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Review Article

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A REVIEW ON RECENT ADVANCEMENT IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS

Samriti Sharma*, Ankit Sharma, Navneet Raj, Vipasha Kango, Ehsas Rana, Muskan and Vishal Attal

Associate Professor (Pharmaceutics) Dreamz College of Pharmacy, Khilra, Sundernagar.

***Corresponding Author: Samriti Sharma**

Associate Professor (Pharmaceutics) Dreamz College of Pharmacy, Khilra, Sundernagar.

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease which causes pain and disability. New developments in its treatment have greatly changed the current understandings and shifted towards preclinical intervention and personalized treatments. Summary this review provides an update of the recent therapeutic advances including targeted biologic agents like TNF inhibitors and IL-6 antagonist, which have drastically improved patient function. Moreover,because of their oral availability and effectiveness in individuals who do not respond to standard therapeutics, Janus kinase (JAK) inhibitors have emerged as additional viable options. In addition to pharmacotherapy, there has been a trend toward the integration of physical therapy (PT), nutritional support and patient education into practice in an MD care model with regards increased quality-of-life. As a phase I study, investigators caution that the results are preliminary and need to be validated prospectively in larger cohorts while advising additional research on biomarkers as well as personalized medicine will help create more targeted intervention programs tailored specifically for the individual. The article highlights the importance of these developments in changing how RA is managed and moving toward a more comprehensive view that involves treating symptoms as well as improving overall health over time. Further research and collaborative efforts are needed in order to continue working towards improved care of patients with RA.

KEYWORDS: JAK inhibitors, targeted biologics, autoimmune diseases, Disease-modifying antirheumatic drugs (DMARDs), TNF inhibitors and IL-6 antagonist.

1. INTRODUCTION

1.1 Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory disorder, affecting many joints especially in the finger, wrists, feet, and ankles. Rheumatoid arthritis is an autoimmune inflammatory disease in which body immune system attack its own healthy cells.[1] Rheumatoid arthritis is a symmetric polyarticular arthritis that primarily affect the small diarthrodial joints of hands and feet. In addition to inflammation in the synovium, which is the joint lining, the aggregation font of tissue called pannus invades and destroys local articular structures. The synovium is normally a relative acellular with delicate intimal lining. These considerations are especially important for emerging nations where the prevalence of non-communicable diseases is quickly rising. The frequency or prevalence of arthritic illnesses in these nations, as well as the societal issues they raise, are relatively poorly understood. This institute previously released a preliminary report on the scope of the rheumatoid arthritis problem in India.[2]

1.2 Sign and Symptoms

- Fatigue
- Morning Stiffness
- Joint stiffness
- Joint pain
- Minor joint swelling
- Fever
- Numbness and tingling
- Decrease in range of motion.[3]

1.3 Etiology: Rheumatoid arthritis is caused by the immune system attacking healthy body tissue.

- Abnormal response of the immune system due to the change of hormone.
- Infectious agent like bacteria or viruses
- Due to obesity
- Triggered by stressful events like physical or emotional trauma
- Environmental factor.[4]

1.4 Types of rheumatoid arthritis

- Seropositive rheumatoid arthritis
- Seronegative rheumatoid arthritis.[5]

1.5 Prevalence

The global prevalence of RA between 1980 and 2019 was 460 per 100,000 population, with variations due to geographical location and study methodology.[6]

A response rate of 89.5% was obtained and 3393 persons were listed as possible cases of RA by the health workers. Of these, 299 satisfied the revised ARA criteria for the diagnosis of RA, giving a prevalence of 0.75%. Projected to the whole population, this would give a total of about seven million patients in India. The prevalence of RA in India is quite similar to that reported from the developed countries.[7]

2. Pathophysiology

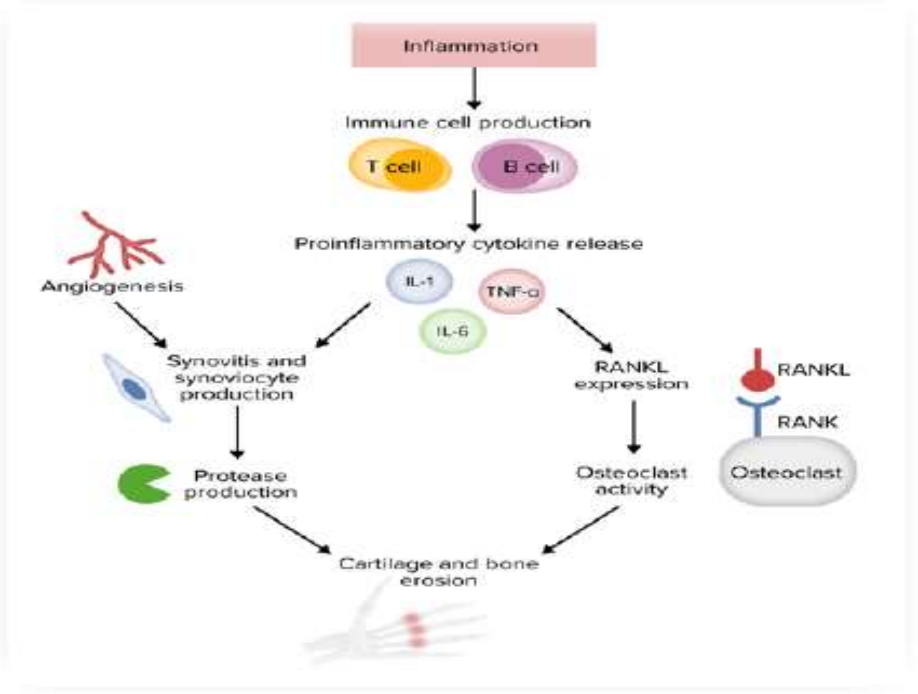


Fig. 1: Pathophysiology of rheumatoid arthritis.

3. Treatment

Drugs used in the treatment of rheumatoid arthritis

- Methotrexate
- Azathioprine
- Cyclosporine
- Sulfasalazine
- Chloroquine
- Leflunomide
- Anakinra
- Etanercept
- Infliximab.[8]

4. Diagnosis of RA

Suspicion based on start symptoms, timely utilisation of serologic testing, and availability to medical and diagnostic services are all necessary for an early diagnosis. RA cannot be diagnosed by a lab; it is a clinical diagnosis. In the following cases, RA should be taken into consideration:

- Multiple joints exhibiting pain, oedema, and stiffness that lasts for 12 weeks or longer
- New-onset carpal tunnel syndrome with persistent joint symptoms;
- First-degree relative of a patient with RA who does not have symptoms in the lower spine or distal interphalangeal [DIP] joints.[9]

- **Guidelines for referrals**

The primary care physician or diagnostic physician should create a treatment plan, start therapy, and take referrals into consideration as soon as the diagnosis of RA is suspected or confirmed. Reducing the duration between the onset of symptoms and the diagnosis, as well as the duration between the diagnosis and the start of DMARD medication.

As per MRI studies, articular erosions can be observed as early as 12 to 16 weeks after beginning, hence prompt referral is imperative. Approximately 70% of patients develop radiographs within the first three years.[10]

5. Recent advancement in the management of rheumatoid arthritis

5.1 DMARDs (Disease –modifying antirheumatic Drug)

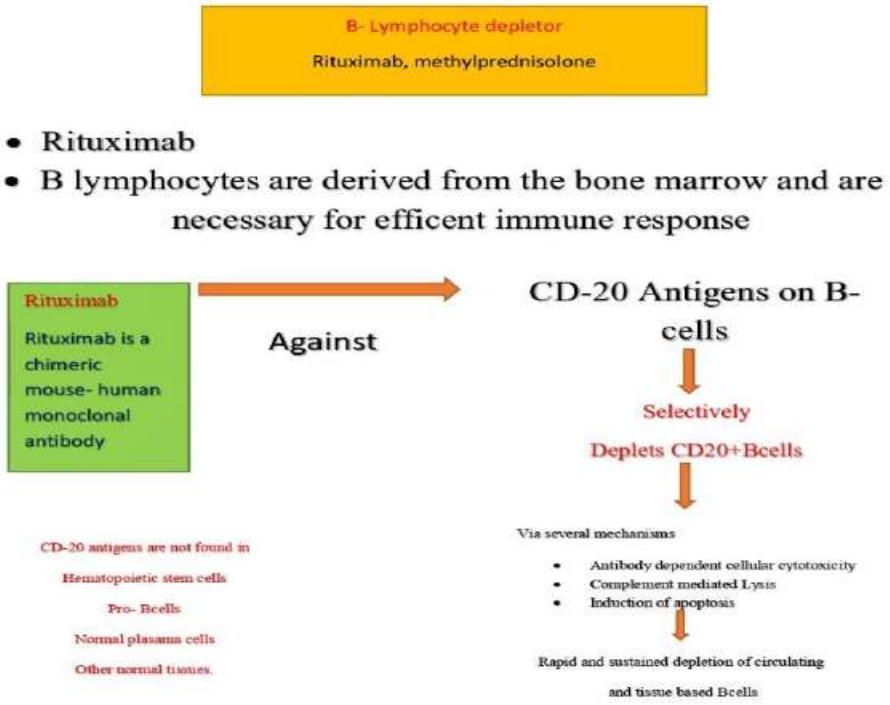
DMARDs are a class of drug indicated for the treatment of inflammatory arthritides, including rheumatoid arthritis, psoriatic arthritis. Examples of DMARDs (methotrexate, leflunomide, hydrochloroquine, sulfasalazine.[11]

- **MOA of Leflunomide:** Leflunomide reversibly inhibit the enzyme dihydroorotate dehydrogenase whichcatalyse the conversion of carbomyl phosphate to osotic acid as a part of the pyrimidine synthesis pathway which inhibit the activation of T cells**,** which reduces anti-inflammatory activity.

5.2 Biological DMARDs: Biological DMARDs such as tumor necrosis factor [TNF] inhibitor, interleukin-1-inhibitor.

- **[TNF] inhibitor:** examples, infliximab, etanercept, golimumab
- **MOA of etanercept:** Etanercept competitive inhibitor of membrane bond TNF alpha receptor, which decrease the activity of TNF alpha or TNF beta and reduces the anti-inflammatory effect.
- **IL-1 inhibitor:** examples, anakinra, canakinumab.
- **MOA OF IL-1 Inhibitor:** these drugs inhibit the IL-1 receptor which inhibit the release of cytokines which reduces the destruction of cartilage and reduce inflammation.

5.3 B-cell depleting agent (beta cell): Rituximab is currently available for the treatment of Rheumatoidarthritis.



5.4 Janus kinase [JAK]-inhibitors

Many rheumatoid arthritis trials with novel oral small molecules have been ineffective. The mitogen-activated protein kinase pathway seemed important in rheumatoid arthritis but trials of agents targeting this pathway were negative.[11,12]

- By contrast, medications that inhibit the JAK pathways have led to a considerable breakthrough in rheumatoid arthritis treatment.
- Although efficacy could be anticipated because of the numerous cytokines that use JAK pathways for intracellular signaling, potential safety concerns arose because knock-out of either JAK1 or JAK2 in rodent models is lethal and a human severe combined immunodeficiency disease exists in which the gene for JAK3 is defective.[13]
- Randomised controlled trials in rheumatoid arthritis have demonstrated both efficacy and acceptable safety for JAK inhibitors.
- In many countries, such as the USA, Russia, Canada, and Switzerland, tofacitinib (JAK1/2/3) was the first JAK inhibitor to be approved. This compound was reassessed by the European Medicines Agency (EMA) in between 2016 and 2017, resulting in approval of tofacitinib with methotrexate for patients with moderate to severe active rheumatoid arthritis who have responded inadequately to, or who are intolerant to one or more DMARDs and can be given as monotherapy if metho trexate is inappropriate or not tolerated.[14]
- The EMA has approved baricitinib (JAK1/2) for treatment in patients with moderate to severe active rheumatoid arthritis with an inadequate response or intolerance to one or more DMARDs as monotherapy or in combination with methotrexate.[15]
- Both tofacitinib and baricitinib have been investigated in extensive clinical trial programmes,

in patients ranging from those with early rheumatoid arthritis who are methotrexate-naïve to patients with an inadequate response to conventional DMARDs, and patients who do not respond to biological drugs, most notably TNF inhibitors. One trial was powered to compare baricitinib and the TNF inhibitor adalimumab in a head-to-head design, which showed a modest, nevertheless significantly better efficacy of baricitinib.[17]

- The ORAL Strategy trial showed that tofacitinib plus methotrexate was not inferior to adalimumab plus methotrexate. Monotherapy with the JAK inhibitors (tofacitinib or baricitinib) were clinically more effective than methotrexate in early rheumatoid arthritis, including the analysis of radiological progression.[18,19]
- Although the 2016 EULAR (European Alliance of Associations for Rheumatology) recommendations place these targeted DMARDs somewhat behind the biologics, preferred treatment strategies might change with more clinical experience. The safety signals of the JAK inhibitors do not differ considerably from biologics with the exception of increased incidence of herpes zoster infection, especially with tofacitinib; most notably in Japanese and Korean patients. However, patient preference for oral drugs instead of injectable compounds and the possibility to use them in monotherapy might lead to a shift in practice in the future.

5.5 Adverse effects of rheumatoid arthritis treatment

- Traditional DMARDs have well known side-effects, including cytopenia, transaminase elevation, poor tolerability (fatigue, nausea, and central nervous system side-effects), rash, and, rarely, interstitial lung disease or liver damage.
- Biologics agentmight lead to more infections (Common and Atypical), elevations of cholesterol, and rarely cytopenia, transaminase elevation, multiple sclerosis type conditions, psoriasis, other autoimmune conditions, bowel perforation, and worsening congestive heart failure. In patients with early rheumatoid arthritis, infection was not different in patients who were naive to methotraxaterandomised to methotrexate or TNF inhibitor.[20]
- Although a single metaanalysis reported a higher incidence of malignancies in patients with rheumatoid arthritis treated with adalimumab or infliximab in randomised controlled trials, registries that include more than 1000 patients showed no evidence of a higher incidence of malignancies, but the incidence of infection was about two times higher in biologic users than in patients treated with conventional DMARDs.
- JAK inhibitors might cause gastrointestinal side-effects, cytopenia (lymphopenia or neutropenia), elevated cholesterol, and more infections (especially viral infections such as herpes zoster)

5.6 Combination treatment of methotrexate with biologics in patients with an inadequate response to methotrexate

- Patients who use biologics with methotrexate might have better responses and durability of treatment than patients who use biologics alone, but approximately one-third of patients in biologic registries are not receiving methotrexate with their biologics.[21]
- Generally, when using TNF inhibitors in patients with rheumatoid arthritis after inadequate response to methotrexate alone, combination therapy with methotrexate is superior to TNF inhibitor monotherapy, but in some patients who are in a low disease state, monotherapy might be a reasonable option.[22]
- Whether tocilizumab is sufficient as monotherapy remains debated. A 2016 meta-analysis showed a slight advantage of tocilizumab in combination with methotrexate compared with tocilizumab monotherapy in patients who did not respond to methotrexate monotherapy.[23]
- In patients with early rheumatoid arthritis who were methotrexate-naive, clinical outcomes did not differ between those treated with baricitinib alone and baricitinib and methotrexate, and patients treated with combination therapy had only a small advantage with regard to radiographic changes.
- Currently, no biomarkers are available that indicate which patients would benefit from continuation of concomitant methotrexate treatment, which patients would benefit from cessation, or which patients would not relapse following cessation of treatment with conventional DMARDs.
- The order of treatment following methotrexate monotherapy varies: some clinicians recommend the addition of more DMARDs, whereas others would prescribe a TNF inhibitor, oral JAK inhibitors, or even rituximab, which is not approved as a first biologic therapy but might be more cost-effective than TNF inhibitor treatment.[24]

5.7 Lifestyle changes in the prevention of rheumatoid arthritis

- Avoid alcohol and smoking.
- Exercise 20-30 minutes daily.
- Avoid high salt in your diet.
- Incorporate fish in your diet.
- Move your body frequently.
- Keep bones strong with a calcium rich diet.
- Reduce exposure to environmental pollutant.
- Get regular dental checkup to avoid inflammation.

6. RESULT AND DISCUSSION

Several strategies and accompanying recommendations can facilitate optimal care for patients with rheumatoid arthritis with a better prognosis than that observed historically. The most important aspects of rheumatoid arthritis management are the early diagnosis of patients,

prompt initiation of DMARD therapy, and regularly assessing patients to achieve a target of remission or low disease state. This management strategy will result in favorable outcomes for most patients.

7. CONCLUSION

The management of rheumatoid arthritis (RA) has recently seen major advances, translating into improved outcomes and quality-of-life for patients. New drugs, such as targeted synthetic and biologic disease modifying anti-rheumatic drugs (DMARDs), have been found that allow remission to be a more frequent goal of therapy. Precision medicine, that provide treatments tailored to individual patient characteristics has allowed for the incorporation of molecular tools improving therapeutic efficacy and reducing adverse effects. In addition, with the help of advanced imaging technologies available today it is possible to identify diseases at an early stage and keep them under control so that interventions can be performed in time. Also had significant reforms in patient centered approaches; shared decision making and lifestyle measures shifting focus on prevention to holistic care. Cumulative guidelines have now progressed to an early aggressive approach in order that joint damage may be minimized and the patient achieve maximal function. In summary, the setting of RA treatmentis shifting under powerful forces related to pharmacotherapy and better understanding of pathogenesis. In addition to providing hope for better control of disease, these advances promote a more prospective and individualized patient care in this sense highlighting the need for continuous research and development on IBD.

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