

REVIEW ARTICLE

JAK Inhibitors for Rheumatoid Arthritis: Assessing Efficacy and Safety in Treatment

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Abstract: Rheumatoid Arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation, progressive joint destruction, and systemic complications. Dysregulated cytokine signaling through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway plays a central role in RA pathogenesis, making JAK inhibitors an important therapeutic option. Tofacitinib, baricitinib, and upadacitinib are oral targeted synthetic disease-modifying antirheumatic drugs that interfere with cytokine signaling and reduce inflammatory activity. In randomized trials, these agents achieved American College of Rheumatology 20% improvement (ACR20) responses in approximately 60–75% of patients and demonstrated efficacy comparable to, and in some studies exceeding, that of adalimumab. Their oral administration and rapid onset of action represent practical advantages, particularly in patients with inadequate responses to conventional synthetic or biologic DMARDs. However, treatment is associated with important safety concerns, including serious infections, herpes zoster, venous thromboembolism, major adverse cardiovascular events, and malignancy. A personalized risk-benefit assessment and ongoing monitoring remain essential to optimize outcomes and ensure long-term safety.

Keywords: Rheumatoid Arthritis, JAK, Autoimmunity, Immune Health, Lipid Metabolism, Therapeutic Strategies

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Introduction

Rheumatoid Arthritis (RA) is a chronic systemic autoimmune disorder characterized by persistent synovial inflammation, progressive cartilage and bone destruction, and substantial impairment in physical function and quality of life. Its pathogenesis reflects a complex interaction among genetic susceptibility, environmental exposures, and dysregulated innate and adaptive immune responses. Central to this process is the production of pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin (IL)-1, and IL-6, which perpetuate synovitis and structural joint damage [1-4].

Methotrexate remains the anchor conventional synthetic disease-modifying antirheumatic drug (csDMARD) [5], while biologic DMARDs targeting TNF- α , IL-6, CD20, and T-cell co-stimulation have transformed outcomes in patients with insufficient response to csDMARDs. Nevertheless, a substantial proportion of patients fail to achieve sustained remission or lose response over time, highlighting the need for additional therapeutic strategies [6, 7].

Janus Kinase (JAK) inhibitors are targeted synthetic DMARDs that block intracellular signaling downstream of multiple cytokine receptors. By inhibiting JAK1, JAK2, JAK3, and/or TYK2, these agents attenuate activation of Signal Transducer and Activator of Transcription (STAT) proteins and suppress transcription of inflammatory genes [8, 9]. Tofacitinib, baricitinib, and upadacitinib have demonstrated efficacy comparable to established biologic agents, with the practical advantage of oral administration and rapid onset of action [10, 11].

Despite their efficacy, important questions remain regarding optimal patient selection, treatment sequencing after biologic failure, and the balance between clinical benefit and risks such as serious infections, venous thromboembolism, major adverse cardiovascular events, and malignancy [12].

The aim of this review is to critically evaluate current evidence on the role of Janus Kinase (JAK) inhibitors in rheumatoid arthritis. In addition to summarizing the pathophysiology of RA and the JAK/STAT signaling pathway, we compare the efficacy and safety profiles of currently approved JAK inhibitors, discuss unresolved controversies regarding treatment sequencing and patient selection, and highlight future directions for personalized therapy [12, 13].

Pathophysiology of RA

Rheumatoid Arthritis (RA) arises from a complex interplay of genetic susceptibility, environmental triggers, and dysregulated immune responses. Among genetic factors, HLA-DRB1 alleles are the strongest predictors of disease risk. Environmental influences such as smoking, infections, and hormonal changes can initiate or aggravate RA in genetically predisposed individuals [14, 15].

The earliest stages of RA involve activation of the innate immune system. Dendritic cells and macrophages recognize pathogen- and Damage-Associated Molecular Patterns (PAMPs and DAMPs) via pattern recognition receptors, including Toll-like receptors. This triggers the release of pro-inflammatory cytokines such as Tumor Necrosis Factor- α (TNF- α), interleukin (IL)-1, and IL-6, which recruit and activate immune cells within the synovium [16, 17].

Adaptive immunity further amplifies inflammation. CD4+T cells, particularly Th1 and Th17 subsets, produce interferon- γ (IFN- γ) and IL-17, while B cells generate Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA). These autoantibodies form immune complexes that activate complement and perpetuate inflammation [18, 19].

Persistent inflammation leads to synovial hyperplasia, pannus formation, and progressive cartilage and bone destruction. Activated synovial fibroblasts secrete Matrix Metalloproteinases (MMPs), which degrade extracellular matrix, and Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL), which stimulates osteoclastogenesis and bone resorption [20, 21]. Hypoxia-induced Vascular Endothelial Growth Factor (VEGF) promotes angiogenesis, sustaining inflammatory cell infiltration and supporting expansion of synovial tissue [22-24]. RA is also associated with systemic complications, including cardiovascular disease, pulmonary involvement, and increased susceptibility to infections, largely driven by chronic inflammation and endothelial dysfunction.

Emerging evidence highlights air pollution and gut microbiota as additional modulators of RA pathogenesis. Exposure to particulate matter, nitrogen dioxide, and sulfur dioxide can activate pulmonary immune cells, induce oxidative stress, and trigger epigenetic modifications that enhance inflammatory signaling [25-28]. Likewise, RA is associated with gut dysbiosis, reduced microbial diversity, and impaired intestinal barrier function, allowing bacterial products such as lipopolysaccharides to enter the circulation and promote systemic inflammation [29, 30]. Reduced production of anti-inflammatory short-chain fatty acids may further exacerbate immune dysregulation [31, 32].

These environmental factors interact with genetic susceptibility, particularly HLA-DRB1 variants, to shape immune responses and increase the likelihood of disease onset and progression [33, 34].

JAK/STAT Pathway

The biochemistry of Janus Kinases (JAK) and the JAK/STAT signaling pathway is central to understanding the development and progression of Rheumatoid Arthritis (RA). JAKs are a family of non-receptor tyrosine kinases comprising

JAK1, JAK2, JAK3, and TYK2. These enzymes mediate signaling by numerous cytokines and growth factors involved in immune responses and inflammation. The JAK/STAT pathway is a key mediator of these processes and includes several sequential steps [35, 36]. Table 1 summarizes the sequential steps of JAK/STAT signaling and highlights their specific contributions to the pathogenesis of rheumatoid arthritis.

Table 1: Influence of JAK/STAT Pathway on Rheumatoid Arthritis step-by-step

Step	Description	Key Components	Impact on RA
1. Cytokine Binding	Cytokines bind to receptors on the cell surface	Cytokines, Cell Surface Receptors	Initiates inflammatory signaling
2. Receptor Dimerization	Binding causes dimerization of receptors, positioning JAKs	JAK1, JAK2, TYK2	Facilitates JAK activation for signal transduction
3. Transphosphorylation	JAKs phosphorylate each other at tyrosine residues	JAK Kinases	Activates JAKs, allowing downstream signaling to occur
4. Cytokine Receptor Phosphorylation	Activated JAKs phosphorylate the receptor's intracellular domain	Cytokine Receptor Complex	Creates docking sites for STAT proteins
5. STAT Recruitment	STAT proteins bind to phosphorylated sites on the receptor	STAT1, STAT2, STAT3	Brings STATs to the receptor complex for activation
6. STAT Phosphorylation	JAKs phosphorylate STAT proteins at conserved tyrosine residues	STAT Proteins	Activates STATs for dimerization and nuclear translocation
7. Nuclear Translocation	Phosphorylated STATs translocate to the nucleus	Nucleus	Regulates transcription of inflammatory genes, exacerbating RA
8. Gene Transcription	STATs bind to DNA, regulating genes involved in inflammation	Target Genes (e.g., IL-6, IFNs)	Drives persistent inflammation and autoimmunity in RA

Cytokines bind to specific cell surface receptors that lack intrinsic kinase activity but are associated with JAKs. Receptor dimerization brings the associated JAKs into proximity, enabling their transphosphorylation and activation. Activated JAKs then phosphorylate tyrosine residues on the intracellular domains of cytokine receptors, creating docking sites for Signal Transducer and Activator of Transcription (STAT) proteins. STATs are subsequently phosphorylated by JAKs, dimerize, and translocate to the nucleus, where they bind specific DNA sequences to regulate the transcription of genes involved in cell proliferation, differentiation, survival, and immune responses [37-39].

In RA, persistent activation of the JAK/STAT pathway contributes to chronic inflammation and autoimmunity. Key cytokines utilizing this pathway include interleukin-6 (IL-6), interferons (IFNs), and interleukin-2 (IL-2). IL-6 signals through a receptor complex involving gp130 and JAK1, JAK2, and TYK2, leading to activation of STAT3 and transcription of pro-inflammatory genes, as well as promoting differentiation of Th17 cells. IFNs activate JAK1 and JAK2, resulting in phosphorylation of STAT1 and STAT2 and induction of genes involved in immune regulation and inflammation [40-42].

Because of its central role in RA pathogenesis, the JAK/STAT pathway has become an important therapeutic target. JAK inhibitors such as tofacitinib, baricitinib, and upadacitinib inhibit the kinase activity of one or more JAKs, thereby blocking STAT activation and reducing transcription of pro-inflammatory genes. This leads to decreased cytokine production, reduced disease activity, and improved physical function in patients with RA [13, 43]. However, JAK inhibition may increase the risk of infections and alter blood cell counts, underscoring the importance of the JAK/STAT pathway in maintaining normal immune homeostasis [44, 45].

JAK Inhibitors in Rheumatoid Arthritis

JAK inhibitors have expanded the therapeutic armamentarium for rheumatoid arthritis by targeting intracellular cytokine signaling rather than individual extracellular mediators. Table 2 summarizes the principal pharmacologic characteristics, efficacy, and monitoring requirements of currently approved agents [13, 46].

Table 2: Summary of JAK Inhibitors in the Treatment of Rheumatoid Arthritis

JAK Inhibitor	Mechanism of Action	Efficacy	Common Side Effects	Monitoring Recommendations
Tofacitinib	Inhibits JAK1 and JAK3 (also JAK2)	Reduces disease activity; improves physical function	Increased infection risk, elevated liver enzymes	Regular liver function tests, complete blood count monitoring
Baricitinib	Primarily targets JAK1 and JAK2	Effective for inadequate response to traditional DMARDs	Upper respiratory infections, thromboembolic events	Monitor blood counts, assess thromboembolic risk
Upadacitinib	Selectively inhibits JAK1	Similar efficacy to Tofacitinib; fewer side effects	Possible cholesterol elevation, risk of infections	Routine lipid profile checks, infection surveillance

Tofacitinib preferentially inhibits JAK1 and JAK3, baricitinib primarily targets JAK1 and JAK2, and upadacitinib is more selective for JAK1. Although increased selectivity may theoretically reduce off-target effects, clinically meaningful differences in safety remain modest and continue to evolve as post-marketing evidence accumulates [47].

Across phase III clinical trials, all three agents consistently improved disease activity, physical function, and radiographic outcomes in patients with inadequate responses to methotrexate or biologic DMARDs. ACR20 response rates generally ranged from 60 to 75% at 12–24 weeks, demonstrating efficacy comparable to established biologic agents [12, 48, 49].

Although differences in kinase selectivity have generated considerable interest, their clinical significance remains incompletely defined. Tofacitinib preferentially inhibits JAK1 and JAK3, baricitinib primarily targets JAK1 and JAK2, and upadacitinib is more selective for JAK1. Current evidence suggests that efficacy is broadly similar across agents, whereas treatment decisions are driven more by patient comorbidities, prior therapeutic response, and regulatory safety considerations than by selectivity alone.

The mechanism of action of JAK inhibitors involves binding to the ATP-binding sites of JAK enzymes, thereby preventing their phosphorylation and subsequent activation. This blockade impedes downstream signaling necessary for the transcription of pro-inflammatory genes. The efficacy of JAK inhibitors in managing RA has been validated through numerous clinical trials, which have shown significant reductions in disease activity and improvements in patient outcomes. These studies have demonstrated that JAK inhibitors can be used alone or in conjunction with other DMARDs [50].

In the RA-BEAM trial, baricitinib demonstrated statistically superior clinical responses compared with adalimumab when combined with methotrexate. Similarly, in the SELECT-COMPARE study, upadacitinib achieved higher rates of low disease activity and remission than adalimumab. These findings suggest that JAK inhibitors are at least comparable to leading biologic DMARDs and may provide advantages in speed of response and patient convenience. However, treatment sequencing remains controversial, particularly in patients with cardiovascular or thromboembolic risk factors [51].

However, the use of JAK inhibitors is associated with a unique safety profile and potential adverse effects. Common side effects include infections, such as upper respiratory infections and herpes zoster, which arise from the broad immunosuppressive effects of these medications. Additionally, there is an increased risk of thrombosis, alterations in lipid profiles, and potential impacts on blood cell production, necessitating vigilant patient monitoring. Due to their potent effects and associated risks, JAK inhibitors are typically prescribed when other therapies fail to provide adequate relief [52, 53].

Consequently, current clinical practice increasingly supports individualized use of JAK inhibitors in patients with inadequate responses to csDMARDs or biologic therapies, with treatment decisions guided by efficacy expectations, comorbidity profiles, and patient preferences.

Safety Concerns With JAK Inhibition

The use of Janus Kinase (JAK) inhibitors in the treatment of Rheumatoid Arthritis (RA) presents several significant risks and challenges that necessitate careful monitoring and patient management. One of the primary concerns associated with JAK inhibitors is the increased risk of infections. Due to their immunosuppressive effects, these medications heighten the likelihood of various infections, including upper respiratory tract infections and urinary tract infections, as well as more serious infections such as herpes zoster (shingles) and tuberculosis. This increased susceptibility stems from the broad inhibition of cytokine signaling, which undermines the immune system's ability to combat pathogens [54, 55].

Herpes zoster occurs more frequently than with many biologic DMARDs, particularly in older adults and Asian populations.

Risk mitigation strategies include screening for tuberculosis and viral hepatitis, vaccination (especially against herpes zoster), baseline and periodic complete blood counts, liver function tests, and lipid monitoring. Assessment of cardiovascular and thromboembolic risk is essential before initiating therapy.

Another important issue is the potential for thromboembolic events. Research suggests that JAK inhibitors may raise the risk of developing blood clots, such as Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), particularly at higher doses. In response, regulatory agencies have issued warnings and guidelines to mitigate these risks, emphasizing the need for comprehensive patient assessment and appropriate dosing strategies. Additionally, JAK inhibitors can cause changes in lipid profiles, including elevated cholesterol levels, necessitating regular monitoring of lipid levels and management of cardiovascular risks to prevent long-term heart-related complications [56, 57]. The ORAL Surveillance trial, conducted in patients aged 50 years or older with at least one cardiovascular risk factor, reported higher rates of MACE and malignancy

with tofacitinib compared with TNF inhibitors, prompting regulatory warnings that have influenced the entire class [58]. Although absolute event rates were low, these findings underscored the importance of individualized risk assessment.

Hematologic concerns also warrant attention with the use of JAK inhibitors. These medications may lead to alterations in blood cell counts, resulting in conditions such as anemia, neutropenia, and lymphopenia. Routine monitoring of complete blood counts is advisable to identify and address these potential side effects promptly. Furthermore, there are concerns regarding the impact of JAK inhibitors on liver health. Some patients have shown elevated liver enzymes, indicating possible hepatotoxicity. Regular liver function testing is crucial to monitor for any signs of liver damage and to enable timely intervention if abnormalities are detected [59].

Ongoing research is exploring the potential long-term effects of JAK inhibitors, particularly regarding cancer risk and overall mortality. Although some studies suggest a possible increased risk of malignancies, definitive evidence is still lacking [60, 61]. This uncertainty underscores the importance of diligent long-term monitoring for patients receiving JAK inhibitors. Additionally, there are concerns about the impact of these drugs on bone health. Given that cytokines play a role in bone remodeling, the inhibition of JAK/STAT signaling could theoretically affect bone density and increase the risk of osteoporosis and fractures.

Conclusion

JAK inhibitors have become an important component of rheumatoid arthritis treatment by providing effective oral suppression of multiple cytokine pathways central to disease pathogenesis. Tofacitinib, baricitinib, and upadacitinib demonstrate efficacy comparable to, and in selected trials superior to, established biologic DMARDs, with rapid onset of action and convenient administration.

Their use, however, requires careful balancing of benefits against risks, particularly in patients with cardiovascular risk factors, prior thromboembolism, recurrent infections, or malignancy concerns. Current evidence supports a personalized approach in which treatment choice is guided by disease severity, previous therapeutic response, comorbidities, and patient preferences.

Future research should focus on identifying biomarkers predictive of therapeutic response, clarifying long-term comparative safety, and refining the optimal place of JAK inhibitors within evolving treatment algorithms.

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Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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