Update on Janus Kinase Antagonists in Inflammatory Bowel Disease

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KEYWORDS

• Janus kinase inhibitors • Small-molecule therapy • Tofacitinib
• Inflammatory bowel disease • Ulcerative colitis • Crohn disease

KEY POINTS

- Janus kinase (JAK) inhibitors represent a novel small-molecule therapy that will likely become a new medical treatment for inflammatory bowel disease (IBD).

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- JAK inhibitors target small intracellular molecules responsible for transducing signals from inflammatory cytokines believed to be involved in the pathogenesis of IBD.
- Based on phase 2 clinical trials, tofacitinib, a JAK1 and JAK3 inhibitor, has a dose-dependent effect in ulcerative colitis and potentially an effect in Crohn disease.
- Tofacitinib is associated with a potential risk of opportunistic infections, lipid abnormalities, bone marrow suppression, and lymphoma; however, the safety profile appears similar to that of the current therapies for IBD.
- Multiple JAK inhibitors with different specificities and side-effect profiles are being studied in the treatment of IBD.

INTRODUCTION

The current treatment options for inflammatory bowel disease (IBD) include aminosalicylates, immunosuppressives, corticosteroids, and monoclonal antibodies to tumor necrosis factor (TNF)-α.[1,2] Progress in understanding the pathogenesis of IBD, together with innovations in technology, have led to the introduction of new monoclonal antibodies directed at other inflammatory cytokines and leukocyte trafficking molecules.[3] Most recently, small-molecule inhibitors have emerged as an appealing therapy, given their potential for oral administration, lack of immunogenicity, and less interpatient pharmacokinetic variability in comparison with monoclonal antibodies.

Janus kinase (JAK) inhibitors have emerged as a new small-molecule therapy for autoimmune disease. These drugs simultaneously target multiple cytokine signaling pathways known to be involved in the pathogenesis of inflammatory and autoimmune diseases.[4] Tofacitinib, a JAK inhibitor targeting JAK1 and JAK3, was recently approved for the treatment of rheumatoid arthritis (RA), and is currently under evaluation for the treatment of both ulcerative colitis (UC) and Crohn disease (CD).[5] With the continued development of drugs that can specifically target JAK proteins individually and in combination, JAK inhibitors, termed JAKINIBs, are an increasingly appealing therapy for autoimmune diseases, allowing clinicians the ability to tailor drug specificity to optimize the balance between desired and adverse effects.

JANUS KINASE FAMILY

The JAK proteins are a family of nonreceptor tyrosine kinases that possess a highly conserved kinase domain responsible for its enzymatic activity. The family consists of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2); these proteins associate with the intracellular portion of cytokine or hormone receptors.[6] The family has been shown to play a central role in the signal transduction pathways for multiple cytokines, including proinflammatory cytokines involved in the pathogenesis of autoimmune diseases.[7,8]

Type I and Type II Cytokine Receptors

The JAK family mediates signals from transmembrane type I and type II cytokine receptors that are expressed on cells capable of responding to cytokines. Type I cytokine receptors have a conserved structure defined by an extracellular WSXWS amino acid motif and intracellular domain through which receptors selectively associate with JAKs. Many receptors possess common subunits, such as the γ-chain (CD132), β-chain (or CD131), and glycoprotein 130 (gp130 or CD130). Receptors with a