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JAK Inhibitors for the Treatment of Inflammatory Bowel Disease

Introduction

Over the past decade, Janus kinase (JAK) inhibitors have been developed for the treatment of several immune-mediated inflammatory diseases, including ulcerative colitis (UC) and Crohn's disease (CD). The JAK-signal transducer and activator of transcription (STAT) pathway plays an essential role in coordinating the human immune response. Phosphorylation and activation of the JAK family of tyrosine kinases results in subsequent activation of intracytoplasmic STAT pathways with upregulation of inflammatory gene transcription.[1] Blocking this signalling results in broad-spectrum immunosuppression, which is effective in the treatment of rheumatoid arthritis (RA), psoriasis, atopic dermatitis, and inflammatory bowel disease (IBD).[2, 3] To date, three oral, small-molecule JAK inhibitors (tofacitinib, filgotinib, and upadacitinib) have received regulatory approval in various jurisdictions globally for the treatment of moderate-to-severely active UC. It is anticipated that upadacitinib will soon become the first novel, advanced oral small molecule therapy approved for moderate-to-severely active CD. While these agents are highly effective, emerging data has highlighted potentially relevant safety signals associated with JAK inhibitors, and that the therapeutic index of these therapies may be distinct from that of monoclonal antibodies. Therefore, JAK inhibitors have a unique position in the therapeutic armamentarium for IBD. Here, we summarize the evidence supporting the use of JAK inhibitors and provide an overview of their practical applications in clinical care.

Evidence Supporting the Efficacy of JAK Inhibitors in IBD

Tofacitinib for UC

Tofacitinib is a pan-JAK inhibitor with preferential affinity for JAK1/JAK3.[4] The efficacy of tofacitinib was demonstrated in the phase 3 OCTAVE program, which included two induction trials (OCTAVE-1 and 2) randomizing 1,139 patients with moderate-to-severely active UC to tofacitinib 10 mg twice daily or placebo for 8 weeks.[5] A total of 593 responders

in induction were subsequently re-randomized to tofacitinib 5 mg or 10 mg twice daily or placebo in the 52-week OCTAVE-Sustain maintenance trial. At week 8, a significantly higher proportion of patients receiving tofacitinib achieved clinical remission (16.6%-18.5% vs 3.6%-8.2%); this difference was observed in both patients who were biologic-naïve and those previously failing tumor necrosis factor (TNF) antagonist(s).[6] At 52 weeks, patients receiving either tofacitinib 5 mg (34.3%) or 10 mg (40.6%) were significantly more likely to be in clinical remission compared to placebo (11.1%, p<0.001 for both comparisons). In a post-hoc analysis, differences in mean stool frequency and rectal bleeding were detectable by day 3 of therapy.[7] Several real-world cohorts evaluating the efficacy of tofacitinib have also been conducted: in a meta-analysis of 17 studies including 1,162 UC patients treated with tofacitinib, Taxonera et al showed that half of patients achieved clinical remission at Week 12-16, and 38.3% were in clinical remission by month 6.[8] Recently, we reported the world's largest real-world experience with tofacitinib to date in the REMIT-UC multicenter Canadian IBD Research Consortium study, which included 334 UC patients who were predominantly biologic-refractory.[9] Tofacitinib induced endoscopic remission, defined as a Mayo endoscopic subscore of 0 or 1, in 18.5%, 23.0% and 25.7% of patients at Weeks 12, 24 and 52, respectively.

Upadacitinib for UC

Upadacitinib is an oral, JAK1 selective small molecule that was evaluated for the treatment of moderate-to-severely active UC in the phase 3 U-ACHIEVE (n=474) and U-ACCOMPLISH (n=522) trials.[10] These 8-week induction studies randomized patients 2:1 to upadacitinib 45 mg daily or placebo. Half of patients had previously failed a biologic therapy and nearly 70% had severe endoscopic disease activity at enrollment. At week 8, 26%-33% of patients treated with upadacitinib achieved clinical remission, compared to 4%-5% of patients receiving placebo (adjusted treatment difference 21.6%-29.0%, p<0.0001 in both trials). All secondary endpoints significantly favoured upadacitinib, including resolution of bowel urgency, endoscopic remission and mucosal healing (combined endoscopic and histologic remission). A post-hoc analysis demonstrated that statistically significant improvements in all UC symptoms were achieved between day 1 and 3 of therapy.[11] A total of 451 responders to upadacitinib induction were subsequently re-randomized to upadacitinib 15 mg, 30 mg or placebo in a 52-week maintenance trial. Both doses of upadacitinib were significantly more effective than placebo for maintenance of clinical remission (adjusted treatment difference 30.7%-39.0%, p<0.0001), and for all secondary endpoints, including endoscopy and histopathology.

Upadacitinib for Crohn's Disease

Upadacitinib was evaluated in moderate-to-severely active CD in the 12-week, phase 3, placebo-controlled U-EXCEED (N=495) and U-EXCEL (N=526) trials.[12] These studies enrolled a highly refractory treatment population: approximately one-third of patients had failed at least 3 biologic therapies prior to enrollment. Furthermore, these trials were the first in CD to force a mandatory corticosteroid taper during induction, starting 4 weeks after the first dose of upadacitinib or placebo. Upadacitinib was significantly more effective than placebo for achieving the co-primary endpoints of clinical remission (adjusted treatment difference 25.9%-28.7%, p<0.0001) and endoscopic response (treatment difference 31.2%-33.0%, p<0.0001) at week 12. At Week 12, adjusted treatment differences of 30.2%-32.6% (p<0.0001) were observed favoring upadacitinib over placebo for achieving corticosteroid-free clinical remission. Both 15 mg and 30 mg upadacitinib were more effective than placebo for maintaining clinical remission and endoscopic response at week 52 in the maintenance U-ENDURE trial. At one year, 28.6% of patients treated with upadacitinib were in endoscopic remission (defined by a Simple Endoscopic Score for CD ≤4, at least 2-point reduction compared to baseline, and with no subscore >1), compared to only 5.5% of patients treated with placebo (p<0.0001); one-quarter of upadacitinib-treated patients achieved complete ulcer-free remission.

What Evidence Supports the Safety of JAK Inhibitors?

Although JAK inhibitors have demonstrated a high degree of efficacy, their safety profile has come under scrutiny. This was underscored by results from the ORAL Surveillance trial.[13] ORAL Surveillance was a U.S. Food and Drug Administration (FDA)-mandated post-authorization, open-label, non-inferiority study. Patients ≥50 years old with RA, with at least one established cardiovascular disease (CVD) risk factor, were randomized to tofacitinib or a TNF inhibitor, in combination with methotrexate. The incidence of the coprimary endpoints, major adverse cardiovascular events (MACE) and cancer (excluding non-melanoma skin cancer), was higher in patients receiving tofacitinib compared to that of TNF antagonists (3.4% vs 2.5% and 4.2% vs 2.9%, respectively), and there were increased incidences of herpes zoster

(HZ), infections and serious infections, and venous thromboembolism (VTE). This prompted the FDA to issue a black box warning, which applied not only to tofacitinib, but to other JAK inhibitors as a class, as well, and to limit their use to patients who had failed a TNF antagonist. In contrast, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee has recommended that JAK inhibitors be considered only if no suitable treatment alternatives are available in patients ≥65 years, current or past long-time smokers, and those with either CVD or malignancy risk factors. Health Canada has issued a public advisory that all JAK inhibitor labels will include warnings around the risks of serious cardiac complications, thrombosis, and malignancy, but both the EMA and Health Canada permit the use of JAK inhibitors as first-line therapy.

Whether the risks observed in ORAL Surveillance are generalizable to patients with IBD is unclear. There was effect modification by age and smoking status, and most IBD patients would not have met the high-risk eligibility criteria used in ORAL Surveillance. Safety data from tofacitinib- and upadacitinib-treated patients with UC is more reassuring. In an analysis of 7.8 years of tofacitinib exposure in UC patients, Sandborn et al did identify an increased risk of HZ (in patients who, generally, had not been vaccinated against zoster), but comparable rates of malignancy, MACE, and VTE compared to other biologics.[14] In an integrated safety analysis of >2,400 patient-years of tofacitinib exposure in UC, only five cases of VTE were reported (all in patients with other VTE-related risk factors), and four UC patients developed a VTE while receiving placebo.[15] Long-term safety results in IBD patients treated with upadacitinib are still needed. While rare cases of infections and serious infections have been reported with upadacitinib, the overall risk of serious adverse events was lower in trial patients receiving upadacitinib compared to placebo, likely reflecting better IBD control. An integrated safety analysis of RA trials did not demonstrate a significantly increased risk of serious or opportunistic infections (excluding HZ), malignancy, MACE, or VTE with upadacitinib compared to adalimumab.[16]

How Should JAK Inhibitors be Used in Clinical Practice?

JAK inhibitors are highly potent therapies for patients with moderate-to-severely active IBD. The primary advantage of this class is its efficacy: multiple network meta-analyses have found JAK inhibitors to be one of the most likely therapies to achieve remission in patients with UC and CD, particularly after previous biologic failure.[17-19] Additional advantages include convenient oral administration, lack of immunogenicity, short half-life with rapid onset, and coverage of certain extraintestinal manifestations (EIMs). However, safety concerns noted with this class of therapy should be balanced against its potential benefits.

In deciding which patients should be considered for a JAK inhibitor in the clinic, in those patients who have failed their first biologic, JAK inhibitors should be considered. The second-line treatment choice is a critical point in a patient's disease journey because efficacy rates are lower at that point and, given the potential consequences of uncontrolled inflammation (i.e., risk of colectomy, surgery or progressive mechanical complications such as strictures/fistula), the risk-benefit ratio heavily favours using the most effective second-line agent next. Some patients may be considered for a JAK inhibitor first-line. This includes: those with advanced endoscopic findings (e.g., severe pancolitis or deep extensive ulcerations); who strongly favour an oral advanced therapy; cannot tolerate or previously experienced corticosteroid-related adverse events; who are highly symptomatic and require immediate relief; or who have EIMs such as enteropathic arthritis, are likely to benefit from a JAK inhibitor. In contrast, patients over the age of 65, patients who are heavily comorbid, have a strong smoking history, or have pre-existing or uncontrolled risk factors for CVD, should also explore therapeutic alternatives.

Recognizing that there have been safety signals associated with JAK inhibitor use, risk mitigation strategies should be considered for all patients (**Table 1**). This includes pre-treatment testing for latent tuberculosis and hepatitis B; detailed medication review for potential drug-drug interactions; patient counselling on smoking cessation; ensuring up-to-date vaccinations for HZ and pneumococcus; evaluating the baseline lipid profile and CVD risk; and discussing contraception in women of child-bearing potential. Estrogen-containing oral contraceptives have been associated with an increased risk of VTE; therefore, progestin-only or other options (e.g., intrauterine device) should be considered. Two-dose, non-live recombinant zoster vaccination (Shingrix® [Mississauga, ON]) should be administered, with the first dose given either before or near the time of induction therapy. Tools such as the Framingham Risk Score or the atherosclerotic cardiovascular disease (ASCVD) Risk Estimator can be considered. In addition, efforts to control metabolic syndrome risk factors such as dyslipidemia, hypertension, obesity, and diabetes may mitigate long-term CVD risk.

Risk/Benefit Scenario	Potential Strategies
Pre-therapy	• Medical history, physical examination, IBD investigations: define IBD phenotype, disease activity and medical profile • Latent tuberculosis screening (quantiferon or tuberculin skin test) • Hepatitis B screening (HBsAg, anti-HBs, anti-HBc [total]) • Medication review for potential drug-drug interactions
Infection Risk	• Herpes zoster vaccination (Shingrix, inactivated recombinant vaccination, first dose before or near first induction dose) • Pneumococcal vaccination • Minimize corticosteroid use, if possible
Cardiovascular Disease Risk	• Evaluate and optimize CVD risk factors (diabetes, hypertension, dyslipidemia) • Consider using formalized risk tool to assess risk (e.g., Framingham Risk Score, American College of Cardiology ASCVD Risk Tool) • Counsel on smoking cessation as appropriate; consider nicotine replacement, pharmacologic therapy for smoking cessation
Malignancy Risk	• Up-to-date age-appropriate cancer screening (e.g., Pap smear, mammogram, colonoscopy, skin examination as appropriate)
Teratogenicity Risk	• Ask about family planning • Counsel on contraceptive options: progestin-only or non-estrogen- containing oral contraception alternatives
Thrombosis Risk	• Ask about thromboembolic risk factors (including personal and family history of VTE)
Post-therapy Monitoring	• Complete blood count and liver enzymes every 3 months • C-reactive protein and fecal calprotectin every 3-6 months • Lipid profile and renal function every 6-12 months • Colonoscopy 6-12 months after induction to evaluate mucosal response to treatment

Table 1. *Practical considerations for starting and monitoring JAK inhibitor therapy in clinical practice; courtesy of Dr Christopher Ma, MD*

After initiating a JAK inhibitor, I generally follow a treat-to-target approach, as endorsed by the Selecting Therapeutic Targets in Inflammatory Bowel Disease-II (STRIDE-II) guidelines.[20] This includes achievement of early symptom improvement, normalization of stool and serum biomarkers and, ultimately, targeting endoscopic normalization. Bloodwork including complete blood count (for cytopenias), C-reactive protein (for subclinical inflammation), and liver enzymes (for potential hepatotoxicity) are monitored every 3 months. Serum lipids are initially assessed within the first 3 months and then, along with renal function, are checked every 6-12 months. I generally do not monitor the creatine phosphokinase (CK): asymptomatic elevations in CK are common but should be checked in patients with myalgia or substantial muscle weakness. Finally, I discuss with the patient dose de-escalation after induction. The efficacy and safety of JAK inhibitors are partially dose-dependent. Although de-escalation (to 5 mg BID tofacitinib or 15 mg daily upadacitinib) has been demonstrated to be potentially effective, up to 20% of patients may lose response.[21] Therefore, I counsel high-risk patients (those with prior biologic failure, no other medical treatment options or severe endoscopic disease activity) on the risks and benefits of continuing on higher-dose maintenance therapy, and confirm clinical, biomarker and endoscopic remission prior to considering stepping down therapy.

Conclusion

JAK inhibitors are highly effective therapies for moderate-to-severely active IBD. They play an important role in achieving both symptomatic and objectively-defined remission, particularly in patients with difficult-to-treat disease. Ongoing trials will define the role of JAK inhibitors for specific phenotypes of patients, including those with postoperative CD, perianal fistulizing CD, or acute severe UC in hospital. While some safety signals have been observed, the majority of patients can be safely treated with a JAK inhibitor, and this class of therapy should be considered an integral part of every gastroenterologist's armamentarium when treating IBD.

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Financial Disclosures:

CM has received consulting fees from AbbVie, Alimentiv, Amgen, AVIR Pharma Inc., BioJAMP, Bristol Myers Squibb, Celltrion, Ferring, Fresenius Kabi, Janssen, McKesson, Mylan, Pendopharm, Pfizer, Prometheus Biosciences Inc., Roche, Sanofi, Takeda, Tillotts Pharma; speaker's fees from AbbVie, Amgen, AVIR Pharma Inc, Alimentiv, Bristol Myers Squibb, Ferring, Fresenius Kabi, Janssen, Organon, Pendopharm, Pfizer, Takeda; royalties from Springer Publishing; research support from Ferring, Pfizer.

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