



## Rheumatoid Arthritis: Assessment Tools & Current Treatment Strategies

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**ABSTRACT:** Rheumatoid arthritis is a chronic inflammatory disorder mainly involving joints. It is a lifelong process & its etiology is poorly understood. It is the result of interaction between the environmental factors with the genetics of persons which is likely to be associated with the disease. Many assessment tools have been used for assessing the disease with each having its own merits & demerits. For its treatment patient has to take medicines for life long which results in tolerance to efficacy & increase in adverse effects. Different treatment guidelines are followed in different parts of world according to their convenience. No doubt drugs like methotrexate, hydroxychloroquine, leflunomide, sulfasalazine are still the pillars of the treatment but there is always a need for newer efficacious & safe drugs for the treatment of rheumatoid arthritis. © 2011 IGJPS. All rights reserved.

**KEYWORDS:** Rheumatoid Arthritis; Autoimmune Disease; Anti-Arthritic Drugs.

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### INTRODUCTION

Rheumatoid arthritis (RA) is the most common chronic inflammatory polyarthritis and it afflicts people of all ages and races. Its prevalence is 1% and is more common in females than males. It can begin at any age, but usually onset is in the fourth or fifth decade for women and the sixth to eighth decades for men.<sup>1</sup> The cause of RA remains unknown. It might be due to the response to an infectious agent in a genetically susceptible host. A number of possible causative agents have been suggested, including mycoplasma, epstein-barr virus, cytomegalovirus, parvovirus, and rubella virus.<sup>2</sup> Although several genetic and environmental factors have been linked to RA, it is the interaction of different environmental factors in genetically predisposed individuals which is likely to trigger the disease. One of its best examples is smoking, which is dominant environmental risk factor as it doubles the risk of

developing rheumatoid arthritis. Its effect is restricted to patients with anti-citrullinated protein autoantibody (ACPA)-positive disease.<sup>3</sup> Other important environmental risk factors include alcohol intake, coffee intake, vitamin D status, oral contraceptive use, and low socioeconomic status.<sup>4</sup> Many advances in the understanding of RA pathogenesis have been discovered like the identification of genetic risk factors e.g. HLA-DRB1 is strongly associated with RA.<sup>5</sup> It is an autoimmune disease involving numerous cells of the immune system with overexpression of inflammatory cytokines like tumor necrosis factor alpha (TNF- $\alpha$ ), certain interleukins, proteinases and multiple other chemokines. The amplification of inflammatory pathways and their interaction with host cells such as fibroblasts, chondrocytes and osteoclasts promote the formation of an invasive pannus tissue (inflamed synovium)

resulting in bone and cartilage destruction of synovial joints, which is characteristics of RA.<sup>6</sup>

The diagnosis of RA is primarily clinical, but also relies on laboratory tests and typical radiographic changes. Many clinical practice guidelines have been developed in the past few years like American College of Rheumatology (ACR), National Institute for Health and Clinical Excellence (NICE), British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR), the European League Against Rheumatism (EULAR). Among these American College of Rheumatology (ACR) classification of RA is most commonly used. Laboratory findings include increase of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) autoantibodies in 70–75% of the cases.<sup>7</sup> Anti-CCP antibodies tend to be more specific but equally sensitive as RF and are of value in the diagnosis of early RA and in predicting joint damage; they are currently used in combination with RF.<sup>8</sup>

**Assessment tools:** A wide variety of assessment tools have been used for assessing the disease activity including various types of joint counts, acute phase reactants (APR), global assessment scales and more general measures such as anaemia, hemoglobin or body weight. The currently available composite disease activity indices that provide a single number on a continuous scale are disease activity score (DAS), the disease activity score using 28 joint count (DAS-28), the simplified disease activity index (SDAI), and the clinical disease activity index (CDAI). The important tools used in the assessment of disease activity are as follows:

**Visual analog scale (VAS):** VAS was first used in psychology in the early 1900s.<sup>9</sup> This approach was based upon fact that ‘severity of pain is only known to the sufferer’.<sup>10</sup> The standard visual analog scale (VAS) is a 10 cm scale with a border at each end. The left border represents ‘no pain’ and the severity of pain increases to the right; accordingly the right border is characterized as ‘pain as severe as it could be’. The patient is asked to keep a finger on the scale depending on the severity of the pain felt by him/her.

**28 Joint count:** Smolen et al investigated the validity of the 28-joint count and they found that the 28-joint count is a reliable and valid measure for joint assessment.<sup>11</sup> In it both swollen & tender joints are counted. Joint swelling is soft tissue swelling that is detectable along the joint margins. When a synovial effusion is present it invariably means the joint is swollen. Joint tenderness is the presence of pain in a joint at rest with pressure or on movement of the joint. These joints include 10 proximal interphalangeal joint (PIP) joints, 10 metacarpophalangeal (MCP) joints, 2 wrist joints, 2 elbows, 2 shoulders and 2 knee joints.

**Morning stiffness duration:** It is ‘slowness or difficulty moving the joints when getting out of bed or after staying in one position too long, which involves both sides of the body and gets better with movement.’ Circadian rhythm has been noted in stiffness as with a peak in the early morning hours, reduction during the day and a smaller new increase in the early evening.<sup>12</sup> Temporal relationship have reported between symptoms of rheumatoid arthritis & elevated levels of pro-inflammatory cytokines.<sup>13</sup> These cytokines are highly elevated in patients in the early hours of the day & after the noon hour, their levels are almost undetectable. It lasts until there is increase in endogenous cortisol which counteracts the inflammatory cascade of disease symptoms.<sup>14</sup>

**Global assessment of disease:** Global assessment of disease by both patient & physician are useful because their evaluation may be quite different. The global assessment is very sensitive to clinical changes. It is of two types:

**Physician disease global assessment:** In this physician assesses the degree of inflammatory disease activity on a 10 cm scale, ranging from left border as ‘mildest disease’ to right border as ‘most severe disease’. They consider symptoms such as joint pain, stiffness, tenderness, swelling & presence of subcutaneous nodules.<sup>15</sup>

**Patient disease global assessment:** It is patient’s overall assessment of how the arthritis is doing. A question is asked to patient “Considering all the ways your arthritis affects you, mark ‘X’ on the scale for how well you are doing.” A 10 cm horizontal scale with a border at each end is used. The left end

represents 'very' good and the severity of disease increases to the right; accordingly the right end is characterized as 'very poor'.<sup>16</sup>

*Disease Activity Score-28 (DAS-28)*: It includes physician's assessment of the joints, the patient's overall self-assessment of disease activity, and a laboratory marker of inflammation i.e. erythrocyte sedimentation rate (ESR) or C- reactive protein (CRP).<sup>17</sup> It is used to quantify disease activity at the first clinic visit and to be used in subsequent visits for comparison. It has been validated for use in clinical trials as well as routine patient care.<sup>18</sup> It is calculated by using the following formula:  $DAS-28 = 0.56 \sqrt{TJC} + 0.28 \sqrt{SJC} + 0.70(\log ESR) + 0.014(GH)$ . Where TJC= Tender Joint Count, SJC= Swollen Joint Count, ESR= Erythrocyte Sedimentation Rate, GH= Global Health on VAS Scale (0-10cm). DAS-28 is a continuous index ranging from 0 to 9.4. Low disease activity is defined as  $DAS-28 \leq 3.2$ , moderate as DAS-28 ranging from 3.2 to 5.1, and high as  $DAS-28 > 5.1$ .<sup>19</sup> A commonly used cut off point for remission is  $DAS-28 < 2.6$ .<sup>20</sup>

*Simplified Disease Activity Index (SDAI)*: It has also been validated in clinical practice to assess RA disease activity.<sup>21</sup> The SDAI is calculated by adding up the SJC and the TJC in the same 28 joints used in the DAS-28. These are added to the patient's global assessment, the physician's global assessment, and CRP. The SDAI has the advantage over the DAS-28 in that the calculations are not as difficult & the results are almost equal.<sup>22</sup>

*Clinical Disease Activity Index (CDAI)*: It is an even more simplified score than the SDAI. It is calculated by the summation of the SJC, TJC, patient's global assessment, and the physician's global assessment.<sup>22</sup> It enables the physician to know the disease activity score immediately and make treatment decisions during the patient encounter. Similar to the SDAI, the CDAI has been reported to perform well in clinical practice.<sup>22</sup>

*Health Assessment Questionnaire (HAQ)*: It is mainly concerned with patient-centered dimensions. It is composed of 20 items which are divided into 8 categories: dressing and

grooming, hygiene, arising, reaching, eating, gripping, walking, and common daily activities. It assesses the presence or absence of arthritis-related pain and its severity over the past week.

*Grip strength*: It is measured by using aneroid sphygmomanometer. Disability in patients of rheumatoid arthritis has been associated with loss of hand grip strength & function.<sup>23</sup> Grip strength testing has been used to follow up the therapeutic response of patients to medical therapies.<sup>24</sup>

*Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)*: These have little use as a specific test in the diagnosis of RA, although they are part of the new ACR Classification Criteria for RA.<sup>25</sup> These tests may be used to follow disease activity and monitor response to therapy. There are two main methods used to measure the ESR: the westergren method and the wintrobe method. Each method produces slightly different results. The wintrobe method is most commonly used. In it ethylenediaminetetraacetic acid (edta) anticoagulated blood is drawn into the wintrobe tube, and the rate of fall of red blood cells is measured in millimeters after 1 hour. Normal values for males: is 0-15mm/hr and for females is 0-20/hr. Normal value of CRP is less than 10mg/L.<sup>2</sup>

## **CURRENT TREATMENT STRATEGIES**

The aims of therapy of RA are (1) to decrease pain & inflammation, (2) protection of articular structures (3) maintenance of function, and (4) control of systemic involvement. Management of patients with RA involves an interdisciplinary approach, includes physical therapy modalities and medical management. Rest ameliorates symptoms and can be an important component of the total therapeutic program. Medical management of RA involves five general approaches. These include: nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), conventional disease-modifying antirheumatic drugs (DMARDs), immunosuppressive drugs and biological DMARDs. We are hereby discussing important facts about these drugs in relation to RA.

**Nonsteroidal anti-inflammatory drugs (NSAID's):** They are rapidly effective in mitigating signs and symptoms, but they appear to exert minimal effect on the progression of the disease. Therefore, NSAIDs should rarely be used to treat RA without the concomitant use of DMARDs. They are among the most widely used medications in the world because of their good efficacy in reducing pain and inflammation.<sup>26</sup> NSAIDs as a class comprise both traditional nonselective NSAIDs (tNSAIDs) that nonspecifically inhibit both COX-1 and COX-2, and selective COX-2 inhibitors. Although effective at relieving pain and inflammation, these are associated with a number of adverse effects. These include alterations in renal function, effects on blood pressure, hepatic injury and platelet inhibition which may result in increased bleeding. Among the set NSAIDs are associated with a significant risk of serious gastrointestinal adverse events with chronic use.<sup>27</sup> Therefore, specific inhibitors of the COX-2 isoenzyme were developed, thus opening the possibility to provide anti-inflammatory and analgesic benefits, while theoretically leaving the gastroprotective activity of the COX-1 isoenzyme intact. However, important concerns have recently been raised regarding the potential cardiovascular toxicity of COX-2 inhibitors.<sup>28</sup> At therapeutic doses, the COX-2 inhibitors are thought to inhibit only the COX-2, but not the COX-1 enzyme. The problem with inhibiting only the COX-2 enzyme is that metabolism imbalances may occur, resulting in an overproduction of harmful byproducts that may damage the arterial wall and induce arterial blood clotting.<sup>29</sup> When COX-2 is inhibited, less PGI<sub>2</sub> is synthesized from arachidonic acid and more leukotriene B<sub>4</sub> and thromboxane A<sub>2</sub> (TXA<sub>2</sub>) are produced. PGI<sub>2</sub> is vasodilatory and antiaggregatory, while TXA<sub>2</sub> is vasoconstrictive and proaggregatory. This tip of balance allows TXA<sub>2</sub> to function unopposed, leading to increased risk for cardiovascular adverse events. Rofecoxib inhibits the COX-2 enzyme 80 times more than the COX-1 enzyme, whereas celecoxib inhibits the COX-2 enzyme only 9 times more than the COX-1.<sup>30</sup>

**Glucocorticoids:** They play a pivotal role in the management of RA. In clinical practice, they are used as bridging therapy

i.e. to treat exacerbations in the period until treatment with the new agent has become effective. For this purpose, low to medium oral doses of glucocorticoids, high-dose intramuscular glucocorticoids, intravenous pulse glucocorticoids are used. GCs show their anti-inflammatory and immunosuppressive effects through different mechanisms.<sup>31</sup> On the cellular level, GCs suppress the functions and the production of leukocyte, fibroblast and endothelial cell. Cytosolic GC receptors (cGCRs) are responsible for most of the functions. GCs down regulate the production of pro-inflammatory cytokines such as tumour necrosis factor  $\alpha$  (TNF $\alpha$ ), interleukin (IL)-1 and IL-6. Rapid effects are mediated through non-genomic effects via membrane-bound GCRs (mGCRs) which are present on monocytes and B-cells of RA patients.<sup>32</sup> These effects likely to contribute in a considerable manner to the very rapid immunosuppressive and anti-inflammatory effects as achieved by their intra-articular injections or intravenous pulse therapy. In vitro, they inhibit macrophage accumulation in injured arterial walls. They also seems to have beneficial role in atherosclerosis.<sup>33</sup>

Administration of higher GC doses for longer periods can result in undesirable side effects, such as cardiovascular and infectious events, gastrointestinal, psychological, endocrine, metabolic, dermatological musculoskeletal and ophthalmologic problems. These enhance cardiovascular risk via their potentially deleterious effects on lipid profiles, glucose tolerance, insulin production and resistance, blood pressure, and obesity.<sup>34</sup> Their use increases the risk of systemic infection and this association is considered to be dose dependent in a large cohort study of patients with RA.<sup>35</sup>

**DMARDs:** i.e disease modifying antirheumatic drugs. Symptomatic control can be achieved with non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose glucocorticoids. However, (DMARDs) are needed for most patients in order to alter the disease progression. DMARDs are needed for most patients in order to alter the disease progression. Essentially, all RA patients should be considered for DMARD therapy in an effort to halt joint damage and disease progression. The

initiation of such therapy should be within the first 3 months (or as soon as possible) for patients with confirmed diagnosis and active disease.<sup>36</sup> Most commonly used non-biologic DMARDs include MTX, sulfasalazine, hydroxychloroquine and leflunomide.

**Non-biologic DMARDs:** This group includes the following drugs-

*Methotrexate:* It is the most crucial drug for the treatment of RA.<sup>37</sup> It is frequently the first DMARD prescribed following the diagnosis of RA, and large number of patients respond favorably to MTX monotherapy. Use of this drug is associated with a significant reduction in mortality (odds ratio for death 0.4) relative to RA patients not treated with MTX.<sup>38</sup> It is a folate antagonist, its anti-rheumatic effects are mainly due to increase in extracellular adenosine— a potent anti-inflammatory molecule.<sup>39</sup> It is given orally or subcutaneously in doses ranging from 5–25 mg as a single dose once a week. Folate supplementation (1–3mg per day) is commonly given with MTX therapy which reduces the frequency and severity of side-effects without affecting efficacy. Although it has a favorable long-term safety profile when monitored appropriately, but it can cause oral ulcers, nausea, hepatotoxicity, bone marrow suppression, and pneumonitis.<sup>40</sup> Transient elevation of hepatic transaminases is seen in 20.2% of RA patients in a metaanalysis of 88 studies, but it rarely require discontinuation.<sup>40</sup> Hepatotoxicity is associated with dose, obesity, alcohol use, and lack of folate supplementation.<sup>41</sup>

*Hydroxychloroquine (HCQ):* Currently, HCQ is the most common antimalarial agent used in the management of RA. In current practice, it is commonly used in combination with other DMARDs, rarely used as monotherapy. It has proven efficacy in controlling the signs and symptoms of RA.<sup>42</sup> It has many known immunomodulatory effects, but its specific mechanism in individual diseases is not clear.<sup>43</sup> The major proposed mechanisms of action of antimalarials on the immune system include: (1) inhibition of macrophage-mediated cytokine production like interleukin (IL)-1 and IL-6<sup>44</sup> (2) interference with lysosomal acidification & proteolysis,

chemotaxis, phagocytosis, and antigen presentation<sup>45</sup> (3) inhibition of matrix metalloproteinases.<sup>46</sup> HCQ may also be beneficial by improving glycemic control in RA and SLE patients.<sup>47</sup> It was also shown to have a favorable effect on lipid profile in patients with rheumatic diseases. Wallace et al showed that HCQ lowered the levels of cholesterol, triglycerides and LDL in RA and systemic lupus erythematosus (SLE) patients, irrespective of concomitant steroid administration, diet, or weight.<sup>48</sup> Irreversible retinopathy and ototoxicity can occur due to high daily doses (>250 mg) of HCQ.<sup>49</sup> Retinopathy is related to drug accumulation in melanin-rich tissues and can avoided if the daily dose is 250 mg or less. Toxic myopathy, cardiopathy, and peripheral neuropathy can occur due to prolonged therapy with high doses although these reactions improve if the drug is withdrawn promptly.<sup>50</sup>

*Sulfasalazine:* It is a prodrug commonly used for the treatment of inflammatory bowel diseases (IBD) such as ulcerative colitis (UC) and Crohn's disease (CD). It has also been found to be an effective drug in rheumatoid arthritis (RA).<sup>51</sup> It consists of sulfapyridine (SP) linked to 5-aminosalicylic acid (5-ASA) by an azo bond. It has been found that most of the sulfasalazine reaches the colon, where it is split by bacterial azo-reductases into SP and 5-ASA.<sup>52</sup> SP is almost completely absorbed in the colon. Then, it is acetylated, hydroxylated and glucuronidized in the liver, and finally excreted into the urine. The rate of metabolism of sulfapyridine to its acetylated form is dependent upon acetylator phenotype i.e slow and fast acetylators. By contrast, 5-ASA is poorly absorbed from the colon. Most 5-ASA is acetylated by luminal bacteria, being finally excreted into the feces. It has been seen that ~ 25% of the 5-ASA component is absorbed and transported to the liver, where it is acetylated and excreted into the urine. The exact mechanisms of action of sulfasalazine still remain unclear.<sup>52</sup> In vitro studies have shown that sulfasalazine or its metabolites inhibit the release of inflammatory cytokines, including those produced by monocytes or macrophages like TNF- $\alpha$ .<sup>53</sup> The most frequently reported adverse events are nausea, vomiting, dyspepsia, anorexia, headache, dizziness and rash.<sup>54</sup> In

general, most of these adverse events occur during the first few months after starting sulfasalazine treatment and their occurrence decreases with continued use. Nephrotoxicity, hepatotoxicity, immunoallergic reactions, skin reaction, pancreatitis, blood dyscrasias and infertility are other rare adverse side effects. Das et al demonstrated that the concentrations of SP metabolites correlated with side effects and these were more in slow acetylators.<sup>55</sup> In clinical practice, most patients with rheumatoid arthritis receive sulfasalazine as enteric-coated tablets. The use of this formulation was shown in a multicentre cross incidence over trial to significantly reduce not only the severity of adverse gastrointestinal effects, but also the incidence of these problems by more than half when compared with the standard formulation of sulfasalazine.<sup>54</sup> In most countries, the initial recommended dosage is 500mg/day which can be increased by 500 mg/day increments at intervals of 1 week to a maximum of 2–3 g/day in two to four divided doses.<sup>54</sup> In a placebo controlled randomized, double-blind trial, patients with rheumatoid arthritis who were treated for 6 months with enteric-coated sulfasalazine 2g/day had statistically significant improvements in the number of swollen and tender joints, Ritchie's articular index (RAI) and ESR. Sulfasalazine had broadly similar clinical efficacy to that of methotrexate, leflunomide, hydroxychloroquine, penicillamine and intramuscular gold. Measures of disease activity evaluated in these randomised, double-blind trials typically included RAI, grip strength, duration of morning stiffness, ESR, pain, and the number of tender and swollen joints.

*Leflunomide* (LEF): It is an isoxazole derivative, is structurally very different from other DMARDs. It is considered a cytostatic rather than cytotoxic agent. Two mechanisms of action have been proposed: the reversible inhibition of dihydroorotate dehydrogenase (DHODH) and the inhibition of tyrosine kinases.<sup>56</sup> DHODH is a key enzyme in pyrimidine synthesis required for uridine monophosphate (UMP) synthesis, a precursor of pyrimidine nucleotides. Lymphocytes treated with teriflunomide, the active metabolite of leflunomide (also known as A771726), are arrested after

stimulation rather than progressing through to mitosis.<sup>57</sup> Symptoms of disease improved within a month of starting treatment and improvement was maintained in the long term. Via its effect on T cells, leflunomide addresses several levels of the inflammatory cascade and has antiproliferative, anti-inflammatory properties.<sup>58</sup> This special mode of action together with its rapid onset of action makes it a promising drug in the treatment of early RA where the prevention of irreversible structural damage is an important goal. It decreases macrophage numbers, intercellular adhesion molecule (ICAM)-1 and metalloproteinases which has been correlated with clinical benefit.<sup>59</sup> It also cause suppression of osteoclast differentiation induced by receptor activator of nuclear factor kappa-B ligand (RANKL) which means that it exerts a T-cell-independent inhibitory effect on bone damage.<sup>60</sup> It has been confirmed in various studies that leflunomide causes improvement in both inflammatory markers such as ESR and C-reactive protein (CRP) & symptoms e.g., joint pain, swelling, measures of physical function, health-related quality of life.<sup>61</sup> Comparing leflunomide treatment with placebo or another DMARD, the most common adverse effects were gastrointestinal (diarrhoea, dyspepsia, nausea/vomiting, abdominal pain, oral ulcers), abnormal liver function tests (LFTs), drug eruptions, alopecia, infections, weight loss and hypertension. It has been found that there is no statistical difference in the frequency of serious adverse events between sulfasalazine, methotrexate and leflunomide.<sup>62</sup> The current monitoring guidelines suggest that LFTs should be checked prior to starting the drug and then monthly for the initial 6 months. Once leflunomide is established, LFTs are required every 8 weeks. An increase in ALT between two to three times the ULN (upper limit of normal) laboratory range requires dose reduction, and LFTs should be checked weekly. If ALT remains twice the ULN or exceeds three times the ULN, treatment should be discontinued and washout with colestyramine undertaken. It should not be used in patients with pre-existing liver disease. A retrospective case-note review evaluating the rates of severe infection found that there was a higher risk of infection in

patients receiving leflunomide treatment, particularly when it was given in combination with methotrexate and prednisolone. Opportunistic infections such as *Pneumocystis carinii* pneumonia have also been reported.<sup>63</sup> The active metabolite of LEF is teratogenic in animal studies the manufacturers recommend to perform pregnancy testing prior to commencing therapy in women of childbearing age. Various studies have shown that the combination of methotrexate, sulfasalazine and hydroxychloroquine is one of the most effective nonbiological treatment strategies.<sup>64</sup> A meta-analysis shows that there was no statistically significant difference between leflunomide, methotrexate apart from between leflunomide and sulfasalazine at 24 months.<sup>65</sup> It is well tolerated with methotrexate. This combination is also logical as MTX is a purine metabolism inhibitor, while LEF is an inhibitor of de novo synthesis of pyrimidines.<sup>66</sup>

#### **Biological DMARDs:**

While conventional DMARDs, such as methotrexate (MTX), remain the basis of therapy, major change in the management of the disease has occurred during the past two decades. According to these changes there should be an early aggressive therapy which is followed by the introduction of biologic therapies that have led to better disease control.<sup>67</sup> These new agents work by selective blockade of certain cytokines or receptors, resulting in a significant reduction of inflammation, slowing the progression of bony erosions. Currently available biologics include the TNF (tumour necrosis factor)- $\alpha$  inhibitors (infliximab, etanercept, adalimumab, golimumab, and certolizumab), IL-1 receptor antagonist (anakinra), cytotoxic T lymphocyte associated antigen 4 immunoglobulin (abatacept), anti-CD20 antibodies (rituximab), and an IL-6 inhibitor (tocilizumab). There are differences in the usage of biologic agents among different countries based on licensing, local guidelines and policies.

Patients often fail or are unable to tolerate traditional DMARDs. Biologic agents are therapies used for different diseases, which have been introduced for the treatment of RA over the past decade, and have quickly gained ground in the management of mainly refractory cases. Furthermore, they

have also been shown to be effective in early RA, but their substantial economic impact and long-term safety concerns have precluded their routine use at the onset of disease, before traditional DMARDs are prescribed. Current status of usage biologics is mostly in conjunction with MTX for resistant RA without adequate response to traditional therapy.<sup>68</sup>

*Anakinra:* It is an IL-1 receptor antagonist, given as subcutaneous injections at 100 mg daily to RA patients. As compared to TNF- $\alpha$  inhibitors, anakinra has shown less benefit in clinical outcomes and frequent reactions at injection site.<sup>69</sup> It is rarely used now, because of the availability of better therapies.

*Inhibitors of TNF- $\alpha$ :* These are the most commonly used biologic agents. There are five currently available inhibitors. Four are antibodies against both soluble and membrane-bound TNF- $\alpha$  i.e. infliximab, adalimumab, golimumab and certolizumab. Etanercept is a recombinant human TNF- $\alpha$  receptor that binds to soluble TNF- $\alpha$ . Infliximab is given by intravenous infusions whereas all other TNF- $\alpha$  inhibitors are given subcutaneously at different intervals. Certolizumab is a humanized, pegylated TNF- $\alpha$  antibody fragment with a long half-life and low manufacturing costs, thus acquiring a potential advantage over the other TNF- $\alpha$  inhibitors. They improve physical function and quality of life.<sup>70</sup> There are no randomized controlled trials (RCTs) comparing the various TNF- $\alpha$  inhibitors but indirect comparison in systematic reviews do not show substantial differences in efficacy among them, although there are some variances in their toxicity profiles.<sup>62</sup> Most common adverse events are injection site reactions (etanercept and adalimumab), hypersensitivity reactions (infliximab) and mild respiratory infections. Concerns regarding safety of TNF- $\alpha$  inhibitors are mostly due to the increased risk of infections and higher incidence of tuberculosis (TB). It has also been seen that TB risk tends to be lower with etanercept due to its different structure and mechanism of action.<sup>71</sup> Routine screening for latent TB is a must for all patients considered for TNF- $\alpha$  inhibitors therapy with continuous vigilance for active TB throughout treatment course; positive cases should be on preventive TB therapy at

least a month prior starting a TNF- $\alpha$  inhibitor. In addition, there is an increased risk for worsening congestive heart failure. While there is some evidence of increased risk for skin cancer and also there may be risk of lymphoproliferative malignancies.<sup>72</sup>

**Rituximab:** It an anti-CD20 antibody was introduced in recent years for the management of patients with RA after gaining better understanding of the role of B-cells in the pathogenesis of RA.<sup>73</sup> It is mostly reserved for patients who have failed therapy to other biologics. Randomized control trials show significant improvement in these patients when compared with MTX alone.<sup>74</sup> Rituximab is given intravenously for only 2 doses 2 weeks apart with likely need of repeated therapy every 6–12 months. Infusions have to be premedicated with intravenous glucocorticoids to reduce the rate of infusion reactions. Based on a prolonged experience from hematology and oncology clinical practice, rituximab does not appear to increase the risk of TB or malignancies.

**Noval approaches:** Newer biologic agents are currently in various stages of development. Agents targeting alternative pathways of inflammation, newer humanized anti-CD-20, B-cell blockers and agents blocking other B-cell targets and small molecules targeting specific inflammatory pathways (i.e. Janus kinase inhibitors) are under development.

One new drug is tocilizumab which is a humanized monoclonal antibody directed against the IL-6 receptor. IL-6 binding to its receptor activates intracellular signaling pathways that affect inflammatory response, cytokine production, and osteoclast activation. Clinical trials have shown the clinical efficacy of tocilizumab in RA patients, both as monotherapy and in combination with methotrexate. However it has been associated with an increased risk of infection, neutropenia and thrombocytopenia but these are reversible upon stopping the drug.<sup>75</sup>

Minocycline has shown beneficial effects in rheumatoid arthritis.<sup>76</sup> It is an effective treatment for RA, particularly when used in early seropositive disease. It has been shown to have antibacterial, anti-inflammatory, immunomodulatory, and chondroprotective activity.<sup>77</sup> The mechanism of action in RA is

uncertain but probably is independent of its antibacterial effects. Its possible mechanisms of action in RA include inhibition of matrix metalloproteinases (MMP), decrease in the production of tumor necrosis factor, decrease of polymorphonuclear leukocyte chemiluminescence and generation of reactive oxygen species.<sup>78</sup> It is a potent suppressor of the erythrocyte sedimentation rate and C-reactive protein levels in RA.<sup>79</sup> Its side effects are gastrointestinal upset like nausea & vomiting, maculopapular rash, headache, vestibular toxicity, skin pigmentation, hepatitis, lupus syndrome, blood dyscrasias i.e. decrease platelet count, renal dysfunction etc.<sup>80</sup> Many studies have shown the benefit with minocycline. In a double blind 48 weeks Placebo controlled trial, 219 adults with rheumatoid arthritis, were randomly assigned to receive minocycline or placebo. 109 patients received minocycline treatment and 110 received a placebo. By the end of the study, 54% of patients in the minocycline group had less joint swelling versus 39% of those in the placebo group. Joint tenderness was also improved in more patients taking minocycline (56%) than in those taking placebo (41%) (p value < 0.023 for both the comparisons). Joint tenderness and swelling continued to improve throughout the study in patients taking minocycline, as compared to placebo group. Laboratory tests also showed that minocycline lowered the degree of disease activity compared with placebo. There were no serious side effects reported.<sup>81</sup>

## CONCLUSION

As RA is a lifelong disease require long treatment & it is important to put the disease in remission also to maintain this remission by continuing therapy. The manipulation of drugs & doses are based on assessment of disease at each follow up by using various parameters like CDAI, DAS-28. These parameters allow physicians to judge the disease activity at the spot without waiting for any blood parameters. Current available therapies are effective but with chronic treatment there is problem with efficacy & safety. The drugs like methotrexate, leflunamide sulfasalazine etc are immunosuppressants, so chronic therapy with these drugs is really problematic. There is always requirements of new drugs



for the treatment of rheumatoid arthritis, which when used for chronic therapy should remain efficacious even on chronic usage i.e. no development of tolerance and should have low side effect profile.

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