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Update on Janus Kinase Antagonists in Inflammatory Bowel Disease

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Abstract

Janus kinase (JAK) inhibitors have emerged as a novel orally administered small molecule therapy for the treatment of ulcerative colitis and possibly Crohn's disease. These molecules are designed to selectively target the activity of specific JAKs and offer a targeted mechanism of action without risk of immunogenicity. Based on data from clinical trials in rheumatoid arthritis and phase 2 studies in inflammatory bowel disease, tofacitinib and other JAK inhibitors are likely to become a new form of medical therapy for the treatment of inflammatory bowel disease.

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Keywords

Janus kinase inhibitors; Small molecule therapy; Tofacitinib; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease

Introduction

The current treatment options for inflammatory bowel disease (IBD) include aminosalicylates, immunosuppressives, corticosteroids, and monoclonal antibodies to 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 the potential for oral administration, lack of immunogenicity, and less inter-patient pharmacokinetic variability, as compared 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 treatment of rheumatoid arthritis (RA), and is currently under evaluation for the treatment of both ulcerative colitis (UC) and Crohn's 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 with the ability to tailor drug specificity to optimize the balance between desired and adverse effects.

Janus Kinase Family

The Janus kinase (JAK) proteins are a family of non-receptor 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 pro-inflammatory cytokines involved in the pathogenesis of autoimmune diseases.^{7, 8}

Type I and II Cytokine Receptors

The JAK family mediates signals from transmembrane type I and 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 common γ -chain bind to interleukin (IL)-2, IL-7, IL-9, IL-15, and IL-4, and signal through JAK1 and JAK3. The β -chain-containing receptors bind to granulocyte macrophage-colony stimulating factor, IL-3, and IL-5, and signal through

JAK2. Receptors containing gp130 bind to IL-6, IL-11, and IL-12, and signal primarily through JAK1 with the exception of IL-12, which utilizes TYK2. Other type I receptors are homodimer receptors for hormones, such as growth hormone, prolactin, erythropoietin, thrombopoietin, and granulocyte macrophage-colony stimulating factor (GM-CSF), and signal through JAK2.⁹⁻¹¹

Type II cytokine receptors are a similar family of receptors that do not possess the amino acid WSXWS motif. Type II receptors bind to cytokines such as interferon (IFN)- α , IFN- β , IFN- γ , IL-10 family cytokines, and IL-20 and primarily signal through JAK1, with the exception of IFN- γ , which utilizes both JAK1 and JAK2.¹¹⁻¹³ Together Type I and Type II receptors associate with JAK family proteins to mediate the effects of cytokines or hormones (Table 1).

Mechanism of JAK Signaling

Though JAK proteins are associated with distinct cytokine and hormone receptors, common intracellular signaling pathways are used to initiate transcriptional changes. Upon cytokine binding, cytokine receptor subunits form multimers bringing the conserved intracellular tails of the subunits with associated TYKs in close proximity to one another, and JAKs phosphorylate tyrosine residues on the cytokine receptor. Phosphorylation of the cytokine receptor tail creates a docking site for transcription factors called signaling transducers and activators of transcription (STATs). STATs are a family of seven transcription factors that initiate the transcription of genes that mediate the effects of cytokine signaling. STATs are recruited to the cytokine receptor complex, and JAKs phosphorylate a tyrosine residue in the SRC homology 2 (SH2) domain of the STAT molecule. This leads to STAT dimerization, translocation to the nucleus, and transcriptional activation of target genes downstream from cytokine signaling.^{9, 10, 12} STAT family members selectively associate with JAK proteins in unique combinations to initiate the unique transcriptional changes induced by a specific cytokine or hormone (Table 2).

JAK Deficiency

While the JAK family utilizes overlapping signaling pathways, each JAK has a unique role in modulating the immune system. Mice or humans completely deficient in a specific gene serve as important models for defining the function of each JAK family member. For example, complete deficiency of JAK1 or JAK2 is lethal. JAK1 is expressed not only in immune cells but also in precursors of the nervous system. As a consequence, deficiency of JAK1 leads to significant neurologic deficits and lymphoid developmental abnormalities with a perinatal lethal phenotype. In contrast, mice lacking JAK2 have defective erythropoiesis and consequently die during embryogenesis. Given the lethality of these mutations, complete deficiencies of JAK1 or JAK2 have not been described in humans; however, activating, gain-of-function mutations in JAK2 have been described in polycythemia vera and myeloproliferative disorders.^{14, 15}

While lack of TYK2 does not appear to be lethal, only two documented cases of TYK2 deficiency have been described in humans with similar phenotypes. Both patients appeared to have increased susceptibility to bacterial and viral infections that were most likely related

to deficient IFN and IL-12 signaling, which are mediated by TYK2. However, only one patient had elevated immunoglobulin E concentration with clinical features of atopy.^{15, 16} Based on mouse models, TYK2 appears to be central not only for IL-12 and IFN signaling, but also for the production of IL-12 and IL-23 by dendritic cells involved in directing the adaptive immune response.⁸

Deficiency of JAK3, which is primarily expressed in immune cells, has been described extensively in humans, where it causes severe combined immune deficiency (SCID) as a result of absent γ -chain cytokine receptor signaling. The phenotype of humans lacking either γ -chain cytokine receptors or JAK3 is nearly identical – profound T lymphocyte and Natural Killer (NK) deficits leading to life-threatening susceptibility to infections. The immune deficits are a result of impaired T lymphocyte development and proliferation. Although B lymphocyte numbers are preserved, significant functional deficits exist in antibody production and class switching.^{15, 17-19} Lymphocyte abnormalities appear to be driven by lack of JAK3-dependent IL-7 signaling that under normal conditions drives development of T and B lymphocytes. Similarly, IL-15 signaling through JAK3 serves as a survival signal for NK cells. Furthermore, JAK3 signaling also drives CD4⁺ T cell differentiation into specialized Type 1 helper T (Th1) and Type 2 helper T (Th2) cells. IL-4 signaling mediated by JAK3 drives the differentiation of Th2 cells,²⁰ and JAK3-dependent alterations in the IFN- γ promoter lead to Type 1 helper T (Th1) differentiation.²¹ JAK3, perhaps more so than its JAK family counterparts, appears to play a critical, non-redundant role in driving lymphocyte development, proliferation, and differentiation.

Genome-Wide Association Studies and JAK Signaling

JAK-STAT signaling is known to be critical in regulating and modulating the immune response based on numerous *in vivo* and *in vitro* models. Moreover, genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) in the genome that are associated with increased risk of disease and provide a definitive link between the JAK-STAT pathway and human autoimmunity. SNPs associated with an increased risk of both UC and CD have been identified throughout the JAK-STAT cytokine signaling pathway, including cytokines (e.g., IL-12 β), cytokine receptors (e.g., IL-23R), JAKs (e.g., JAK2), and downstream STAT proteins (e.g., STAT3).^{22, 23} Furthermore, studies of IBD patients revealed excess production of cytokines initiating JAK-STAT signaling, such as IL-1 β , IL-6, IL-12, and IL-23.²⁴ Together with the animal studies, these genetic studies underscore the importance of JAK-STAT signaling in the immune system, identifying this pathway as a potential therapeutic target.

Tofacitinib: JAK Inhibitor

Knowledge of the JAK-STAT signaling pathways has been applied to the development of orally administered small molecule inhibitors, which are being tested in clinical trials for the treatment of autoimmune diseases. Tofacitinib (CP-690550) was the first small molecule JAK inhibitor tested in clinical trials for treatment of autoimmune diseases, such as psoriasis, RA, prevention of allograft rejection, and IBD.⁵ Tofacitinib interferes with the JAK-STAT signaling by competing with ATP for binding to the kinase domain of JAKs and

inhibits JAK1, JAK2, and JAK3. *In vitro* studies, however, showed preferential inhibition of JAK1 and JAK3 with less effect on JAK2 (Figure 1).^{25,26}

Preclinical mechanistic studies of tofacitinib showed a reduction in production of inflammatory cytokines and differentiation into cell lineages associated with autoimmunity.²⁰ *In vitro* studies confirmed that tofacitinib disrupted signaling downstream of JAK3-dependent γ -chain cytokine receptors, including IL-2, IL-4, IL-7, IL-15, and IL-21 dependent signals.²⁰ Treatment with tofacitinib also reduced JAK1 and JAK2-dependent signaling by IL-6, IFN- γ , and IL-12.^{20, 27} Tofacitinib also inhibited differentiation of naïve murine CD4+ T cells into Th1, Th2, and Th17 cells, subsets that have been implicated in autoimmunity and in the pathogenesis of IBD. In addition, tofacitinib disrupted lipopolysaccharide signaling, an important activator of the innate immune system.²⁰ In these mechanistic studies, tofacitinib had significant effects on dampening both the adaptive and innate immune responses that appear to be overactive in IBD and autoimmunity.

Tofacitinib in Autoimmune Diseases

Based on the immune modulation seen in mechanistic studies, tofacitinib has been studied in treatment of numerous autoimmune diseases. The greatest progress has been in the treatment of RA, where phase 3 clinical trials demonstrated the effectiveness of tofacitinib in improving clinical scores and physical function of patients with RA. The trials have been consistent in demonstrating clinical efficacy as monotherapy in patients with inadequate response to a biologic or non-biologic disease modifying drugs (DMARDs).^{28, 29} Subsequently, the combination of tofacitinib in combination with methotrexate was not inferior to adalimumab and methotrexate, the standard of care, for treatment of active RA.³⁰ The FDA has approved tofacitinib for use in RA at a dose of 5 mg twice daily. A dose of 10 mg twice daily was not approved by the FDA, and neither the 5 mg nor the 10 mg doses were approved by the European Medicines Agency (EMA), pending requirements for additional safety information.

Ulcerative Colitis and Tofacitinib

A recent phase 2 randomized controlled trial of tofacitinib demonstrated efficacy in patients with moderately to severely active UC (NCT00787202).³¹ The study enrolled 194 patients with moderately to severely active UC with a baseline Mayo Clinic disease activity score of 8 who were randomized to tofacitinib 0.5 mg, 3 mg, 10 mg, 15 mg, or placebo twice daily. Tofacitinib was administered for 8 weeks twice daily without concomitant immune modulators or biologics. The primary endpoint was clinical response at 8 weeks, as defined by a decrease in the baseline Mayo score of 3 or more, a 30% reduction from baseline in the Mayo score, and at least a 1 point reduction in the rectal bleeding sub-score or absolute rectal bleeding sub-score of 0 or 1. There was a dose-dependent effect with clinical response observed in 32%, 48%, 61%, and 78% of patients treated with tofacitinib 0.5 mg, 3 mg, 10mg, and 15mg doses, respectively, as compared to 42% of patients on placebo. Clinical remission at 8 weeks, as defined by Mayo score of 2 or lower without any subscore greater than 1, was observed in 13%, 33%, 48%, 41% of patients treated with tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg doses, respectively, as compared to 10% on placebo. Overall, the

study showed promising differences in clinical response and remission between tofacitinib and placebo.

The endoscopic endpoints measured in this phase 2 trial provide additional evidence of efficacy for tofacitinib in the treatment of UC. Specifically, endoscopic response at 8 weeks was also observed in a dose-dependent manner in 52%, 58%, 67%, and 78% of patients treated with tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg doses, respectively, as compared to 46% on placebo, with significant differences between the 15 mg dose and placebo (p-value of 0.001). Endoscopic remission, a more stringent endpoint defined as Mayo subscore of 0 or 1, was achieved in 10%, 18%, 30%, and 27% of patients treated with tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg doses, respectively, as compared with 2% on placebo. The differences in the proportion of patients who achieved endoscopic remission in the three higher doses compared to placebo were significant. Overall, the dose-dependent endoscopic results provide additional support that tofacitinib is effective for the treatment of moderately-to-severely active UC.

Additional support for the efficacy of tofacitinib in the treatment of UC comes from the reduction in inflammatory biomarker concentrations that occurred during treatment. Significant reductions in the log-transformed concentration of serum C-reactive protein (CRP) were seen in the 15 mg group compared to the placebo arm ($p < 0.001$), and reductions in the log-transformed concentration of fecal calprotectin were also observed in the 10 mg and 15 mg groups compared to the placebo arm (p-value of 0.01, < 0.001 , respectively).³¹ The reductions in C-reactive protein and fecal calprotectin seen in patients treated with tofacitinib provide additional evidence for its efficacy in UC.

Overall, this Phase II study provides promising data that tofacitinib at doses of 10 and 15 mg twice daily is effective in patients with moderate to severely active UC. Phase 3 studies are currently underway to evaluate the efficacy of tofacitinib 10 mg twice daily as induction therapy in patients with active UC, and 5 mg and 10 mg twice daily as maintenance therapy in patients with UC who responded to induction therapy with tofacitinib.

Crohn's Disease and Tofacitinib

Results from a phase 2 randomized, controlled trial of tofacitinib in CD (NCT00615199) were also recently published. One hundred thirty-nine patients with moderate to severe CD with a baseline CDAI of 220-450 were enrolled.³² The patients were not treatment-naïve but could not be receiving concomitant immunomodulators or biologics. Patients were randomized to tofacitinib 1 mg, 5 mg, 15 mg, or placebo twice daily for a total of 4 weeks. The primary endpoint was clinical response at week 4 as defined by a reduction in CDAI score from baseline of 70 or more points, and the secondary clinical endpoint was clinical remission, defined by CDAI of < 150 .

Given the previously described results in UC, the results from this study in CD were surprising, in that the primary endpoint of clinical response was achieved in 36%, 58%, and 46% of patients in the 1 mg, 5 mg, and 15 mg tofacitinib arms, respectively, and were not significantly different from the 47% response rate in the placebo group. Clinical remission occurred in 31%, 24%, and 14% of the patients in the 1 mg, 5 mg, and 15 mg tofacitinib

arms, respectively, compared to 21% in the placebo group. Similarly, the changes from baseline to week 4 in mean CDAI scores were similar in each of the groups. While there were no significant differences in clinical response or remission rates between tofacitinib and placebo, there were dose-related reductions from baseline to week 4 in the concentrations of CRP and fecal calprotectin, and the greatest changes were observed in the group receiving the highest dose (15 mg) of tofacitinib.³² While the clinical responses did not show compelling dose-dependent responses, the reduction in the objective inflammatory biomarker concentrations suggested that tofacitinib might have a biologic effect in CD.

The response and remission rates for CD at 4 weeks in the placebo arm were higher than anticipated for a short duration 4 week study, and higher than those reported in comparable trials with biologics.^{33, 34} High clinical response and remission rates in the placebo arm, together with the high rate of screening failure (41%), raise the possibility that patients may have been enrolled in the study on the basis of symptoms that were not related to active CD. The primary inclusion criteria relied upon CDAI scores, which do not always correlate with active inflammatory or endoscopic disease.³⁵⁻³⁷ Only 65% of the patients in the placebo arm had elevated CRP concentrations, and only 56% had elevated fecal calprotectin concentrations. These results were analogous to those from a 6-week induction trial of certolizumab pegol, in which the primary clinical endpoints were not met potentially due to high placebo response rates associated with a significant proportion of patients with a normal CRP concentration at baseline.³⁸

While the clinical endpoints were not met, the improvement in objective biomarker concentrations in the tofacitinib 15 mg group supports the possibility that there was a biologic effect in CD. With the knowledge gained from the first trial in CD, a Phase 2b tofacitinib induction (NCT01393626) trial in CD is ongoing. The study relies upon confirmation of active CD with endoscopy or radiography prior to enrollment with the goal of reducing high placebo response rates.³² However, it is also possible that differences in the pathogenesis between CD and UC account for the divergent clinical responses to tofacitinib, and perhaps a JAK inhibitor with different selectivity will be more efficacious in CD.

Safety and Tolerability Profile of Tofacitinib

The safety profile of tofacitinib has been primarily derived from the large phase 3 and extension trials of tofacitinib in RA, typically with dosages of 5 mg or 10 mg twice daily. A meta-analysis that included 8 randomized controlled studies of tofacitinib in RA reported no significant increase in serious adverse events. In terms of tolerability, there was no increase in adverse events leading to cessation of therapy during the first 3 months of treatment.³⁹ The cumulative safety data for tofacitinib was presented to FDA by Pfizer.⁴⁰ In a 12-month phase 3 randomized control trial including 792 patients with RA (NCT00856544), the incidence of adverse events and serious adverse events was highest in the placebo group, though not statistically significant.²⁹ The phase 2 studies in UC and CD were 4-week and 8-week studies, respectively, and were not powered for safety. In both studies, there were neither significant differences in adverse events, nor adverse events leading to medication discontinuation.^{31, 32} The most common adverse events were influenza and nasopharyngitis

in the UC patients, whereas nausea, vomiting, abdominal pain, and worsening of CD were the most common in CD patients.

Risk of Infection with Tofacitinib

Tofacitinib may be associated with an increase in risk of serious infections as predicted by its immune-modulating effects. The 6-month multi-national phase 3 trial of 611 patients with RA (NCT00814307) reported a higher incidence of serious infections with tofacitinib therapy as compared to placebo. The infections involved different organ systems and included cellulitis, liver abscess, bronchitis, and tuberculous pleural effusion.²⁸ In another large phase 3 RA study (NCT00856544), serious infections were more common in the first three months in the tofacitinib 10 mg arm and included two cases of pneumonia, diabetic foot infection, and bronchiectasis that affected 1.3% of the study group. In the tofacitinib 5 mg arm, there were two infections, including disseminated herpes zoster and bronchitis, with a rate of 0.6%. In contrast, there were no serious infections in the placebo group.²⁹ In the phase 2 UC trial that was not specifically powered for safety, there was an intra-abdominal post-operative and a peri-anal abscess reported in the tofacitinib 10 mg group.³¹ In the phase 2 CD study, there was a single vulvar abscess in the tofacitinib 5 mg group, and the remaining infections, including two anal abscesses, pneumonia, and sepsis, occurred in the placebo group.³² The most commonly reported infections, however, were influenza and nasopharyngitis, but the incidence did not appear to be significantly higher in tofacitinib groups.^{28, 29} In sum, based on the phase 3 RA studies, the incidence rate for serious infections was 1.5, 1.7, and 2.9 per 100 patient years for individuals on placebo, adalimumab, and tofacitinib, respectively, but with overlapping confidence intervals.⁴⁰ Thus, tofacitinib appears to potentially increase the risk of bacterial, fungal, and viral infections.

Opportunistic Infections

Though opportunistic infections have not been reported in the studies of tofacitinib and IBD, only limited numbers of patients have been studied for short durations of time and were not sufficient to draw conclusions; in patients with RA, tofacitinib has been associated with an increased risk of mycobacterial infections and viral reactivation. While one of the phase 3 trials of tofacitinib monotherapy in RA did not diagnose any opportunistic infections,²⁸ another phase 3 trial of tofacitinib in combination with disease-modifying anti-rheumatic drugs (DMARDs) for RA reported 4 opportunistic infections, including disseminated herpes zoster and cryptococcal pneumonia, and 2 cases of pulmonary tuberculosis (TB).²⁹ The pulmonary TB cases were diagnosed in endemic areas for TB, and the risk of TB in non-endemic countries is not entirely clear. To date, twelve cases of TB have been reported with tofacitinib, and they appear to be primary infections, as 11 of the 12 were negative for latent TB prior to the study, and there may be a dose-dependent risk.^{13, 40} Screening for TB and initiation of treatment for latent TB is therefore recommended prior to initiation of tofacitinib. While tofacitinib increases the risk of mycobacterial and viral infections, data from ongoing extension phase 4 studies with more patients will be crucial in providing further information regarding the magnitude of the risk for opportunistic infections.

Bone Marrow Suppression

Given the known role of JAK2 in mediating erythropoietin and GM-CSF signaling, JAK inhibitors have the potential to cause neutropenia, anemia, and thrombocytopenia. Tofacitinib has less potent inhibition of JAK2 that should reduce potential adverse effects on hematologic lineages. In the 4-week phase 2 CD study, there were no cases of leukopenia, nor absolute neutrophil counts (ANC) below 1×10^9 cells/L.³² However, in the 8-week phase 2 study in UC, the ANC dropped below 1.5×10^9 cells/L, but remained over 1×10^9 cells/L, in three patients on the higher doses of tofacitinib.³¹ In phase 3 RA studies, neutrophil counts declined modestly with tofacitinib monotherapy (both 5 mg and 10 mg), with more frequent neutropenia as compared with the placebo group; however, there did not appear to be an increase in infections as a consequence.²⁸ Similarly, tofacitinib used in combination with DMARDs reduced neutrophil concentration after 3 months, but there were no incremental reductions over the subsequent 9 months.²⁹

The risk of anemia due to disruption of erythropoietin signaling does not appear to be clinically significant with tofacitinib. In the summary safety data presented by Pfizer to the FDA, hemoglobin levels remained stable and even modestly increased as compared to baseline in patients with RA who were treated with tofacitinib.⁴⁰ Other JAK inhibitors with higher affinity for JAK2, in contrast, may have more significant effects on hematologic cell counts.

Lipid Abnormalities

Dose-related increases in low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) levels have been consistently observed in studies of tofacitinib in RA and IBD. In a large phase 3 RA study, after three months of therapy with 5 mg and 10 mg, LDL levels increased by 13.6 $\pm$ 1.6% and 19.1 $\pm$ 1.6%, respectively, and these abnormalities persisted at 6 months.²⁸ Concentrations appear to remain elevated during therapy, and reverse after cessation of the drug or with statin therapy.⁴¹ In the phase 2 UC study with 8 weeks of treatment, LDL concentrations increased by a mean of 2.97, 4.63, 9.36, and 11.81 in patients on 0.5 mg, 3 mg, 10 mg, and 15 mg tofacitinib, respectively, as compared to a reduction of 2.14 in the placebo group. HDL concentrations increased with similar magnitude, rising by 3.27, 5.35, 5.95, and 12.13 in patients on 0.5 mg, 3 mg, 10 mg, and 15 mg tofacitinib, respectively, as compared to 0.94 in placebo group.²⁸ The mechanism causing an increase in cholesterol is not entirely understood but may be related to interference with IL-6 signaling, as similar effects were observed in clinical trials of an IL-6 receptor antagonist tocilizumab.⁴² Ultimately, while tofacitinib increases LDL and HDL in a dose-dependent manner, the clinically relevant question is whether cholesterol derangements translate into increased cardiovascular events and mortality.

The phase 2 studies in IBD were not sufficiently powered to evaluate for infrequent cardiovascular events. In a large RA study of tofacitinib, there were three potential cardiovascular events, including a transient ischemic attack (5 mg), cerebrovascular accident (5 mg), and congestive heart failure with decompensation followed by death (10 mg).²⁹ In another large study in RA, two patients taking tofacitinib 10 mg with congestive heart

failure had acute exacerbations with one culminating in death.²⁸ In the summary data presented by Pfizer to the FDA, the rate of cardiovascular events in the phase 3 RA studies was not higher in the tofacitinib group as compared to placebo and adalimumab groups.⁴⁰ Larger safety trials are needed to determine the magnitude and significance of the risk for cardiovascular effects with tofacitinib.

Nephrotoxicity and Hepatotoxicity

Abnormalities in renal and liver function were rare events in the phase 3 studies of tofacitinib in RA; however, tofacitinib does not appear to cause serious hepatotoxicity or nephrotoxicity. In the large tofacitinib monotherapy study, there were no significant episodes of elevated aminotransferases, and there were only mild increases in creatinine with values within the normal range.²⁸ In the large study of tofacitinib in combination with DMARDs, 3 patients stopped the study drug as a result of elevations in aminotransferase levels, and 4 patients stopped the study drug as a result of a rise in creatinine.²⁹ Further studies are needed to characterize potential interactions between tofacitinib and other immune modulating medications, particularly as it may alter side effect profiles. It should be noted that to date there are no data on the combination of tofacitinib and azathioprine or 6-mercaptopurine.

Risk of Malignancy

While the potential risk for malignancy from tofacitinib therapy at this point is predominantly speculative, tofacitinib interferes with IFN signaling which is a central part of the tumor surveillance system that constantly works to prevent cancer. Based on data presented to the FDA by Pfizer, there may be a small increase in the incidence of malignancies. Of 4791 RA patients treated with tofacitinib, 65 were diagnosed with a malignancy, most commonly lung cancer, breast cancer, and lymphoma. However, the incidence rates for breast and lung cancer were similar to those reported in RA trials of TNF- α inhibitors or immune modulators. The risk for lymphoma was estimated at 0.07 per 100 patient years, resembling rates of lymphoma in RA with immune modulators and biologics.⁴⁰ Additional long-term safety data is needed to estimate the potential magnitude of effect on malignancy.

In summary, the side effect profile for tofacitinib appears to be similar to that of the current therapies for IBD with respect to infection and lymphoma (Table 3).

Future JAK Inhibitors in Inflammatory Bowel Disease

While tofacitinib is the only JAK inhibitor currently in clinical trials for IBD, there has been an explosion of JAK inhibitors with differing selectivity for the JAK family members that are being tested in RA and other autoimmune diseases. The new drugs have different specificities, changing the precise effects of the drug as well as the safety profiles (Table 4).

Ruxolitinib (Incyte) selectively inhibits JAK1 and JAK2, and was initially shown to be effective in the treatment of myelofibrosis.^{43, 44} Early clinical trials with ruxolitinib in RA showed a favorable safety profile and response rates comparable to that seen with tofacitinib

treatment. However, larger studies need to be completed in RA, and potentially other autoimmune diseases, to further evaluate its efficacy and safety.⁴⁵ Baricitinib (Lilly and Incyte), also known as INCB028050, is another selective JAK1 and JAK2 inhibitor that showed efficacy in early studies of RA patients who were refractory to existing treatments.⁴⁶ Clinical trials in RA and psoriasis are ongoing.⁴⁷ JAK1 and JAK2 inhibitors will likely have distinct safety profiles with higher rates of anemia and neutropenia, but potentially lower rates of serious infections.

GLPG0634 (AbbVie and Galapagos) primarily inhibits JAK1 with less effect on JAK2 and TYK2, and showed clinical efficacy in early phase 2 studies of RA. The side effect profile was particularly appealing, as there were no changes in cholesterol or hemoglobin concentrations; however, additional studies are needed to evaluate the clinical safety and efficacy.⁴⁸ Pre-clinical dextran-sulfate sodium models of colitis show that GLPG0634 effectively treats colitis in mice based on macroscopic indicators and histology.⁴⁹ A phase 2 study of GLPG0634 is being conducted to evaluate its efficacy in treatment of active CD.⁴⁷

Given the known effects of JAK3 deficiency in humans, JAK3 is an attractive target for immune modulating therapies. VX-509 (Vertex) is a JAK3 inhibitor that selectively blocks common γ -chain receptor signaling. Early phase 2 studies of VX-509 showed promising clinical responses in RA, and larger clinical trials are currently ongoing.⁵⁰ JNJ-54781532 (Janssen), also known as ASP015K (Astellas), selectively inhibits JAK1 and JAK3, offering effects similar to VX-509 and tofacitinib. JNJ-54781532 is being evaluated in the treatment of moderately to severely active UC in a phase 2b study.⁴⁷

As the number of unique JAK inhibitors expands, other small molecules are also emerging in parallel as alternatives to biologics. Specifically, GLPG0974 (Galapagos) is a free fatty acid receptor antagonist that blocks neutrophil activation and migration. Like other small molecules, GLPG0974 lacks immunogenicity and can be administered as an oral medication, representing an appealing therapy for patients with IBD. A phase 1 study in healthy controls showed a favorable safety profile, leading to a phase 2 clinical study to examine the efficacy of GLPG0974 in treating active mild-to-moderate UC.^{47, 51} Novel small molecules acting upon different pathways will continue to emerge as potential therapies for IBD.

Summary

JAK inhibitors are an emerging and promising treatment for IBD and autoimmune diseases. These drugs target small intracellular molecules responsible for transducing the signals by potent inflammatory cytokines that orchestrate the immune response. These medications can be administered through an oral route and are not immunogenic. Based on biological plausibility, extensive molecular studies, and now early studies in IBD, tofacitinib has a dose-dependent effect in UC, and potentially an effect in CD, with tolerable safety profiles. The optimal dosing and specificity of JAK inhibitors, however, will require additional studies in order to optimize the balance of effects on the immune system with side effects.

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Key Points

- Janus kinase (JAK) inhibitors are a novel small molecule therapy that will likely become a new medical treatment for inflammatory bowel disease.
- JAK inhibitors target small intracellular molecules responsible for transducing signals from inflammatory cytokines believed to be involved in the pathogenesis of inflammatory bowel disease.
- 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's 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 the current therapies for inflammatory bowel disease.
- Multiple JAK inhibitors with different specificities and side effect profiles are being studied in the treatment of inflammatory bowel disease.

Figure 1.

JAK signaling pathways related to inflammatory bowel disease and therapeutic targets of JAKINIBs.

Upon cytokine binding to its receptor, a JAK phosphorylates its associated cytokine receptor and creates a docking site for STAT signaling molecules. The JAK then phosphorylates STAT proteins to facilitate STAT dimerization, followed by their translocation to the nucleus and activation of downstream target genes.

Note: For simplicity, some non-essential JAK family members have been omitted.

Table 1
Cytokine-JAK Signaling Pathway Molecular Associations

Cytokine-JAK Signaling pathway				
Type	Cytokine Common Chain	Cytokines	JAK Signaling Molecules	STAT Signaling Molecules
Type I	γ - chain	IL-2, IL-7, IL-9, IL-15 IL-4	JAK1, JAK3	STAT5 STAT6
	β -chain	GM-CSF, IL-3, IL-5	JAK2	STAT5
	gp130	IL-6, IL-11	JAK1, JAK2, TYK2	STAT3
		IL-12	JAK2, TYK2	STAT4
	other	GH, Epo, PRL, TPO	JAK2	STAT5
Type II		IFN- α , IFN- β	JAK1, TYK2	STAT1, STAT2
		IFN- γ	JAK1, JAK2	STAT1
		IL-10	JAK1, Tyk2	STAT3

JAK, Janus kinase; STAT, signaling transducer and activator of transcription; IL, interleukin; GM-CSF, granulocyte monocyte colony stimulating factor; TYK, tyrosine kinase; GH, growth hormone; Epo, erythropoietin; PRL, prolactin; TPO, thrombopoietin.

Table 2
JAK Family Association with Receptors

Receptor	Associated JAK Family Member			
	JAK1	JAK2	JAK3	TYK2
IL-2 Receptor	+	–	+	–
IFN- γ Receptor	+	+	–	–
IFN- α Receptor	+	–	–	+
IL-12 Receptor	–	+	–	+
IL-23 Receptor	–	+	–	+
IL-6 Receptor	+	+	–	+
Epo Receptor	–	+	–	–

JAK, Janus kinase; TYK, tyrosine kinase; IL, interleukin; IFN, interferon; Epo, erythropoietin.

Table 3
Summary of Adverse Events with Tofacitinib

Major Adverse Effect	Mechanism	Incidence rate [*]	Dose Dependence	Observed in IBD Trials?
Serious Infection	Blocks cytokine signals via γ -chain	3.00	No	Yes
Malignancy [^]	Blocks IFN- γ signaling and NK cell proliferation	0.94	Yes	No
Lymphoma	Blocks IFN- γ signaling and NK cell proliferation	0.07	Yes	No
Major Cardiovascular Event ⁺	Unclear, possibly related to lipid changes	0.57	No	No

IBD, inflammatory bowel disease; IFN, interferon; NK, natural killer.

^{*} Incidence rate per 100 patient-years

[^] Malignancy includes lymphoma and solid tumors but excludes non-melanoma skin cancer

⁺ Major cardiovascular events as measured in all of the phase 3 clinical trials Incidence ratio was calculated based on Pfizer's report on tofacitinib to the FDA based on all phase 2, 3, and long term extension studies in RA, except for the major cardiovascular events

Table 4
Novel Small Molecule Inhibitors in Clinical Trials

Drug	Primary Inhibition	Populations Studied
Tofacitinib	JAK1 & JAK3 > JAK2	RA, UC, CD
Ruxolitinib (Incyte)	JAK 1 & JAK2	RA, Psoriasis
Baricitinib (INCB028050)	JAK1 & JAK2	RA, Psoriasis *
GLPG0634	JAK1 > JAK2 & TYK2	RA, CD *
GLPG0974	Free fatty acid receptor	UC *
VX-509	JAK3 inhibitor	RA
JNJ-54781532	JAK1 & JAK3	UC *

JAK, Janus kinase; RA, rheumatoid arthritis; UC, ulcerative colitis; CD, Crohn's disease; TYK, tyrosine kinase.

* Indicates an ongoing clinical study