and TNF- α Inhibitors: Mechanisms of action. Pediatric Rheumatology Online Journal 2004; 2(1):7-22.
22. Kokkonen H, Soderstrom I, Rocklov J, Hallmans G, Lejon K and Dahlqvist SR: Up-Regulation of Cytokines and Chemokines predates the onset of Rheumatoid Arthritis. Arthritis & Rheumatism 2010; 62(2): 383–391.
23. Rindfleisch JA and Muller D: Diagnosis and Management of Rheumatoid Arthritis. Am Fam Physician 2005; 72:1037-47.
24. Finckh A, Bansback N, Marra CA, Anis AH, Michaud K, Lubin S et al: Treatment of very early Rheumatoid arthritis with symptomatic therapy, Disease-modifying antirheumatic drugs, or Biologic agents: A costeffectiveness analysis. Ann Intern Med 2009; 151:612-621.
25. O'Dell JR: Editorial- The Best way to treat early Rheumatoid arthritis? Ann Intern Med 2007; 146:459-460.
26. Van Everdingen AA, Jacobs JWG, Van Reesema DRS and Bijlsma JWJ: Low-Dose Prednisone Therapy for Patients with Early Active Rheumatoid Arthritis: Clinical Efficacy, Disease-Modifying Properties, and Side Effects: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Ann Intern Med 2002; 136:1-12.
27. Ravindran V, Rachapalli S and Choy EH: Safety of medium- to long-term glucocorticoid therapy in rheumatoid arthritis: a meta-analysis. Rheumatology 2009; 48:807–811.
28. Schipper LG, Fransen J, Barrera P and Van Riel PLCM: Methotrexate in combination with sulfasalazine is more effective in rheumatoid arthritis patients who failed sulfasalazine than in patients naive to both drugs. Rheumatology 2009; 48:828–833.
29. McLean-Tooke A, Aldridge C, Waugh S, Spickett GP and Kay L: Methotrexate, rheumatoid arthritis and infection risk- what is the evidence? Rheumatology 2009; 48:867–871.
30. Shankar S and Handa R: Biological agents in rheumatoid arthritis: Journal of Post graduate Med 2004; 50:293-299.
31. Thornton SC, Por SB, Penny R, Richter M, Shelley L and Breit SN: Identification of the major fibroblast growth factors released spontaneously in inflammatory arthritis as platelet derived growth factor and tumor necrosis factor-alpha. Clin Exp Immunol 1991; 86:79-86.
32. Perez C, Albert I, DeFay K, Zachariades N, Gooding L and Kriegler M: A nonsecretable cell surface mutant of tumor necrosis factor (TNF) kills by cell-to-cell contact. Cell 1990; 63:251–8.
33. Mpofu S, Fatima F and Moots RJ: Anti-TNF-a therapies: they are all the same (aren't they?). Rheumatology 2005; 44:271–273.
34. Pocock JM, Vasconcelos JC and Ostor AJK: Assessment of anti-TNF-*a* efficacy in rheumatoid arthritis: is 3 months sufficient? Rheumatology 2008; 47:1073–1076.
35. Zidi I, Bouaziz A, Mnif W, Bartegi A, Al-Hizab FA and Amor NB: Golimumab Therapy of Rheumatoid Arthritis: An Overview. Scandinavian Journal of Immunology 2010; 72:75–85.

36. Weinblatt ME: Rheumatoid arthritis: More aggressive approach improves outlook. Cleveland Clinic Journal of Medicine 2004; 71(5): 409- 413.
37. Chung ES, Packer M, Hung Lo K, Fasanmade AA and Willerson JT: Randomized, double-blind, placebo-controlled, pilot trial of Infliximab, a chimeric monoclonal antibody to tumor necrosis factor-α, in patients with moderate-to-severe heart failure, Results of the Anti-TNF therapy against congestive heart failure (ATTACH) trial. Circulation 2003; 107: r99-r106.
38. Hyrich KL, Deighton C, Watson KD, Symmons DPM and Lunt M: Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. Rheumatology 2009; 48:1323–1327.
39. Lange U, Teichmann J, Muller-Ladner U and Strunk J: Increase in bone mineral density of patients with rheumatoid arthritis treated with anti-TNF-a antibody: a prospective open-label pilot study. Rheumatology 2005; 44:1546–1548.
40. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI et al: A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving Methotrexate. N Engl J Med 1999; 340:253-9.
41. Fatima F and Rao URK: Biologic Response Modifiers. J Indian Rheumatol Assoc 2004: 12: 16 – 21.
42. Schuna AA: Etanercept in the treatment of Rheumatoid arthritis. European Association of Hospital Pharmacists (EJHP) 2001;7(2): 57-59.
43. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH et al: Etanercept Versus Methotrexate in Patients With Early Rheumatoid Arthritis: Two-Year Radiographic and Clinical Outcomes. Arthritis & Rheumatism 2002; 46(6):1443–1450.
44. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ *et al*: Etanercept Therapy in Rheumatoid Arthritis: A Randomized, Controlled Trial. Ann Intern Med 1999; 130:478-486.
45. Misra R, Amin S, Joshi VR, Rao URK, Aggarwal A, Fatima F et al: Open label evaluation of the efficacy and safety of Etanercept in Rheumatoid Arhritis. J Indian Rheumatol Assoc 2005; 13: 131-134.
46. Gera C, Kumar N and Berry V: Drug Review: Etarnacept. JK Science 2008; 10(3): 151-154.
47. Baumgartner SW, Fleischmann RM, Moreland LW, Schiff MH, Markenson J and Whitmore JB: Etanercept (Enbrel®) in patients with Rheumatoid Arthritis with recent onset versus established disease: Improvement in Disability. J Rheumatol 2004; 31:1532–1537.
48. Kremer JM, Weinblatt ME, Bankhurst AD, Bulpitt KJ, Fleischmann RM and Jackson CG: Etanercept Added to Background Methotrexate Therapy in Patients With Rheumatoid Arthritis: Continued Observations. Arthritis & Rheumatism 2003; 48 (6):1493–1499.
49. Vollenhoven RF, Ernestam S, Harju A, Bratt J and Klareskog L: Etanercept versus etanercept plus methotrexate: a registrybased study suggesting that the combination is clinically more efficacious. Arthritis Res Ther 2003, 5:R347-R351.
50. Blumenauer BBTB, Cranney A, Burls A, Coyle D, Hochberg MC, Tugwell P and Wells GA: Etanercept for the treatment of rheumatoid arthritis. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD004525 (DOI: 10.1002/14651858.CD004525).
51. Horneff G, Ebert A, Fitter S, Minden K, Foeldvari I and Kummerle-Deschner J: Safety and efficacy of once weekly etanercept 0.8 mg/kg in a multicentre 12 week trial in active polyarticular course juvenile idiopathic arthritis. Rheumatology 2009; 48:916–919.
52. Lipsky PE, Vander Heijde DMFM , Clair EW St, Furst DE, Breedveld FC, Kalden JR *et al*; Infliximab and methotrexate in the treatment of Rhumatoid arthritis. N Engl J Med 2000; 343: 1594-602.
53. Wolfe F, Michaud K, Anderson J and Urbansky K: Tuberculosis Infection in Patients with Rheumatoid Arthritis and the Effect of Infliximab Therapy. Arthritis & Rheumatism 2004; 50(2):372–379.
54. Raval A, Akhavan-Toyserkani G, Brinker A and Avigan M: Brief Communication: Characteristics of Spontaneous Cases of Tuberculosis Associated with Infliximab. Ann Intern Med 2007; 147:699-702.
55. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS et al: Radiographic, Clinical, and Functional Outcomes of Treatment With Adalimumab (a Human Anti–Tumor Necrosis Factor Monoclonal Antibody) in Patients With Active Rheumatoid Arthritis Receiving Concomitant Methotrexate Therapy: A Randomized, Placebo-Controlled, 52-Week Trial. Arthritis & Rheumatism 2004; 50(5):1400–1411.
56. Sharma R: Biologicals in Ankylosing Spondylitis: Current Concepts. Journal of Clinical and Diagnostic Research 2007; 1(6):540-545.
57. Tandon VR, Mahajan A, Khajuria V and Kapoor V: Biologics and Challenges ahead for the Physician. Journal of Indian Academy of Clinical Medicine 2006; 7(4): 334-43.
58. Rudwaleit M, Olivieri I, Boki KA, Griep EN, Jarvinen P, Wong RL et al: Adalimumab is effective and well tolerated in treating patients with ankylosing spondylitis who have advanced spinal fusion. Rheumatology 2009; 48:551–557.
59. Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R et al: Adalimumab Induction Therapy for Crohn Disease Previously Treated with Infliximab: A Randomized Trial. Ann Intern Med 2007; 146:829-838.
60. New drugs: Certolizumab. Australian prescriber. 2010; 33(4): 129-131. www.australianprescriber.com.
61. Strand V, Mease P, Burmester GR, Nikaï E, Coteur G, Vollenhoven RV et al: Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. Arthritis Research & Therapy 2009; 11:R170.
62. Mahajan A, Sharma R and Singh JB: Biological therapy in Rheumatoid Arthritis: Current Status. Indian Journal of Rheumatology 2006; 1(1):13–19.
63. Bresnihan B and Cobby M: Clinical and radiological effects of anakinra in patients with rheumatoid arthritis. Rheumatology 2003; 42(Supple. 2):ii22–ii28.
64. Cohen SB and Rubbert A: Bringing the clinical experience with anakinra to the patient. Rheumatology 2003; 42(Suppl. 2):ii36–ii40.
65. New drugs: Anakinra. Australian prescriber 2004; 27 (6): 160-161. www.australianprescriber.com

66. Fleischmann RM: Addressing the safety of anakinra in patients with rheumatoid arthritis. Rheumatology 2003;42(Suppl. 2):ii29–ii35.
67. Salliot C, Dougados M and Gossec L: Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis 2009; 68:25–32.
68. Dayer JM and Choy E: Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. Rheumatology 2010; 49:15–24.
69. Hillyer P, Larche MJ, Bowman EP, McClanahan TK, Malefyt RW, Schewitz LP et al: Investigating the role of the interleukin-23/-17A xis in rheumatoid arthritis. Rheumatology 2009; 48:1581–1589.
70. Ohsugi Y and Kishimoto T: Pharmacotherapy Options in Rheumatoid Arthritis: Focus on Tocilizumab, a Recombinant Humanized Anti-Interleukin-6 Receptor Antibody. Clinical Medicine: Therapeutics 2009; 1: 1677–1691.
71. Herlin T: Tocilizumab: The evidence for its place in the treatment of uvenile idiopathic arthritis. Core Evidence 2009:4 181–189.
72. Cohen MD: Abatacept and Rituximab, American College of Rheumatology HOTLINE. Editors: Kavanaugh A, Matteson EL. 2200 Lake Boulevard NE. Atlanta, GA 30319. May 18, 2006; www.rheumatology.org.
73. Haque MA, Ekram ARMS and Islam QT: Role of Biological Response Modifiers in the Treatment of Rheumatoid Arthritis-A Review. Journal of Teachers Association, RMC, Rajshahi 2004; 17(1): 71-76.
74. Rubbert-Roth A, Tak PP, Zerbini C, Tremblay JL, Carreno L, Armstrong G et al: Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a Phase III randomized study (MIRROR). Rheumatology 010; 49:1683–1693.
75. Magnusson M, Brisslert M, Zendjanchi K, Lindh M and Bokarewa MI: Epstein–Barr virus in bone marrow of rheumatoid arthritis patients predicts response to rituximab treatment. Rheumatology 2010; 49:1911–1919.
76. Soriano ER, Galarza-Maldonado C, Cardiel MH, Pons-Estel BA, Massardo L, Caballero-Uribe CV ***et al***: Use of rituximab for the treatment of rheumatoid arthritis: the Latin American context. Rheumatology 2008; 47:1097–1099.
77. Hallinen TA, Soini EJO, Eklund K and Puolakka K: Cost–utility of different treatment strategies after the failure of tumour necrosis factor inhibitor in rheumatoid arthritis in the Finnish setting. Rheumatology 2010; 49:767–777.
78. Ziswiler HR, Aeberli D, Villiger PM and Moller B: High-resolution ultrasound confirms reduced synovial hyperplasia following rituximab treatment in rheumatoid arthritis. Rheumatology 2009; 48:939–943.
79. Weisman M, Durez P, Hallegua D, Nuamah I, Vratsanos G and Becker JC: Abatacept (CTLA4Ig; BMS-188667) inhibits T-cell activation and the subsequent activation of inflammatory cell types, as demonstrated by sustained reductions in multiple inflammatory biomarkers. Ann Rheum Dis 2004; 63: Suppl 1:i138. Abstract.
80. Kremer JM, Westhovens R, Leon M, Giorgio ED, Alten R, Steinfeld S. et al: Treatment of Rheumatoid Arthritis by Selective Inhibition of T-Cell Activation with Fusion Protein CTLA4Ig. N Engl J Med 2003; 349:1907-15.
81. Vera-Llonch M, Massarotti E, Wolfe F, Shadick N, Westhovens R, Sofrygin O et al: Cost–effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to Methotrexate. Rheumatology 2008; 47:535–541.
82. Nixon R, Bansback N and Brennan A: The efficacy of inhibiting tumour necrosis factor -α and interleukin -1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. Rheumatology 2007; 46; 1140–1147.
83. Boers M: Abatacept in Rheumatoid Arthritis: A New Branch on the "Biologics" Tree (Editorial). Ann Intern Med 2006; 144:933-935.
84. Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Tanjong Ghogomu E and Tugwell P: Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2009; Issue 4. Art. No.: CD007848. DOI: 10.1002/14651858.CD007848.pub2.
85. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C *et al*: Effects of Abatacept in Patients with Methotrexate-Resistant Active Rheumatoid Arthritis: A Randomized Trial. Ann Intern Med 2006; 144:865-876.
86. Cole JC, Li T, Lin P, MacLean R and Wallenstein GV: Treatment impact on estimated medical expenditure and job loss likelihood in rheumatoid arthritis: re-examining quality of life outcomes from a randomized placebo-controlled clinical trial with abatacept. Rheumatology 2008; 47:1044–1050.
87. D'Aura Swanson C, Paniagua RT, Lindstrom TM and Robinson WH: Tyrosine kinases as targets for the treatment of rheumatoid arthritis. Nat Rev Rheumatol 2009; 5: 317–324.
88. Tebib J, Mariette X, Bourgeois P, Flipo RM, Gaudin P, Loët XL et al: Masitinib in the treatment of active rheumatoid arthritis: results of a multicentre, open-label, dose-ranging, phase 2a study. Arthritis Research & Therapy 2009, 11:R95.
89. Weinblatt ME, Kavanaugh A, Vargas RB, Dikranian AH, Ramirez GM, Torres JLM *et al*: Treatment of Rheumatoid Arthritis with a Syk Kinase Inhibitor: A Twelve-Week, randomized, placebo-controlled trial. Arthritis & Rheumatism 2008; 58 (11):3309–3318.
90. Das BK, Pradhan PK, Shukla AK and Misra R: Role of Radiosynovectomy in Rheumatoid Arthritis. J Indian Rheumatol Assoc 2004; 12: 98 – 103.
91. Das BK: Role of radiosynovectomy in the treatment of rheumatoid arthritis and hemophilic arthropathies. Biomed Imaging Interv J 2007; 3(4):e45.
92. Buttgereit F, Doering G, Schaeffler A, Witte S, Sierakowski S, Gromnica-Ihle E et al: Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. Ann Rheum Dis 2010; 69:1275–1280.
93. Timofeyev VT, Poryadin GV and Goloviznin MV: Laser irradiation as a potential pathogenetic method for immuno-correction in rheumatoid arthritis. Pathophysiology 2001; 8: 35–40.
94. Sumariwalla PF, Palmer CD, Pickford LB, Feldmann M, Foxwell BMJ and Brennan FM: Suppression of tumour necrosis factor production from mononuclear cells by a novel synthetic compound, CLX-090717. Rheumatology 2009; 48:32–38.
95. Montecucco F, Burger F, Pelli G, Poku NK, Berlier C, Steffens S and Mach F: Statins inhibit C-reactive protein-induced chemokine secretion, ICAM-1 up regulation and chemotaxis in adherent human monocytes. Rheumatology 2009; 48:233–242.

96. Cassim B, Shaw OM, Mazur M, Misso NL, Naran A, Langlands DR et al: Kallikreins, kininogens and kinin receptors on circulating and synovial fluid neutrophils: role in kinin generation in rheumatoid arthritis. Rheumatology 2009; 48:490–496.
97. Ostendorf B, Wirrwar A, Mattes-Gyorgy K, Iking-Konert C, Blondin D, Modder U et al: High-resolution SPECT imaging of bony pathology in early arthritis of finger joints. Rheumatology 2009; 48:853–854.
98. Eshed I, Feist E, Althoff CE, Hamm B, Konen E, Burmester GR et al: Tenosynovitis of the flexor tendons of the hand detected by MRI: an early indicator of rheumatoid arthritis. Rheumatology 2009; 48:887–891.
99. Blank N, Max R, Schiller M, Briem S and Lorenz HM: Safety of combination therapy with rituximab and etanercept for patients with rheumatoid arthritis. Rheumatology 2009; 48:440–441.
100. Moore JJ, Snowden J, Pavletic S, Barr W and Burt R: Hematopoietic stem cell transplantation for severe rheumatoid arthritis. Bone Marrow Transplantation 2003; 32: S53–S56.
101. Pap T, Müller-Ladner U, Gay R and Gay S: Gene therapy in rheumatoid arthritis: how to target joint destruction? [Commentary]. Arthritis Research 1999; l: 5-9 http://arthritisresearch.com/26Oct 99/ar0101c02.
102. Thornton S and Hirsch R: Gene therapy for arthritis. Gene Ther Mol Biol 1999; 3: 243-248.

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