Orthopedics and Rheumatology
Open Access Journal
ISSN: 2471-6804

Review Article
Volume 22 issue 3 - November 2023
DOI: 10.19080/OROAJ.2023.22.556088

Ortho & Rheum Open Access J


# Use of Janus Kinase (JAK) Inhibitors in the Treatment of Rheumatoid Arthritis: A Review of Efficacy and Safety Compared to Conventional Therapies

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**Submission:** October 21, 2023; **Published:** November 02, 2023

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## Abstract

Rheumatoid Arthritis (RA) is a complex autoimmune disorder characterized by chronic synovial inflammation, leading to progressive joint deterioration and substantial morbidity. While conventional disease-modifying antirheumatic drugs (DMARDs) have been the cornerstone of RA management, the emergence of Janus Kinase (JAK) inhibitors has revolutionized the treatment paradigm. This comprehensive review paper analyzes the efficacy, safety, and practical considerations associated with JAK inhibitors in managing RA juxtaposed with conventional therapies. Through an exploration of the mechanism of action, the efficacy of JAK inhibitors in ameliorating disease activity and improving patient outcomes is underscored. The review also addresses the safety concerns surrounding using JAK inhibitors, emphasizing the need to monitor potential adverse events. Furthermore, the paper discusses the role of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and DMARDs in RA management, highlighting their limitations and benefits. Practical clinical recommendations for using JAK inhibitors are elucidated, considering their positioning as a second-line therapy for patients with inadequate response or intolerance to conventional DMARDs. Finally, the abstract emphasizes the importance of ongoing research and post-marketing surveillance to comprehensively evaluate the long-term implications of JAK inhibitors, aiming to optimize their integration within personalized treatment strategies for RA.

**Keywords:** Rheumatoid Arthritis (RA); Janus Kinase (JAK) inhibitors; Disease-modifying antirheumatic drugs (DMARDs); Nonsteroidal anti-inflammatory drugs (NSAIDs); Corticosteroids

**Abbreviations:** RA: Rheumatoid Arthritis; JAK: Janus Kinase; DMARDs: Disease-Modifying Antirheumatic Drugs; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; COX: Cyclooxygenase; IL-6: Interleukin-6; TNF: Tumor Necrosis Factor; ACR: American College of Rheumatology; FDA: Food and Drug Administration; HPA: Hypothalamic-Pituitary-Adrenal; TB: Tuberculosis; HIV: Human Immunodeficiency Virus; CBC: Complete Blood Count; HCV: Hepatitis C Virus; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus

## Introduction

Rheumatoid Arthritis (RA) is a multifaceted autoimmune disorder characterized by persistent synovial inflammation, which leads to progressive joint destruction, systemic complications, and diminished quality of life for millions of affected individuals worldwide [1]. Traditionally, the management of RA has heavily relied on the use of conventional disease-modifying

antirheumatic drugs (cDMARDs) to suppress the inflammatory cascade and prevent irreversible joint damage [2]. Despite the advancements in cDMARD therapy, many patients continue to experience disease progression and significant morbidity [3]. In this context, the introduction of Janus Kinase (JAK) inhibitors has signified a revolutionary stride in the therapeutic landscape of RA. By selectively targeting JAK enzymes involved in mediating cytokine signaling pathways integral to the pathogenesis of RA, these inhibitors offer a tailored approach to modulate the immune response and ameliorate the underlying inflammatory processes [2,4].

Consequently, the emergence of JAK inhibitors has sparked considerable interest and discourse within the medical community, fostering a paradigm shift in managing this incapacitating ailment [3-5]. This comprehensive review paper aims to delve into the intricate efficacy and safety profiles of JAK inhibitors, juxtaposing their outcomes with conventional therapies. With the dynamic nature of RA therapeutics, an updated and holistic evaluation of these novel agents is imperative in delineating their pivotal role within the armamentarium of treatment options. Thus, this review endeavors to navigate the evolving landscape of RA therapy, providing critical insights into the transformative impact of JAK inhibitors on patient outcomes and addressing the therapeutic challenges that persist in RA management.

## Mechanism of action of JAK Inhibitors

Janus Kinase (JAK) inhibitors selectively target members of the JAK family, which are crucial intracellular enzymes involved in signaling various pro-inflammatory cytokines and growth factors. Upon binding cytokines such as interleukins and interferons to their respective receptors, JAKs are activated, leading to the phosphorylation of signal transducers and activators of transcription (STATs). Phosphorylated STATs then translocate to the nucleus, where they regulate the transcription of genes involved in inflammation, immune response, and cell proliferation [6]. By inhibiting JAK activity, JAK inhibitors disrupt this signaling cascade, thereby modulating the immune response and dampening the production of pro-inflammatory mediators implicated in the pathogenesis of rheumatoid arthritis [7]. This targeted approach effectively attenuates the aberrant immune activation and reduces the inflammatory burden within the affected joints, consequently alleviating symptoms and impeding disease progression in patients with RA.

## Efficacy of JAK Inhibitors

JAK inhibitors have shown significant efficacy in managing rheumatoid arthritis, reducing disease activity, alleviating symptoms, and inhibiting structural damage progression. Studies have indicated that JAK inhibitors, used as monotherapy or combined with conventional DMARDs, lead to notable improvements in joint tenderness, swelling, and pain, along with enhanced physical function and quality of life for RA patients. The rapid onset of action associated with JAK inhibitors is particularly beneficial for patients with aggressive disease, providing early symptom relief and preventing irreversible joint damage [8]. The JAK family, comprising JAK1, JAK2, JAK3, and TYK2, plays a crucial role in the JAK-STAT pathway, governing the transcriptional regulation of genes involved in inflammatory, immunological, and oncogenic processes relevant to RA. Various JAK inhibitors, including tofacitinib, baricitinib, and upadacitinib, have been approved by the FDA and subjected to comprehensive clinical trials, demonstrating their efficacy and satisfactory safety profiles in treating RA. Notably, exploratory studies on filgotinib, tofacitinib, and baricitinib have shown substantial efficacy in achieving the American College of Rheumatology (ACR) response criteria, with statistically significant results in disease remission and reduction in radiographic progression. Moreover, clinical trials with tofacitinib, baricitinib, and upadacitinib in patients with RA have demonstrated clinically and statistically significant ACR responses, further supporting the efficacy of JAK inhibitors in managing RA [8,25-28].

## Safety and Side Effects of JAK Inhibitors

Janus Kinase inhibitors in treating RA have recently gained significant attention. JAK inhibitors, such as tofacitinib and baricitinib, have effectively controlled RA symptoms by targeting the inflammatory pathways mediated by cytokines like interleukin-6 and interferon-gamma [9]. Clinical trial studies have shown that JAK inhibitors can rapidly relieve pain and joint inflammation in RA patients, often achieving clinical remission [10]. However, safety concerns have emerged regarding the use of these drugs. Common side effects of JAK inhibitors include an increased risk of infections, cytopenias, thrombosis, gastrointestinal complications, elevations in liver enzymes, and malignancies [9]. Long-term studies are still needed to better understand their safety profile over extended treatment periods [10-13]. According to, the clinical outcomes and the risk of concomitant therapy of Herpes Zoster and Tofacitinib must be taken seriously [13]. Comparatively, conventional therapies for RA, such as disease-modifying antirheumatic drugs (DMARDs) and nonsteroidal anti-inflammatory drugs (NSAIDs), have been used for decades, as opined by [11]. While these treatments can effectively alleviate symptoms and slow disease progression, they may not be as potent as JAK inhibitors in providing rapid and sustained relief. Moreover, conventional therapies are associated with side effects, including gastrointestinal issues, liver toxicity, and immunosuppression. In conclusion, JAK inhibitors represent a promising addition to the armamentarium of RA treatments, offering a potentially more practical option for managing the disease's symptoms. However, their safety profile should be carefully monitored, especially in long-term use, and weighed against conventional therapies' known risks and benefits [12].



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## NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) significantly manage Rheumatoid Arthritis (RA) by providing symptomatic relief from pain and inflammation. Both Naproxen and Ibuprofen, commonly prescribed NSAIDs, are known to effectively alleviate joint pain, stiffness, and swelling associated with RA, thereby improving patients' overall quality of life. These medications exert their therapeutic effects by inhibiting the cyclooxygenase (COX) enzymes, particularly COX-2, responsible for synthesizing pro-inflammatory prostaglandins. By modulating the production of these inflammatory mediators, NSAIDs mitigate the localized inflammatory response within the joints, consequently reducing pain and improving joint function in RA patients. However, it is essential to note that while NSAIDs provide symptomatic relief, they do not alter the long-term progression of the disease or prevent joint damage. Additionally, their use is often associated with adverse effects, such as gastrointestinal complications and cardiovascular risks, necessitating careful consideration when prescribing these agents for RA management [14].

## Corticosteroids

This kind of medicament diffuses passively across the cellular membrane and binds to the intracellular receptor. This binding creates a complex, which then translocates into the nucleus, exerting effect by interacting directly with specific DNA sequences and other transcription factors [15]. Corticosteroids are potent medications. For this reason, they are only indicated for a short period at low doses, during exacerbations or flares. Intra-articular injections of corticosteroids can be used for local symptoms of inflammation. The side effects include bone thinning, weight gain, diabetes, and immunosuppression. It is critical not to suspend injected or oral corticosteroids abruptly because this leads to suppression of the hypothalamic-pituitary-adrenal axis (HPA) or flares of rheumatoid arthritis [16]. Low-dose corticosteroids (less than or equal to 10 mg/d of prednisone or equivalent) are used increasingly to manage rheumatoid arthritis. They are frequently substituted for nonsteroidal anti-inflammatory drugs (NSAIDs), particularly in patients with gastrointestinal or other intolerance to NSAIDs, or as "bridge therapy". At the same time, patients await the benefits of delayed-acting, disease-modifying agents. Despite their clinical acceptance, published data concerning efficacy are meager. This dosage has not proven fetal wastage, prematurity, or congenital malformations [17].

## Disease-Modifying Antirheumatic Drugs (DMARDs) in the Management of Rheumatoid Arthritis

Disease-modifying antirheumatic Drugs (DMARDs) represent the cornerstone of pharmacological treatment for Rheumatoid Arthritis (RA). These agents aim to suppress inflammation, slow disease progression, and preserve joint function, thereby improving patient outcomes. Conventional DMARDs, such as methotrexate, sulfasalazine, and hydroxychloroquine, have been extensively used as first-line therapies in early RA owing to their disease-modifying properties and favorable safety profiles [18]. These medications work by modulating the immune response and dampening the inflammatory processes associated with RA pathogenesis, ultimately leading to reduced joint destruction and improved functional status. Additionally, the advent of biologic DMARDs, including tumor necrosis factor (TNF) inhibitors, interleukin-6 (IL-6) inhibitors, and B-cell depleting agents, has revolutionized the management of RA by providing targeted therapy for patients with refractory disease [19]. These biologics specifically target vital components of the immune system, thereby mitigating the underlying inflammatory pathways responsible for joint damage and systemic complications in RA. The use of conventional and biologic DMARDs has significantly transformed the therapeutic landscape of RA, offering patients a comprehensive approach to disease control and improved quality of life.

## Practical Considerations and Clinical Recommendations about JAK Inhibitors uses

The usage of JAK inhibitors like tofacitinib, upadacitinib, and baricitinib is an excellent alternative to methotrexate, DMARD, in treating rheumatoid arthritis due to their anti-inflammatory properties [20,21]. The American College of Rheumatology (ACR) has placed these as 2nd line treatments in specific scenarios [22]. Because of severe side effects, they are carefully monitored and selectively given to individuals who meet specific criteria, beginning with patients whose disease severity and failed treatments have led the healthcare professional and patient to seek alternative, more effective care.

JAK inhibitors are FDA-approved as a treatment of RA and intended for patients who exhibit moderate to severe active symptoms, inadequate/poor response, or intolerance to traditionally used DMARDs such as methotrexate [21]. Before beginning treatment with these, all patients must get screened for infections such as TB, HIV, and Hepatitis B and C, and blood tests such as CBC with differential, hepatic and kidney function panel, and baseline lipid panel [23]. Lastly, these should be used with caution and carefully monitored if any pre-existing cardiovascular risk factors and/or history of cancer/malignancies due to their increased risk of incidence while taking JAK inhibitors [24].

## Conclusion

The management of Rheumatoid Arthritis (RA) has witnessed substantial advancements with the advent of Janus Kinase (JAK) inhibitors, which represent a groundbreaking addition to the therapeutic armamentarium. Their targeted mechanism of action


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demonstrated efficacy in ameliorating disease activity, and rapid symptom relief has reshaped the landscape of RA treatment. Nevertheless, the safety profile of JAK inhibitors warrants meticulous monitoring, given the associated risks of infections, cytopenias, thrombosis, and gastrointestinal complications. Comparatively, the long-standing use of conventional therapies, such as Disease-Modifying Antirheumatic Drugs (DMARDs), Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), and corticosteroids, continues to be integral in managing RA, albeit with their own set of limitations and side effects. The judicious use of JAK inhibitors, guided by patient-specific factors and stringent monitoring protocols, presents a promising avenue for enhancing treatment outcomes and improving the quality of life for RA patients. However, it is imperative to consider the long-term implications and weigh the benefits against potential risks, especially in patients with pre-existing cardiovascular risks or a history of malignancies. Furthermore, the evolution of clinical guidelines and the incorporation of JAK inhibitors as a second-line therapy, particularly in cases of inadequate response or intolerance to conventional DMARDs, underline their growing significance in managing RA. Looking ahead, ongoing research endeavors and comprehensive post-marketing surveillance are crucial to elucidate the long-term safety and efficacy profiles of JAK inhibitors, ensuring their optimal utilization within the context of personalized medicine. By understanding the evolving landscape of RA treatment options, informed decisions can be made, and therapeutic strategies can be tailored to optimize patient outcomes, thus addressing the persistent challenges associated with treating this disease.

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