American Journal of Medicine and Medical Sciences 2023, 13(9): 1232-1237
DOI: 10.5923/j.ajmms.20231309.12

# Modern Treatment Approaches in Rheumatoid Arthritis: Review of Literature

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**Abstract** Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by joint inflammation leading to pain, stiffness and swelling. It affects approximately 1% of the world's population and has a significant impact on patients' lives, causing functional limitations and reducing their overall quality of life. Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects millions of people worldwide. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a widely prescribed class of medications used to treat a variety of inflammatory conditions, including rheumatoid arthritis (RA). Access to innovative therapies, cost considerations, and the potential for drug-related side effects are barriers that need to be addressed. Ongoing research efforts and collaboration between clinicians, researchers and pharmaceutical companies are necessary to further improve treatment strategies and optimise patient care. At the moment, combination therapy remains the most optimal treatment option as other methods need to be developed. However, with continued progress in understanding the underlying mechanisms of the disease and the development of innovative treatment approaches, the future holds great promise for improving outcomes and quality of life for people living with RA.

**Keywords** RA, Rheumatoid arthritis, Treatment, Traditional, DMARDs, JAS, NSAIDs, Glucocorticosteroids, TNF-a inhibitor

## 1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by joint inflammation leading to pain, stiffness and swelling. It affects approximately 1% of the world's population and has a significant impact on patients' lives, causing functional limitations and reducing their overall quality of life [1]. RA, characterised by inflammation of the synovial membrane of several joints, leads to progressive joint damage, reducing quality of life. By delving into the efficacy, safety profiles, and long-term outcomes of each treatment option, healthcare providers can gain a comprehensive understanding of the changing landscape of RA treatment. This knowledge can then be used to provide individualised patient care that optimises outcomes and improves quality of life. Although there is currently no cure for RA, there are several treatment options that can help manage symptoms and prevent joint damage. There are many variations of RA symptom management available today. This research paper will review traditional RA treatment options including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs). Moreover, advances in RA treatment due to the emergence of biologic DMARDs such as tumour necrosis factor (TNF) inhibitors, as well as new targeted therapies such as Janus kinase (JAK) inhibitors and targeted synthetic DMARDs will be discussed. All these therapies offer hope for improved outcomes, but careful consideration of their mechanisms, safety profiles and long-term effects is needed. This provides an opportunity to develop individualised treatment plans tailored to the specific needs of each patient.

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Received: Sep. 5, 2023; Accepted: Sep. 21, 2023; Published: Sep. 22, 2023
Published online at http://journal.sapub.org/ajmms

## 2. Traditional Therapies

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects millions of people worldwide [2]. It is characterised by inflammation of several joints, resulting in pain, swelling and stiffness. Although there is currently no cure for RA, traditional therapies play a key role in managing symptoms, slowing disease progression and improving the overall quality of life for people living with the disease.

### 2.1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a widely prescribed class of medications used to treat a variety of inflammatory conditions, including rheumatoid arthritis

(RA). RA is a chronic autoimmune disease characterised by joint inflammation, pain and functional impairment. NSAIDs play a crucial role in treating these symptoms and improving the quality of life of patients with RA [3]. The mechanism of action of NSAIDs involves the inhibition of cyclooxygenase (COX) enzymes, particularly COX-1 and COX-2, which are responsible for the production of prostaglandins, substances that contribute to inflammation and pain. By inhibiting these enzymes, NSAIDs reduce the production of inflammatory mediators, thereby relieving pain and reducing joint swelling in patients with RA [4]. This mechanism helps to restore joint function and improve overall health. Several types of NSAIDs are available for the treatment of RA. These include traditional non-selective NSAIDs such as ibuprofen and naproxen, and the newer selective COX-2 inhibitors such as celecoxib [5].

The choice and efficacy of NSAIDs may vary from person to person depending on factors such as disease severity, patient response, and concurrent use of other RA medications. Since NSAIDs are commonly used as first-line agents for symptom relief in various inflammatory conditions, many clinical trials have been conducted. In clinical trials, they have been compared to placebo, aspirin, and other medications. NSAIDs demonstrate superior efficacy for 1-2 weeks in patients with active RA without corticosteroids or other anti-inflammatory drugs [6]. In addition, it has been shown that the use of combination therapy with serratiopeptidase, bromelain, and methylsulfonylmethane may be an effective strategy to improve outcomes in inflammatory joint disease [6]. Although NSAIDs provide significant symptom relief, they are associated with potential side effects, especially with prolonged use or high doses. Gastrointestinal complications, including gastric ulcers, bleeding, and perforations, are the most common adverse events associated with taking NSAIDs. Other risks include cardiovascular complications such as increased risk of heart attack and stroke, especially with selective COX-2 inhibitors. Renal toxicity is another concern that requires caution in patients with pre-existing kidney disease or those taking certain medications such as diuretics. Clinicians should carefully assess individual patient profiles and consider risk factors when prescribing NSAIDs, ensuring appropriate dosage and duration of therapy [3]. In conclusion, NSAIDs play a crucial role in the treatment of rheumatoid arthritis by reducing inflammation and relieving pain. They are effective in improving joint function and overall quality of life in patients with RA. However, their prolonged use or administration of high doses can lead to side effects such as gastrointestinal complications and cardiovascular risks. Strategies to improve safety and efficacy include the use of selective COX-2 inhibitors, co-administration of gastroprotectants, and consideration of combination therapy with other drugs such as DMARDs. Healthcare professionals should carefully weigh the benefits and potential risks of prescribing NSAIDs to patients with RA and provide adequate monitoring and patient education to minimise side effects.

### 2.2. Corticosteroids

It has now been approximately 75 years since Hench's study provided evidence for the use of corticosteroids in the treatment of rheumatoid arthritis [7] for this reason it can be argued that corticosteroids have long been the therapeutic armoury in RA because of their potent anti-inflammatory and immunosuppressive properties. Corticosteroids exert anti-inflammatory and immunosuppressive effects through different mechanisms. They inhibit the production of pro-inflammatory cytokines such as interleukins and tumour necrosis factor-alpha (TNF-α), and suppress the migration and activation of immune cells involved in the inflammatory response. In addition, corticosteroids suppress the immune system by reducing T- and B-lymphocyte activity, further attenuating the autoimmune response in RA [8]. There have been many studies on the efficacy of corticosteroids in the use of RA. Short-term and long-term perspectives of corticosteroid prescribing have been investigated. In the short term, corticosteroids have shown remarkable efficacy in treating RA symptoms. A study by Sigurgeirsson et al. involving paediatric patients with juvenile idiopathic arthritis (JIA) with systemic onset showed that intravenous administration of high-dose methylprednisolone resulted in rapid improvement of clinical symptoms within 24-48 hours [9].

The fast-acting nature of corticosteroids makes them particularly valuable in exacerbations or exacerbations of RA. On the other hand, even though corticosteroids provide immediate relief of pain and inflammation, their long-term efficacy in the treatment of RA remains a matter of debate. Some studies suggest that long-term use of corticosteroids may slow disease progression and improve patient outcomes. Children with Duchenne muscular dystrophy who received chronic corticosteroid treatment were also found to have reduced muscle inflammation and lower levels of biomarkers associated with disease severity [10]. However, when taking a long-term view of corticosteroid use, side effects should not be overlooked. Prolonged use of corticosteroids may be associated with more serious effects including osteoporosis, aseptic joint necrosis, adrenal insufficiency, gastrointestinal, hepatic and ophthalmological effects, hyperlipidaemia, growth retardation and possible congenital malformations [10,11]. To reduce the side effects of corticosteroids, low doses and short-term use of corticosteroids should be preferred to minimise the risk of side effects. Intra-articular injections can provide targeted relief to specific joints while minimising systemic effects. In addition, treatment plans should include strategies to prevent and manage corticosteroid-related side effects, such as taking calcium and vitamin D supplements and monitoring bone density [11]. As new therapies such as targeted synthetic DMARDs and biologics become increasingly important in the treatment of RA, the role of corticosteroids may continue to evolve. Future research should focus on identifying prognostic markers of response to corticosteroids, exploring new delivery methods to minimise systemic side effects and investigating optimal combination therapy with corticosteroids to achieve

improved disease control and minimise corticosteroid-related side effects [12]. In conclusion, corticosteroids are a valuable treatment option for rheumatoid arthritis because of their potent anti-inflammatory action. They provide short-term efficacy in providing rapid relief of pain and inflammation during acute exacerbations. Although long-term efficacy remains controversial, corticosteroids can slow disease progression when used judiciously alongside other treatments. However, the potential side effects associated with long-term use require careful monitoring and consideration of alternative or complementary therapies in some cases. Overall, corticosteroids play an important role in the comprehensive treatment of rheumatoid arthritis, but they should be used with caution and the risk-benefit ratio should be regularly assessed.

### 2.3. Baseline Anti-Inflammatory Drugs (BIDs) for RA

Baseline anti-inflammatory drugs (BIDs) for RA have revolutionised the treatment of RA by suppressing inflammation, protecting joint integrity and improving patient outcomes. DMARDs encompass a heterogeneous group of drugs that aim to alter the course of RA by suppressing inflammation, preventing structural damage, and preserving joint function [13]. The most common PDMPs are Methotrexate Leflunomide and Sulfasalazine. Methotrexate is the gold standard treatment for rheumatoid arthritis due to its efficacy and safety [13,14].

It inhibits purine synthesis and modulates immune cell function, making it a major drug in the treatment of RA. It reduces disease activity, improves physical function and slows radiological progression. Methotrexate is effective in the short-term treatment of rheumatoid arthritis, reducing pain, improving function and reducing joint damage as seen on radiographs. However, monitoring of potential hepatotoxicity and haematological side effects is required [14]. On the other hand, studies show that the use of two DMARDs as therapy can show significantly good results. For example, the combination of Methotrexate and Sulfasalazine has shown significant success in the treatment of RA. Combination therapy with Methotrexate, helps to reduce disease activity and prevent joint damage [15]. Also, leflunomide, a widely used BMP, effectively reduces disease activity in patients with rheumatoid arthritis by inhibiting pyrimidine synthesis, reducing the proliferation of immune cells involved in joint inflammation [16].

However, it may cause hepatotoxicity, gastrointestinal symptoms and teratogenicity, potentially leading to side effects [17]. In conclusion, synthetic DMARDs are effective in the treatment of rheumatoid arthritis, but their response rates may vary, resulting in incomplete remission or inadequate symptom control. Common side effects include gastrointestinal symptoms, hepatotoxicity, haematological abnormalities and cutaneous and mucosal reactions. Prolonged use may lead to interstitial lung disease and suppression of bone marrow function, while less common but potentially serious side effects include nausea, diarrhoea, hepatotoxicity, anaemia, leucopenia and rash. Careful monitoring and management of these potential side effects is essential for effective treatment.

In addition to synthetic PAPs, there are also biological types that have fewer side effects. One such is Abatacept. Abatacept selectively binds to the costimulatory molecule CD80/86 on antigen-presenting cells, thereby inhibiting T-cell activation. This leads to a decrease in T-cell activation and a subsequent decrease in the production of pro-inflammatory cytokines, ultimately leading to a reduction in joint inflammation and symptoms [18]. Data from clinical trials have shown that abatacept is effective in reducing disease activity and improving physical function in patients with RA, both as monotherapy and in combination with other DMARDs such as methotrexate. It has been shown to slow the progression of joint damage, leading to improved long-term outcomes. It has also demonstrated efficacy in patients who have not responded to other DMARDs or biologic agents [19]. Since abatacept has minimal side effects it is a promising option in the future for the treatment of RA. In addition, another biologic PDMP that has minimal side effects is Rituximab. Rituximab acts by binding CD20 antigen on B-cells, which leads to their depletion through antibody-dependent cytotoxicity, complement-mediated cytotoxicity and apoptosis. This results in reduced autoantibody production, modulation of the immune response and reduction of joint inflammation. Rituximab, a drug being used in clinical trials, has been shown to reduce disease activity and improve physical function in patients with RA who have responded poorly to traditional DMARDs or TNF inhibitors, and to slow the progression of joint damage, leading to improved long-term outcomes [20].

It should also be considered that tocilizumab, a drug that binds to the IL-6 receptor, reduces inflammation in patients with RA by inhibiting pro-inflammatory pathways. In clinical trials it showed minimal side effects and was also found to be effective in treating RA [21]. Also in the management of RA, TNF inhibitors such as Infliximab, Etanercept and Adalimumab are important therapies that target TNF-α, a pro-inflammatory cytokine, to reduce inflammation in joints [22]. Infliximab, a chimeric monoclonal antibody, has been widely studied in clinical trials and has demonstrated significant efficacy in reducing disease activity, improving joint function and relieving symptoms in patients with RA. However, it is also associated with safety concerns such as infusion reactions, infections, increased risk of malignancy, hepatotoxicity and haematological disorders [23]. Etanercept, another TNF inhibitor, has demonstrated significant efficacy in treating RA symptoms but may increase the risk of serious infections, injection site reactions, and autoimmune disorders [23,24]. Adalimumab, another TNF inhibitor, has become one of the most widely prescribed TNF inhibitors for the treatment of RA, but it has the same risks as other TNF inhibitors, including increased susceptibility to infections and injection site infusion reactions [24]. In conclusion, TNF inhibitors have revolutionised the treatment of patients with rheumatoid arthritis, but each drug has its own safety issues that need to

be carefully considered in clinical practice.

Summarising all these data, there are many variations of PAPs. However, the selection and use of PAPs should be tailored to individual patients, taking into account factors such as disease severity, comorbidities, safety profiles and preferences. Using an integrated approach that combines effective use, regular monitoring and preventive management of side effects, clinicians can optimise the benefits of PAP therapy for RA, providing long-term control and improved quality of life for people living with this chronic autoimmune disease.

## 3. Current Treatments Methods for RA

Jasus kinase inhibitors: Janus kinase inhibitors (JAK inhibitors) have emerged as a new class of drugs for the treatment of rheumatoid arthritis (RA). These drugs, including tofacitinib, baricitinib, and upadacitinib, have shown efficacy in reducing disease activity and improving patient outcomes [25]. JAK inhibitors are small-molecule drugs that selectively inhibit Janus kinase enzymes within cells. They act by modulating cytokine signalling pathways involved in RA pathogenesis [26]. Tofacitinib was the first JAK inhibitor approved for the treatment of RA in 2012. It is administered orally and inhibits several Janus kinases (JAK1/JAK3) [27]. The mechanism of action of JAK inhibitors involves blocking intracellular signalling cascades mediated by cytokines such as interleukin-6 (IL-6), IL-12/23p40, interferon gamma (IFNγ) and others. Inhibition of downstream signalling pathways of these cytokine receptors through inhibition or modulation of Janus kinases leads to a reduction in cell proliferation and production of inflammatory mediators, resulting in a reduction in joint inflammation observed clinically through improvement in symptoms and radiographic findings [27]. Clinical trials have demonstrated the efficacy of JAK inhibitors in reducing disease activity in patients with RA. For example, a study by Schippers and Jones (2022) compared the drug resistance of JAK inhibitors and biologic DMARDs in Australian patients with RA. The results showed that tofacitinib had higher rates of treatment resistance compared to biologic DMARDs over two years. This indicates its efficacy and tolerability as a long-term treatment option for RA [28]. Although JAK inhibitors have therapeutic advantages, it is important to consider their safety profile. Side effects commonly associated with these drugs include infections, gastrointestinal disorders, laboratory abnormalities such as anaemia or liver function abnormalities, hypertension, lipid elevation and skin reactions [29]. There are also serious concerns about the risk of venous thromboembolism associated with the use of JAK inhibitors [29]. Since the full information about JAK inhibitors is still unknown to science, scientists are still conducting studies. The studies investigate new uses or formulations of JAK inhibitors and identify biomarkers that predict response or resistance to therapy. For example, researchers are exploring combination therapies that include JAK inhibitors with other targeting agents or conventional synthetic DMARDs to optimise treatment outcomes [27].

However, some side effects are already known. The safety profile of JAK inhibitors is characterised by an increased risk of infections, especially upper respiratory tract infections and serious bacterial infections [30]. Other common side effects include anaemia, neutropenia, thrombocytopenia, elevated liver enzymes and lipid metabolism abnormalities. In conclusion, JAK inhibitors are a new class of targeted therapy for RA that inhibit JAK enzymes, reducing inflammation and alleviating disease symptoms. They have demonstrated efficacy both as monotherapy and in combination with other JAK inhibitors. Despite their efficacy, careful patient selection and monitoring is necessary due to potential side effects, especially increased risk of infections.

Combination therapy in RA: Combination therapy aims to target multiple pathways involved in the inflammatory process of RA, thereby improving disease control and alleviating symptoms. By utilising different mechanisms of action, a combination of DMARDs can provide synergistic effects and potentially improve treatment outcomes compared to monotherapy. Combination therapy also allows for lower doses of individual drugs, potentially reducing the risk of side effects. A randomised trial aimed to evaluate the efficacy of combination therapy with HDBPs in patients with active RA. Patients were divided into three groups: single BVAP, methotrexate + sulfasalazine or methotrexate + hydroxychloroquine and a combination of all three drugs. Regular follow-up examinations and radiological evaluations were performed to assess specific rheumatic activity. At the end of the study, there were significant improvements in clinical and laboratory parameters in all 3 groups. However, the improvements were greater and more significant in patients receiving combination therapy. The combination of MTX + SSZ + HCQ was more effective than monotherapy and combinations of the two drugs [31]. Other clinical evidence suggests that combination therapy with BVAPs and NSAIDs results in better outcomes than monotherapy. NSAIDs provide rapid pain relief, reduced inflammation, and improved quality of life in patients with RA. On the other hand, NSAIDs slow the progression of joint damage and control the underlying autoimmune response. The combination of these two therapeutic strategies has been shown to effectively reduce disease activity, improve physical function and alleviate RA symptoms [32]. Since many drugs are currently under development or investigation at this time, combination therapy is the optimal option for managing RA.

## 4. Non-Pharmaceutical Treatment of RA

Physical therapy is a medical speciality that uses physical methods such as exercise, massage, electrotherapy, etc. to treat various conditions and diseases. In case of RA, physical therapy plays an important role in managing pain symptoms,

improving motor function and preventing joint deterioration. Exercise plays an important role in the treatment of RA as it helps to strengthen muscles, improve flexibility and maintain joint health. Regular exercise helps improve blood circulation, reduce inflammation and improve the overall health of patients with RA. Exercise also helps control weight, which is especially important for patients with RA, as being overweight can put extra pressure on joints. Physiotherapy and exercise offer several benefits for patients with RA. They can help reduce joint pain and inflammation, improve muscle strength and flexibility, and improve overall physical activity and quality of life. Physiotherapy can also help patients manage the depression and anxiety that often accompany RA. In addition, physiotherapy can be effective in improving function and self-management in patients with RA. Exercise recommendations for patients with RA can vary depending on the severity of the disease and the patient's physical condition. However, some general recommendations include moderate exercise such as walking, swimming, cycling, and gymnastics. Regular exercise can be beneficial for keeping joints moving, strengthening muscles, and improving overall health. Many studies support the effectiveness of physiotherapy and exercise in treating RA. Some studies show that physiotherapy can reduce joint pain and inflammation, and improve physical function and quality of life in patients with RA [33].

Other studies confirm that moderate exercise can improve flexibility, strength and aerobic endurance in patients with RA [33,34]. Physical therapy and exercise play an important role in the treatment of rheumatoid arthritis, providing patients with effective tools to cope with pain symptoms and improve joint function. However, despite the advances already made, there is a need for further research and development of physical therapy and exercise for RA. Future directions include the development of innovative physiotherapy techniques, improved accessibility and integration of physical therapy into standard RA treatment practice.

## 5. Conclusions

In conclusion, the treatment of rheumatoid arthritis (RA) has made significant progress in recent years. One of the key areas of progress in the treatment of RA is the use of biologic therapies such as TNF inhibitors, monoclonal antibodies and Janus kinase (JAK) inhibitors. These agents have demonstrated efficacy in reducing disease activity, improving clinical outcomes and preventing joint damage. Moreover, the development of biosimilars has expanded treatment options and increased their availability to patients. In addition, targeted therapies have emerged as a promising strategy for the treatment of RA. Low molecular weight inhibitors such as the phosphodiesterase-4 (PDE-4) inhibitor apremilast and the spleen tyrosine kinase (SYK) inhibitor fostamatinib have shown efficacy in reducing disease activity and improving physical function. These targeted therapies offer an alternative for patients who may have contraindications to or fail to respond to traditional treatment options. Moreover, advances in immunotherapy techniques have shown promising efficacy in the treatment of RA. Tolerogenic dendritic cells, mesenchymal stem cells, and regulatory T cells have demonstrated potential in modulating the immune system and inducing immune tolerance, thereby potentially preventing disease progression and achieving long-term remission. However, despite significant advances in the treatment of RA, challenges remain. Access to innovative therapies, cost considerations, and the potential for drug-related side effects are barriers that need to be addressed. Ongoing research efforts and collaboration between clinicians, researchers and pharmaceutical companies are necessary to further improve treatment strategies and optimise patient care. At the moment, combination therapy remains the most optimal treatment option as other methods need to be developed. However, with continued progress in understanding the underlying mechanisms of the disease and the development of innovative treatment approaches, the future holds great promise for improving outcomes and quality of life for people living with RA.

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