Malignancy and Janus Kinase Inhibition

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KEYWORDS

• Malignancy • Rheumatoid arthritis • Jak inhibitors • Tofacitinib • Lymphoma • Lung cancer

KEY POINTS

- Janus kinase inhibitors have been shown to be effective for treatment of rheumatoid arthritis (RA).
- The risk of malignancy in patients with RA treated with tofacitinib is similar to what has been reported with disease-modifying antirheumatic drugs and biologics.
- The risk of malignancy with tofacitinib in the RA population was not dose related except for an increased risk of nonmelanoma skin cancers in the long-term extension studies with the 10-mg dose.
- Based on clinical trial and long-term extension data, the rate of malignancy in patients with RA treated with tofacitinib does not increase over time with treatment.
- Based on clinical trial and long-term extension data, the risk of malignancy with tofacitinib treatment is similar to what is expected in the RA population.

INTRODUCTION

The management of rheumatoid arthritis (RA) has dramatically transformed over the last 20 years. The use of early aggressive therapy targeting low disease activity and the development of biologic therapies has dramatically improved patient outcomes with slowing of structural damage, improved physical function, and prolonged survival.[1–4]

However, biologic therapies have limitations; more than half of the patients continue to have active disease and require either subcutaneous or intravenous administration; they are associated with significant expense; and they can induce immunogenicity. Over the last 25 years, the intracellular signaling pathways involved in signal transduction from the cell surface to the nucleus after ligand-receptor binding have been

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identified. This improved understanding of these pathways has provided opportunities for development of small molecule therapies that could target these pathways modifying proinflammatory cytokine production. Multiple preclinical studies have shown benefit in inhibiting various intracellular kinases, such as p38 Map kinase, and SyK (spleen tyrosine kinases) but failed to show benefit in RA clinical trials.[5]

In 2012, tofacitinib, an oral Janus kinase (Jak) inhibitor, was approved for RA treatment and other Jak inhibitors are under development, with baricitinib recently completing phase III trials in RA and selective inhibitors for Jak1 in phase II/III trials.[6] Jaks are protein tyrosine kinases that bind the cytoplasmic region of transmembrane cytokine receptors and mediate signaling through type I and type II cytokine receptors. After receptor-ligand interaction, various Jaks are activated, resulting in tyrosine phosphorylation of the receptor and subsequent activation of STATs (signal transducer and activators of transcription), which act as transcription factors. Jak/STAT signaling mediates cellular responses to multiple cytokines and growth factors. These responses include proliferation, differentiation, migration, apoptosis, and cell survival, depending on the signal and cellular context. Activated STATs enter the nucleus and bind to specific enhancer sequences in target genes, affecting their transcription.[7] Jaks consists of 4 types: Jak1, Jak2, Jak3, and Tyk2. The JAKs signal as pairs. Jak3 is primarily expressed in hematopoietic cells and is critical for signal transduction from the common gamma chain of the receptors for interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21 on the plasma membrane to the nuclei of immune cells. Jak3 only signals in combination with Jak1. The cytokines are integral to lymphocyte activation, function, and proliferation. Jak3-knockout mice have defects in T and B lymphocytes and natural killer cells, with no other defects reported. Humans lacking Jak3 develop a severe combined immunodeficiency with a deficiency in natural killer cells and T lymphocytes.[8] Tofacitinib is a more selective inhibitor of Jak3/Jak1 based on enzymatic/cellular assays, but at the serum levels that have been achieved it also has an impact on Jak2.[9]

Jak1 and Jak2 were initially not considered as potential therapeutic targets because knocking out these kinases results in germline lethality. Baricitinib, which is a Jak1/Jak2 inhibitor, is in development for RA and has shown similar efficacy and safety to tofacitinib. Ruxolitinib, which has selectivity for Jak1/Jak2 is approved for myelofibrosis.[10,11] Hormones like the cytokines erythropoietin, thrombopoietin, growth hormone, granulocyte-macrophage colony-stimulating factor, IL-3, and IL-5 all signal through Jak2. IL-6, IL-10, IL-11, IL-19, IL-20, IL-22, and interferons gamma, alfa, and beta signal through Jak1. Tyk2 facilitates signaling for IL-12, IL-23, and type 1 interferons.[12] Tyk2 pairs with either Jak1 or Jak2 to facilitate signaling. At present, no specific Tyk2 inhibitors are under development for RA.[13,14]

Tofacitinib was approved by the US Food and Drug Administration (FDA) for patients with RA with active disease despite methotrexate treatment at a dosage of 5 mg twice daily in combination with nonbiologic disease-modifying antirheumatic drugs (DMARDs) or as monotherapy. The American College of Rheumatology guidelines recommend the use for moderate to severe RA that is nonresponsive to conventional DMARDs, and additionally also recommended their continued long-term use in patients who attain clinical remission.[15]

RA and other autoimmune conditions are chronic inflammatory states and are characterized by abnormalities of the immune system. Treatment of RA consists of medications that alter the upregulated immune system. The immune system is thought to play an important role in immune surveillance and protection from development of malignancy, with increased risk of certain malignancies, such as lymphomas, lung cancer, and nonmelanoma skin cancers (NMSCs), in patients with RA compared with

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