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# AN OVERVIEW OF JANUS KINASE INHIBITORS

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## Abstract

With a better understanding of the pathogenesis of inflammatory rheumatic diseases, different treatments pathways have emerged. In recent years, Janus kinase inhibitors (JAKinibs) have become one of these treatment pathways. It has come into clinical use as an effective treatment agent, especially in rheumatoid arthritis and spondyloarthropathy. In the 21st-century, experimental and clinical studies are being conducted on JAKinibs in different disease groups apart from rheumatological diseases around the world. In this review, we aimed to briefly discuss the historical development and clinical use of JAKinibs.

**Keywords:** Janus kinase inhibitor, rheumatological diseases, history

## INTRODUCTION

There are many reasons for the pathogenesis of rheumatic diseases. Many environmental, epigenetic, genetic, and cellular causes may be involved in the pathogenesis of diseases. When we look at the genetic causes, some mutations, translocation of some genetic regions in DNA gene sequence, overexpression, and irregularities in intracellular protein kinase activation play an important role in the pathogenesis of autoimmune diseases, inflammatory rheumatic, neuropsychiatric, cardiovascular diseases, and malignancies.

Since the beginning of the 21st century, with a better understanding of the pathogenesis of rheumatic diseases, new generation treatment agents that act at the level of many targeted receptors and cytokines have been added to the conventional treatment agents that we use today. Treatment agents that act especially at the protein kinase level constitute the most important treatment agents in the 21st century (1,2). Perhaps 25-33% of drug development efforts in the United States of America (USA) and around the world target these enzymes (3).

### Brief History of JAKs and their Mechanism of Action

Protein kinases control metabolism, transcription, cell division, movement, and programed cell death. Protein phosphorylation provides a balance between phosphoprotein kinases and protein kinases that perform reversible phosphorylation-dephosphorylation functions in the cell (4,5). Because of the general importance of protein phosphorylation, significant efforts have been made to identify the various functions of protein kinase signal transduction pathways. Inflammatory rheumatic diseases and malignancies may occur because of derangements in the activation of protein kinase.

From this perspective, the first protein kinase inhibitor was developed by Hidaka et al. (6) in 1980. Isoquinoline sulfonamide was shown to inhibit protein kinase in 1984. However, protein kinase inhibition did not enter clinical trials until the late

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1980s. Toward the end of the 1990s, pharmaceutical companies began to study protein kinase inhibition. In these years, the three-dimensional form of protein kinase has been shown. Cyclosporine inhibits protein phosphatase, whereas rapamycin inhibits protein kinase (7). The first protein kinase inhibitor (Fasudil) was used for treating cerebral ischemia in Japan (8,9). Following this development, the imatinib molecule began to take part in clinical trials in chronic myeloid leukemia (CML) in 1996 and was accepted as a treatment option in CML in 2001 in the USA. On the other hand, rapamycin entered clinical use in USA as an immunosuppressive therapy in 1999 (10).

Cytokine binding to these receptors activates phosphotransferases (kinases) associated with the intracellular part of these receptors. These kinases belong to a small family called Janus kinase (JAK), which consists of four members: JAK1, JAK2, JAK3, and tyrosine kinase (TYK)2. Different receptors are coupled with different JAKs working in pairs in a heterodimeric or homodimeric complex. JAKs are intracellular enzymes that are activated by the binding of cytokines to cell surface receptors. Following receptor binding, JAKs phosphorylate themselves and tyrosine residues on the receptor chains that recruit the signal transducers and activators of transcription of DNA-binding proteins. These factors are phosphorylated by JAKs, resulting in dimerization, translocation to the nucleus, and subsequent regulation of gene expression. A number of mutant cell lines revealed the essential functions of JAKs in cytokine signaling. However, identification of JAK3 mutations in patients with severe combined immunodeficiency revealed criticality *in vivo*, as in various knockout mice (11,12). These considerations led to the suggestion that JAK inhibitors could be used as a new immunomodulatory drug therapy (13). Recognition of JAK2 gain-of-function (GOF) mutations in MPN provides further evidence of JAK inhibition as an attractive therapeutic option (14). In humans, mutation of TYK2 causes primary immunodeficiency (15). TYK2 is associated with systemic lupus erythematosus and Crohn's disease (16,17) and JAK2 polymorphisms are associated with Behçet's disease (18). Considering the role of cytokines in autoimmunity, inhibition of JAK blocks the effects of many cytokines and appears as an alternative treatment option for some diseases. The rationale for targeting JAKs derives from the vast amount of data demonstrating the role of cytokines in autoimmune disease, the success of biologics, and conclusive evidence of the necessary role of JAKs in cytokine signaling both *in vitro* and *in vivo*. JAK1 blockade inhibits signaling by interferon (IFN)-α, IFN-gamma, interleukin (IL)-6 , and others Blockade of JAK2 reduces the signaling of IL-3, IL-5, and IFN-gamma and reduces the hematopoietic growth factor erythropoietin, thrombopoietin, and granulocyte macrophage colony-stimulating factor. On the other hand, JAK3 blockade interferes with the effects of IL-2, IL-4, IL-15, IL-21, and other cytokines (19).

## Clinical use of JAKs

**Tofacitinib:** Tofacitinib is the first Jakinib drug developed for autoimmune diseases. It inhibits JAK1 and JAK3 and, to a lesser extent, inhibits JAK2 (20). After promising results in preclinical and early phase clinical trials, it was extensively evaluated in key studies in 2012 (21). Multiple phase 2 and phase 3 studies demonstrated the efficacy of tofacitinib when used as monotherapy or in combination with other disease-modifying antirheumatic

drug (DMARD) treatment agents for rheumatoid arthritis (RA) (22,23). Later, it entered clinical use for treating psoriatic arthritis (PsA) (24) and was subsequently approved for clinical use for treating ulserative colitis (25).

**Baricitinib:** As a JAK1/JAK2 inhibitor, it has been approved in the USA for patients with RA limited to 2 mg per day in combination with a conventional synthetic DMARD (csDMARD) or as monotherapy in patients with RA who are resistant to a biological

DMARDs (bDMARDs) based on phase 3 trial results. In other countries, it has been approved for clinical use as 2 and 4 mg in patients resistant to csDMARD (26,27). In addition, it has been approved for use for treating atopic dermatitis in Europe.

**Peficitinib:** Peficitinib is a pan Jakinib that has been approved for use for treating RA in Japan, South Korea, and Taiwan (28,29).

**Upadacitinib:** The second generation selective JAK inhibitor upadacitinib has a selective and potentially more pronounced inhibitory effect on JAK1 than the other subtypes. Phase 3 trials demonstrated clinical, functional, and radiographic efficacy, both along with a csDMARD and as monotherapy, in patients who did not respond completely to a csDMARD or bDMARD (30,31). It has also been approved for spondylitis and PsA (32,33) and is effective in inflammatory bowel disease.

**Filgotinib:** Filgotinib is a second-generation JAK1 inhibitor that has recently been approved for clinical use in Europe (33). *In vitro* selective JAK 1 inhibitors, such as upadasitinib, but clinical and safety measures are similar to pan JAKinibs, but herpes zoster and anemia are less frequent with filgotinib treatment.

Ruxolitinib: Ruxolitinib, a JAK1/JAK2 inhibitor, was the first agent to be approved for myeloproliferative neoplasms (MPN) that frequently display GOF JAK2 mutations. It has also been approved for steroid-resistant acute graft-versus-host disease (GvHD).

**Oclacitinib:** Oclacitinib is a non-selective JAKinib approved for treating eczema in dogs.

**Side effect profile of JAKinibs:** Although jakinib treatments have similar side effects as other bDMARD treatments, some side effects are different. Common side effects include infection, serious and opportunistic infections, and herpes zoster. Cytopenias such as neutropenia and anemia are also common adverse events, likely due to JAK2 inhibition. Upadacitinib, a relatively JAK1-selective molecule, has similar effects as pan-JAKinibs on anemia, whereas filgotinib appears to produce less anemia. JAKinibs can also cause lymphopenia, specifically a decrease in natural killer cells due to the JAK3 inhibitor.

There is an increased risk of pulmonary thromboembolism and deep vein thrombosis complications in patients with RA, and it seems difficult to associate this complication with a cytokine pathway. JAK2 inhibition may impair thrombotic haemoastasis, but this side effect may be associated with the comorbidity of some non-target treatment comorbid conditions.

From the point of view of malignancy, it is important to use JAKinibs in some solid and hematological malignancies other than rheumatological diseases. The use of this group of drugs in other rheumatological diseases, especially in RA, does not increase the risk when compared with other treatment agents and has been safely used for many years.

## CONCLUSION

In recent years, approximately 180 protein kinase inhibitors have been used in clinical trials worldwide, and there are 72 FDA-approved protein kinase inhibitors. JAKinibs have started to be used for treating many rheumatic diseases. Ral use in particular is an advantage and is important in terms of patient compliance. In terms of side effects, long-term results should be closely monitored. It seems that more Jakinib will be used in clinical use in the coming years.

### Footnote

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