International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1844-1850 www.ijprajournal.com ISSN: 2456-4494

Rheumatoid Arthiritis – Recent Advances in Therapies and Treatment

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Submitted: 05-06-2022 Revised: 18-06-2022 Accepted: 20-06-2022

ABSTRACT

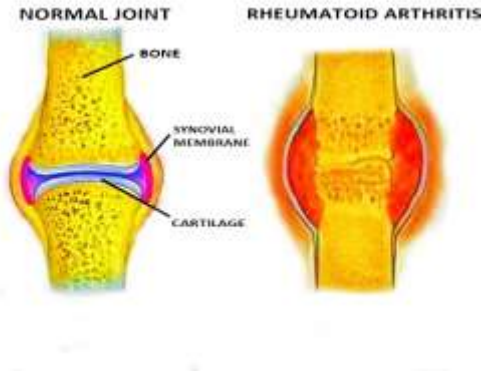
Rheumatoid arthritis is a chronic, painful inflammatory disorder marked by joint severe damage to cartilage and bone marrow. It can also impact the entire body, including the tissues, resulting in cardiac, respiratory, neurological, and ocular diseases. It's a severe and painful inflammatory disorder that causes significant loss of movement due to discomfort and joint degeneration. Rheumatoid arthritis is a systemic illness that frequently affects constriction tissues. Remission or a condition of minimal disease activity is the goal of treatment. Because rheumatoid arthritis has no cure, the treatment goals are to reduce discomfort and prevent or reduce the progression of the disease. As a result, accurate diagnosis and therapy are essential beginning at the earliest stages of disease. Although steroids and anti-inflammatory medicines were previously utilised as supportive therapy, diseases modifying anti-rheumatic drugs(DMARDS) and biomarkers are now employed to decrease inflammatory abnormalities and manage disease activity.

KEYWORDS: Rheumatoid arthritis, autoimmune disease, systemic disease, biomarkers, DMARDS.

I. INTRODUCTION

The autoimmune disease rheumatoid arthritis damages the joints over time with the common adverse effects of warm, swollen, and painful joints. The illness may have an impact on different sections of the body. Low pink blood cell counts, pulmonary pain, and hepatic inflammation are all possible side effects. There's also a chance of fever and unconsciousness. Symptoms can occur in weeks or months. Rheumatoid arthritis is a rheumatic disease that affects the articular and extra-articular systems, producing pain, disability, and death. Rheumatoid arthritis leads to early death, incapacity, and a loss of first-class status in life. Several factors, including genetic background, frequency of swollen joints, serum autoantibody levels, and the severity of the inflammatory process, can all influence the course of sickness [1]. Women are two to five times more likely than men to have the disease in middle life. Rheumatoid arthritis is thought to be caused by a mix of hereditary and environmental causes. Part of the underlying mechanism is that the immune system targets the joints. This leads to pain and a thickening of the joint capsule. The underlying bone and cartilage are also affected [2]. The main objective of inhibiting enzymes like COX and LOX in chronic inflammatory illnesses is to modify arachidonic acid metabolism. TNF, IL, and IL-6 are pro-inflammatory cytokines that play a role in the duration of illness [3]. Treatment seeks to decrease pain and inflammation while also increasing a patient's overall function. To help with symptom relief, pain medications, steroids, and nonsteroidal anti-inflammatory medicines (NSAIDs) are commonly utilised. Disease-modifying anti-rheumatic drugs (DMARDs) such as hydroxychloroquine and methotrexate can be used to help decrease the progression of the disease. Biological DMARDs can be used when other treatments fail [4].

Diagram represents difference between normal joint and rheumatoid arthritis affected joint



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II. TREATMENT OF RHEUMATOID ARTHRITIS

Nonsteroidal antiinflammatory drugs (NSAIDs) and glucocorticoids, which reduce inflammation, have traditionally been employed as first-line treatments. These medications also alleviate edoema and pain associated with Rheumatoid arthritis quickly. Disease-modifying antirheumatic drugs (DMARDs) include methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide, which was recently approved [5]. Three approaches are frequently utilised in the pharmaceutical treatment of rheumatoid arthritis patients. To reduce the inflammatory process and treat the disease's symptoms, aspirin and other non-steroidal anti-inflammatory and moderate analgesics are used first. These drugs help with the symptoms of rheumatoid arthritis, but they don't seem to affect the disease's course. The second approach is to treat pain and inflammation with low-dose corticosteroids. Low-dose corticosteroids taken orally may assist in preventing rheumatoid arthritis-related bone erosions from developing and progressing. DMARDs (disease-modifying anti-rheumatic or slow-acting medicines) are used in the third approach. Gold salts, D-penicillamine, sulfasalazine, and other drugs appear to reduce the disease's course by reducing articular damage [6].

2.1. Rheumatoid arthritis treatment and its limitations:

When it comes to controlling Rheumatoid arthritis, postoperative analgesia, reducing long-term joint damage, and decreasing inflammation are all critical considerations. The cornerstones of treatment for the disease's symptoms and adverse effects have been disease-modifying anti-rheumatic drugs (DMARDs) and non-steroidal anti-inflammatory medications (NSAIDs). Another steroidal medicine used to treat Rheumatoid arthritis inflammation is corticosteroids, which are anti-inflammatory hormones produced by the adrenal glands. A good steroid should be able to meet the demand at a low dose while avoiding negative consequences [7]**.** In the short term, both steroidal and non-steroidal drugs can help control symptoms, but they cannot treat or prevent disease in the long run. Aside from that, prolonged use of such medications may lead to more serious side effects, such as effects on the kidney, liver, and heart. Some of the short-term negative effects mentioned include shortness of breath, nausea, infections, and allergic reactions. This underlines a fundamental limitation and cause for caution when using steroidal drugs to treat rheumatoid arthritis [8].

2.2 NSAIDS and Corticosteroids as First-Line Therapy

The primary goal of first-line treatment is to alleviate pain and reduce inflammation. NSAIDs, such as acetylsalicylate, naproxen, ibuprofen, and etodolac, are fast-acting pain relievers. Because it inhibits prostaglandins, aspirin is a potent anti-inflammatory for Rheumatoid arthritis when taken in large dosages. It's a nonsteroidal anti-inflammatory medicine (NSAID) that's been around for a long time. Taking far too much aspirin can induce tinnitus, hearing loss, and gastrointestinal distress. There are newer nonsteroidal anti-inflammatory drugs (NSAIDs) on the market that are equally as effective as aspirin. These drugs also require fewer daily doses. By inhibiting cyclo-oxygenase, NSAIDs stop the production of prostaglandins, prostacyclin, and thromboxane. Nausea, stomach pain, ulcers, and GI bleeding are all typical side effects. These symptoms can be reduced by taking it with food, antacids, proton pump inhibitors, or misoprostol. A relatively modern NSAID, celecoxib (Celebrex), is a selective Cox-2 inhibitor with fewer GI harmful effects. Anti-inflammatory medications such as corticosteroids are more effective than NSAIDs, but they have more side effects. As a result, they're only used in small doses for a short length of time during Rheumatoid arthritis flare-ups or exacerbations. In order to mitigate local inflammatory symptoms, corticosteroids might be administered intra-articularly. They minimise inflammation by reducing phospholipid release and diminishing eosinophil activity. Possible side effects include bone weakening, weight gain, diabetes, and immunosuppression. It is feasible to prevent bone deterioration by recommending calcium and vitamin D tablets to the patient. Reduced doses can help to reduce adverse effects if a patient's symptoms worsen. Stopping injectable or oral corticosteroids abruptly can cause suppression of the hypothalamic-pituitary-adrenal axis (HPA) and Rheumatoid arthritis flare-ups [9].

2.3. Disease-Modifying Antirheumatic Drugs as Second-Line Therapy

Second-line therapy aims to elicit remission by slowing or preventing the progression of joint deterioration and deformity. Medication that takes weeks to months to take effect is classified as slow-acting. DMARDs can also help to reduce the risk of lymphoma, which is connected

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to Rheumatoid arthritis. Methotrexate (MTX) is the first and second-line treatment (also considered an anchor drug). It's a folic acid analogue that competes with FH2 for binding to the enzyme that converts FH2 to folic acid (FH4). FH4 inhibits the metabolism of purines and pyrimidines, as well as the synthesis of amino acids and polyamines. MTX is an immunosuppressive drug that requires regular blood testing due to its side effects, which include liver problems, cirrhosis, and bone marrow degeneration. Folic acid supplementation can help reduce the risk of unfavourable consequences. It is a safe and effective DMARD with fewer side effects than other DMARDs and dose flexibility, allowing for dose modifications as needed. There hasn't been enough evidence to back up the usage of typical synthetic DMARDs in combination with MTX monotherapy until now. On the other hand, biological and synthetic. Combining DMARDs is said to be more effective than MTX, although it comes with additional side effects and costs. Hydroxychloroqyine is a long-acting antimalarial drug that can be used to treat Rheumatoid arthritis. This medication inhibits the release of proinflammatory cytokines from monocytes [10]. Common adverse effects include issues with the gastrointestinal tract, skin, and central nervous system. When this medicine is taken in large doses, it can harm the eyes in particular. Patients should see an ophthalmologist on a frequent basis while using this medication. Irritable bowel syndrome is treated with sulfasalazine, which is a DMARD. When used with anti-inflammatory medications, this DMARD can help treat Rheumatoid arthritis. The mechanism of action of this medication in treating Rheumatoid arthritis is still unknown. Interleukin (IL)-8 and monocyte chemoattractant protein production are thought to be inhibited by sulfapyridine, a reduced version of the drug after delivery . The gastrointestinal (GI) and central nervous system (CNS) symptoms, as well as a rash, are all associated with this medicine. Patients tolerate it well in general, but individuals with sulpha allergies should avoid it because it contains sulpha and salicylate components.

III. METHOTREXATE (MTX)

MTX has been shown to be effective in the treatment of psoriasis, in addition to its original use as a cancer chemotherapeutic medication. Later, placebo-controlled studies confirmed its safety and efficacy in the treatment of Rheumatoid arthritis. MTX, on the other hand, is presently the most widely used DMARD for the treatment of both early and established Rheumatoid arthritis, thanks to its long history of proven safety and efficacy. Furthermore, MTX has been widely used as a "anchor" medicine in combination therapy with other DMARDs and biological agents for the effective treatment of Rheumatoid arthritis. The US Food and Drug Administration approved MTX for the treatment of Rheumatoid arthritis in 1988, and it is now considered the gold standard. Because tetrahydrofolates are depleted, MTX suppresses purine and thymidylate production by inhibiting dihydrofolate reductase with high affinity. As a result, DNA and RNA synthesis, as well as other metabolic processes, are hampered. However, the exact mechanism of action of MTX in Rheumatoid arthritis is still unknown. MTX works against the cells that generate joint inflammation in Rheumatoid arthritis as both an antiproliferative and an anti-inflammatory medication. According to the findings, MTX suppresses the immune system by inhibiting dihydrofolate reductase and other folate-dependent enzymes, resulting in an excess of adenosine [11].

IV. DMARDS CONVENTIONAL

The most commonly prescribed traditional DMARDs include methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide. Azathioprine and other drugs are used much less frequently. Standard DMARDs and conventional synthetic DMARDs are terms used to describe this class of drugs**.**

4.1. Methotrexate: Methotrexate was first used as a cancer treatment, then latterly used at much lower doses for rheumatoid arthritis and other rheumatic disorders, helps to reduce inflammation and joint damage. These lower doses are far less harmful and well tolerated than cancer doses. Once a week, it's taken as a tablet, a drink, or an injection (on the same day each week). It may take four to six weeks for you to observe a difference in your symptoms after starting treatment. If methotrexate fails to control disease on its own, it can be used with other DMARDs, a biologic medication, or another targeted DMARD. Because of liver function problems can occur even at low dosages, if using methotrexate should undergo regular blood tests [12]. If the person gets a new cough or shortness of breath, which is an uncommon consequence, methotrexate should be stopped and Careful monitoring is essential to detect medication toxicity in those using methotrexate. Testing is done prior to starting treatment to determine baseline blood counts as well as kidney and liver function. These

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 1844-1850 www.ijprajournal.com ISSN: 2456-4494

tests are done every 4 to 6 weeks for the first several months, then every 8 to 12 weeks after that. The dose of methotrexate might be changed if problems emerge. Anyone using methotrexate should take folic acid (1 mg daily) or folinic acid (1 mg daily) to reduce the risk of some adverse effects, such as stomach upset, mouth sores, low blood cell counts, and abnormal liver function (5 mg weekly).

4.2. Sulfasalazine is a drug used to treat rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel illness (ulcerative colitis and Crohn disease). The mechanism of action for sulfasalazine is uncertain. If one DMARD does not work, it may be combined with others & It's taken as a pill twice a day, and it's usually started at a low dose and gradually increased to avoid unpleasant side effects. After one to two months on medication, symptoms may improve. Sulfasalazine's adverse effects include changes in blood counts, nausea or vomiting, sensitivity to sunlight, skin rash, and headaches. Those who are allergic to sulfonamide medicines such as sulfamethoxazole-trimethoprim should avoid sulfasalazine. Sulfasalazine has a yellow-orange colour to it, and people who take it may notice an orange tinge in their urine, tears, and sweat, which can stain clothing and contact lenses. It's critical to stay hydrated when taking sulfasalazine and to avoid taking it on an empty stomach or with antacids.

4.3. Hydroxychloroquine: Hydroxychloroquine, which was first developed to treat malaria, was later proven to be helpful in the treatment of arthritis symptoms. It's usually taken in combination with other DMARDs and can be started early on in the course of rheumatoid arthritis [13]. It's also widely prescribed for systemic lupus erythematosus (SLE). It can be combined with steroid medications to reduce the quantity of steroids needed. It's usually taken once or twice a day in pill form, and results can take up to three months to see. Although high dosages of hydroxychloroquine are not usually required for the treatment of rheumatic illnesses, consuming a high dose for a lengthy period of time can increase the risk of retinal damage. A visit to an ophthalmologist is recommended at the start of treatment and on a frequent basis thereafter. It is customary to have your eyes checked once a year.

4.4. Leflunomide: By reducing the development of inflammatory cells, leflunomide decreases inflammation. It is commonly used alone, but in people who haven't responded well to methotrexate alone, it can also be used in combination with methotrexate or with a biologic medication. It is administered orally once a day. Side effects (nerve damage) include rash, temporary hair loss, abnormal liver function tests, nausea, diarrhoea, weight loss, abdominal pain, and neuropathy. [14**]** High blood pressure affects approximately 10% of the population. Prior to exposure, examinations as well as monthly blood testing while on therapy are required to evaluate for liver damage and other complications. Women should avoid becoming pregnant while taking leflunomide or while it is still detectable in their bodies.

4.5. Azathioprine: Azathioprine has been used to treat cancer, rheumatoid arthritis, lupus, and other inflammatory illnesses since the 1950s [15]. It's also been used to prevent organ rejection during transplantation. The most common azathioprine side effects include nausea, vomiting, loss of appetite, liver problems, low white blood cell counts, and infection. It's usually taken by mouth once a day. Blood tests should be performed on a regular basis when using azathioprine **[**16**].**

V. DMARDS (DISEASE MODIFYING ANTI- RHEUMATIC DRUGS)

Although a variety of medications can be used to treat Rheumatoid arthritis, methotrexate is the most commonly recommended drug as a first-line treatment. Treatment for Rheumatoid arthritis is multifaceted, and a variety of factors, such as disease activity and severity, comorbidities, and patient preference, all factor into treatment decisions (including cost, route of administration, and frequency of monitoring). Rheumatoid arthritis treatment can be monotherapy or combination therapy, despite the fact that several randomised controlled trials have shown that combining a biologic DMARD with a classical DMARD like methotrexate is better than either agent alone. Establishing remission or low disease activity, as well as preventing disease progression on radiographs, should be among your treatment goals. Early treatment has been shown to prevent radiographic progression, which occurs most often in the first few months of the disease.

5.1. Mechanism of action

Each DMARD works in a different way, but they all work by interfering with essential inflammatory pathways. Methotrexate stimulates adenosine release from fibroblasts, inhibits neutrophil adhesion, inhibits neutrophil leukotriene B4 synthesis, reduces local IL-1 production, suppresses cell-mediated immunity, and inhibits synovial collagenase gene expression, to name a

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few effects. Other medications in this family inhibit lymphocyte proliferation or cause them to malfunction. Leflunomide inhibits dihydroorotate dehydrogenase, which reduces pyrimidine synthesis, and so inhibits lymphocyte proliferation. The capacity of sulfasalazine to suppress oxidative, nitrative, and nitrosative damage is responsible for its anti-inflammatory effects [17]. The intracellular toll-like receptor TLR9 is inhibited by hydroxychloroquine, a mild immunomodulatory medication. Bio-logics, on the other hand, has a very specific method of operation. Interfering with cytokine activity or production, blocking the "second signal" essential for T-cell activation, and depleting or inhibiting chemicals that activate B-cells are just a few of the functions that biologics play. Tofacitinib, a small molecule inhibitor, inhibits JAK, a protein tyrosine kinase that plays a role in cytokine signalling. Some of these medications are monoclonal, humanised chimeric fusion antibodies, while others are receptors fused to human immunoglobulin or tiny compounds such as Janus kinase (JAK) inhibitors [18].

VI. TRAGETED DRUG DELIVERY SYSTEMS IN TREAMENT OF RHEUMATOID ARTHRITIS

The current therapies of RA treatment comprise conventional, small molecule and biological antirheumatic drugs. Their utility as therapeutic agents is limited because of poor absorption, rapid metabolism and adverse effects (dose-escalation, systemic toxicity, lack of selectivity and safety). To overcome these limitations, the novel drug delivery systems are being investigated. The currently approved therapies along with emerging advanced drug-delivery systems for RA treatment. Further, active targeting of therapeutic agents to inflamed joints via folate receptor, CD44, angiogenesis, integrins and other provided an improved therapeutic efficacy in the treatment of RA. Conventional antirheumatic medications, small-molecule antirheumatic pharmaceuticals, and biological antirheumatic drugs are now used in the treatment of RA. They are limited in their ability to be used as therapeutic agents due to inadequate absorption, fast metabolism, and undesirable effects (dose-escalation, systemic toxicity, lack of selectivity and safety). Novel medication delivery technologies are now being studied as a means of overcoming these restrictions. For the treatment of RA, already licenced medicines, as well as new innovative drug-delivery technologies, are being investigated. Through the active targeting of therapeutic drugs to inflamed joints through the use of the folate receptor (CD44), angiogenesis, integrins, and other mechanisms, there was increased therapeutic effectiveness in the treatment of arthritis.
[19].

VII. RECENT ADVANCEMENT THERAPY'S

Rheumatoid arthritis is a chronic autoimmune disease marked by joint inflammation and degradation, which can lead to loss of function, a lower quality of life, and an increase in morbidity and mortality. The main goal of Rheumatoid arthritis treatment is to reduce long-term complications by lowering inflammation early in the disease's progression, relieving symptoms, preventing joint and organ damage, and restoring physical function. There are several new Rheumatoid arthritis therapies on the market. Sarilumab, an interleukin-6 (IL-6) receptor blocker, was approved in 2017. Overall, the sarilumab studies suggest that it is beneficial in Rheumatoid arthritis, particularly for people who have had partial responses to methotrexate and anti-tumor necrosis factor inhibitors, and that it is superior to standard-dose adalilumab when given at a higher dose (200 mg every 2 weeks). Sarikumab, an IL-6 cytokine blocker, filgotinib, a tiny targeted molecule, and a host of novel biosimilars are among the drugs under evaluation. Because of apparent safety concerns, the Food and Drug Administration (FDA) rejected baracitinib approval. The two biosimilar medications now approved are CT-P13 and SB2, both of which are based on the reference product infliximab [20]. In recent years, the use of biotechnology drugs has dramatically altered the treatment strategy and course of rheumatoid arthritis. Interleukin-6 (IL-6) has been identified as a key cytokine in the disease's pathogenesis, playing a role in the disruption of both the innate and adaptive immune systems, as well as the production of acute-phase proteins that are vital in the disease's systemic presentation. The first IL-6 blocker to hit the market was tocilizumab, a humanised anti-IL-6 receptor (anti-IL-6R) monoclonal antibody. Tocilizumab's efficacy in Rheumatoid arthritis has led the development of a number of biologic medications that target the IL-6 pathway, either by targeting the IL-6 cytokine (sirukumab, olokizumab, and clazakizumab) or the IL-6 receptor (sirukumab, olokizumab, and clazakizumab) (sarilumab). In one Phase II and six

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Phase III randomised controlled studies, sarilumabdemonstrated broad efficacy across all Rheumatoid arthritis patient categories, from methotrexate (MTX) deficient responders to tumour necrosis factor inhibitor insufficient responders. Sarilumab as monotherapy outperformed adalimumab in MTX-intolerant patients. Furthermore, sarilumab exhibited a comparable safety profile to tocilizumab, but with a much higher affinity and longer half-life, leading to a reduction in the frequency of administration (every other week instead of weekly). All of these characteristics could influence how sarilumab is used in the treatment of Rheumatoid arthritis. Indeed, observational data from post-marketing real-world studies could provide crucial new information for a better understanding of sarilumab's role in illness treatment. This paper summarises the biological significance of IL-6 in Rheumatoid arthritis, as well as the clinical evidence for sarilumab as a second-line treatment for Rheumatoid arthritis patients [21]

VIII. CONCLUSION

Methotrexate is one of the most promising disease-modifying anti-rheumatic medicines currently available (DMARDS). The poor pharmacokinetics and tight safety margin of MTX limit its use. For the treatment of early and established rheumatoid arthritis, MTX is the most extensively used drug (DMARDS). MTX changes metabolic reactions by inhibiting dihydrofolate reductase with high affinity, resulting in purine and thymidylate syntheses inhibition. In rheumatoid arthritis, MTX acts as an antiproliferative and anti-inflammatory drug against the cells that cause joint inflammation.

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