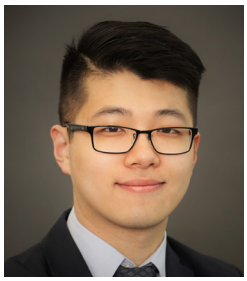
About the Author



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What the Rheumatologist Needs to Know about IBD Treatment

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The Intersection of Immune-mediated Inflammatory Diseases

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), affect almost 1% of the Canadian population and are characterized by debilitating gastrointestinal (GI) symptoms including chronic diarrhea, rectal bleeding and abdominal pain.[1] Beyond involvement of the GI tract, up to half of patients with IBD will also experience extraintestinal manifestations (EIMs) or be diagnosed with comorbid immune-mediated inflammatory diseases (IMIDs), which are associated with substantial morbidity and impaired quality of life.[2,3] The most common of these are inflammatory joint diseases, including peripheral and axial spondyloarthritis or concomitant rheumatoid (RA) or psoriatic arthritis (PsA), affecting up to 1 in 5 patients with IBD.[4,5]

Inflammatory joint and bowel diseases share many pathophysiological similarities: both the joints and the gut mucosa represent the interface required to maintain tissue homeostasis and are under constant exposure to mechanical, microbial and chemical forces.[6,7] The pathogenesis of inflammatory arthritis and IBD are both characterized by genetic susceptibility with shared risk loci, triggered by environmental exposures that result in aberrant immune activation with complex downstream cytokine and regulatory cell signaling, culminating in progressive end-organ joint or gut damage. Given these similarities, there has been a recent emphasis on classifying IMIDs not based on anatomical organ involvement, but rather, by shared signature molecular cytokine hubs, which better characterize the mechanistic underpinnings of these conditions.[8]

Over the past 20 years, tremendous progress has been made in the medical management of moderate-to-severe IBD. In 2024, multiple classes of both monoclonal biologic therapies as well as novel small molecule immunosuppressants have been approved for the treatment of CD and UC. This includes biologics targeting common effector pathways and inflammatory cytokines such as tumor necrosis factor (TNF)-α, Janus kinases (JAKs) and interleukin (IL)-23.[9] Notably, many, if not most, of the therapeutic options and treatment strategies that have shaped IBD care have been "borrowed" from rheumatology. For example,

promising molecular targets generally have demonstrated efficacy in inflammatory skin or joint diseases before clinical development for CD or UC. Many therapeutic strategies in rheumatology have been adopted in IBD, including a "treat-to-target" approach which is now the standard of care in 2024.[10] This concept of optimizing or changing therapy for patients who have not achieved their therapeutic goals was pioneered by rheumatologists and was only recently adopted by gastroenterologists.

Recognizing the growing therapeutic armamentarium that may have efficacy for joint, skin and gut manifestations, this review will summarize the state-of-the-art evidence supporting medical therapies for this complex patient population and provide practical considerations for these often difficult treatment decisions. Surgical treatment decisions will not be reviewed here, recognizing that although surgery plays an important role in managing IBD, its place in managing other immune-mediated inflammatory disorders is limited.

Tumor Necrosis Factor Antagonists: Do they Still Play a Role?

TNFα is a common downstream effector pathway for many IMIDs and was the first advanced therapeutic target approved for the treatment of moderate-to-severely active CD and UC.[11,12] Inhibiting this master cytokine has proved to be highly effective in almost all major forms of inflammatory arthritis. For gastroenterologists, TNF antagonism was the only advanced mechanism of action available until the mid-2010s and accordingly, there was substantial interest in understanding how TNF antagonists could be optimized for IBD care. Several observations are worth noting. First, TNF antagonists remain the preferred first-line treatment option for many forms of IBD. Despite an increasing armamentarium of therapeutic options, infliximab remains the only therapy with robust data to support its use as a rescue agent in acute, severe UC and has been demonstrated to reduce the short-term likelihood of colectomy among hospitalized patients.[13] Infliximab is also the only molecule currently with randomized controlled trial (RCT)-level evidence to support its use in perianal fistulizing CD.[14,15] Second, the immunogenicity of TNF antagonists remains a clinical challenge. In the United Kingdom PANTS study, 62.8% of infliximab-treated and 28.5% of adalimumab-treated patients developed anti-drug antibodies.[16] To ameliorate this risk, the combination of infliximab and azathioprine has been demonstrated to improve clinical, corticosteroid-free and endoscopic remission in CD and UC, compared to infliximab monotherapy.[17,18] Third, there has been substantial investigation evaluating whether monitoring of serum anti-TNF concentrations can be used to improve treatment outcomes.[19] To date, monitoring drug levels and proactively adjusting treatment dosing based on these drug concentrations has not proven more effective in adult patients with IBD. However, reactive testing of therapeutic drug monitoring in patients who lose response can help delineate mechanisms of drug failure and guide future decision-making.[20]

Given their efficacy in both joint and gut diseases, as well as a long track record of clinical efficacy and safety, should TNF antagonists remain the "go-to" therapy for patients with IBD and concomitant IMIDs? TNF antagonists have flexibility in the route of administration and dosing, as well as broad anti-inflammatory effects and consequently, dynamic efficacy across many different phenotypes of IBD, as well as for several IMIDs, including ocular, dermatologic and rheumatologic indications. However, several drawbacks should also be considered. First, TNF antagonists may not be the most effective treatment for some patients with IBD: for example, vedolizumab is superior to adalimumab for achieving clinical, endoscopic and histologic outcomes in UC.[21] Second, TNF antagonists have been associated with an increased risk of serious infections and some malignancies, including melanoma.[22,23] Third, the optimal strategy for using TNF antagonists involves concomitant immunosuppression with azathioprine or methotrexate, which may be beneficial for joint-related EIMs but also increase the risk profile of therapy, particularly for older adults.[24] Fourth, TNF antagonist dosing in IBD is generally higher than for rheumatologic indications, and not all TNF antagonists used for rheumatologic diseases are effective for IBD: for example, golimumab is not approved in CD, etanercept is not effective in either CD or UC, and certolizumab is not approved for IBD management in Canada. Therefore, although TNF antagonists remain a principal therapeutic option in patients with EIMs or IMIDs, other treatment options that are effective across multiple disease states also warrant consideration **(Table 1)**.

Mechanism of Action	Treatment Options	IBD Approvals	Approved for other IMIDs
TNF antagonists	Infliximab Adalimumab Golimumab	CD/UC CD/UC UC	Yes
Anti-integrin	Vedolizumab	CD/UC	No
Anti-IL12/23p40	Ustekinumab	CD/UC	Yes
Anti-IL23p19	Risankizumab Mirikizumab	CD UC	Yes
Janus kinase inhibitors	Tofacitinib Upadacitinib	UC CD/UC	Yes
S1P receptor modulators	Ozanimod Etrasimod	UC UC	No

Table 1. Therapeutic options approved for the treatment of IBD in Canada; courtesy of Christopher Ma, MD, MPH, FRCPC
Abbreviations: CD Crohn's disease; IL interleukin; IMID immune mediated inflammatory disease; S1P sphingosine 1 phosphate; TNF tumor necrosis factor; UC ulcerative colitis

JAK Inhibitors: Potent Immunosuppression but at What Cost?

In 2018, tofacitinib was approved in Canada for the treatment of moderate-to-severe UC.[25] This marked an important moment in the landscape of IBD therapeutics, representing the first non-biologic, oral advanced therapy available for treatment. In the past two years, upadacitinib, a reversible JAK-1 selective inhibitor, has also been approved for both UC and CD, with 8-12 weeks of high-dose induction dosing (45 mg daily) and then with maintenance dosing with either 15 mg or 30 mg daily.[26,27] Upadacitinib is currently the only oral advanced therapy that has demonstrated efficacy in CD; tofacitinib is not approved in CD.

Overall, the efficacy profile of JAK inhibitors offers substantial promise for IBD care. Although no direct treatment comparisons are available, multiple network meta-analyses have found that upadacitinib is likely to be the single most efficacious therapy for achieving clinical and endoscopic remission in patients with moderate-to-severely active UC.[28-30] In the registrational trial program, upadacitinib was demonstrated to be superior to placebo for inducing and maintaining clinical, endoscopic and histologic endpoints at Weeks 8 and 52, and importantly, this was observed in both patients naïve to other advanced therapies and in highly refractory patients who had failed multiple prior biologics.[26] Early treatment response was observed: statistically significant improvements in patient-reported outcomes compared to placebo were observed even within 24 hours of treatment.[31,32]

In two Phase 3 induction trials (U-EXCEL and U-EXCEED), participants with moderate-to-severe CD treated with upadacitinib 45 mg daily for 12 weeks were more likely to achieve clinical remission and endoscopic response (defined by at least a 50% reduction in endoscopic disease severity).[27] These induction trials were also the first IBD trials to require mandatory corticosteroid tapering during induction, and a significantly greater proportion of patients treated with upadacitinib achieved corticosteroid-free remission at Week 12 and Week 52 compared to placebo. A post-hoc analysis suggests that upadacitinib is effective for reducing the burden of perianal fistulizing CD, and in patients with active baseline EIMs, treatment with upadacitinib has been demonstrated to

reduce the proportion of patients with active joint symptoms (43.5%-54.8% among patients receiving upadacitinib compared to 20.0% of patients receiving placebo at Week 52).[33,34]
Beyond the efficacy signal, the other advantages of oral advanced therapy in CD should be highlighted. These agents can be initiated quickly without the need for concomitant corticosteroid induction; maintenance dosing is flexible (15 mg and 30 mg for upadacitinib); there is no risk of immunogenicity; the short half-life is favourable for holding treatment if required; and upadacitinib is effective across multiple IMIDs, including RA, PsA, axial spondyloarthritis, and atopic dermatitis.[35]

The broad efficacy signal in IBD has been somewhat tempered by concerns about the safety of this class of treatment. In patients with RA over age 50 with established cardiovascular risk factors, the ORAL Surveillance trial emphasized the potential risks of tofacitinib concerning major adverse cardiovascular events (MACE), malignancy, venous thromboembolism (VTE), herpes zoster (HZ), and other serious and opportunistic infections.[36] Whether these concerns are generalizable to patients with IBD is less clear. For example, in over 9.5 years of follow-up data from the tofacitinib UC trials, a similar signal for VTE or malignancy has not been demonstrated.[37] While the signal for HZ was observed in IBD trials of tofacitinib, filgotinib (not licensed in Canada), and upadacitinib, <5% of trial participants were vaccinated, and observational Canadian data suggests that the risk of HZ is much lower in real-world experiences where >80% of patients have received HZ vaccination before induction therapy.[38] JAK inhibitor safety has now undergone formal regulatory review with multiple agencies, including the US FDA, the European Medicines Agency and Health Canada. While there are risks associated with this class of treatment, they remain an especially potent therapeutic option in IBD, particularly for patients with severe or extensive disease and those with prior biologic treatment failure.

Targeting IL23p19: Superior to IL12/23p40?

There has been substantial investment in the development of IL23p19-specific antagonists for treatment of IBD, given observations that p19 inhibition was significantly better than IL12/23p40 blockade in patients with psoriasis.[39] The past two years have seen the approvals of two p19 antagonists, risankizumab and mirikizumab for moderate-to-severe CD and UC, respectively.[40-42]

Do these agents represent a significant advance compared to previously available therapies for IBD? In CD, the efficacy and safety of risankizumab was demonstrated in the Phase 3 ADVANCE, MOTIVATE and FORTIFY trials.[40,41] These were the first RCTs in CD to measure endoscopic response as a coprimary endpoint, both after induction at Week 12 and among induction responders at Week 52. The proportion of participants who achieved and sustained endoscopic response was significantly higher than that of participants receiving placebo, and this observation was confirmed in both treatment-naïve and treatment-experienced patients. For many gastroenterologists, the more relevant clinical question was whether risankizumab would be superior to ustekinumab, an established IL12/23p40 antagonist that has proven efficacy in both CD and UC.[43,44] This question was evaluated in the Phase 3 SEQUENCE trial, an open-label, head-to-head comparator trial in patients with moderate-to-severe CD, all of whom had failed a prior TNF antagonist.[45]
A total of 520 patients were randomized. At Week 24, 58.6% (75/128) of participants receiving risankizumab vs 39.5% (54/137) of participants receiving ustekinumab were in clinical remission. At Week 48, risankizumab demonstrated superiority over ustekinumab for achieving endoscopic remission (31.8% vs. 16.2%, P<0.001). Risankizumab was also superior to ustekinumab for achieving Week 48 clinical remission, steroid-free endoscopic and clinical remission, and Week 24 endoscopic response. Currently, two other IL23p19 antagonists (guselkumab, mirikizumab) are in late-stage clinical development for CD; both registrational trials have internal comparison arms to ustekinumab.

Results in UC with p19 antagonism are also significant, albeit less dramatically superior to existing treatment options when compared to CD. In the Phase 3 LUCENT trial, a significantly higher proportion of participants with moderate-to-severely active UC treated with mirikizumab achieved clinical remission (treatment difference 11.1%, P<0.001), clinical response (Δ21.4%, P<0.001), endoscopic remission (Δ15.4%, P<0.001), and histologic-endoscopic mucosal improvement (Δ13.4%, P<0.001).[42] Positive results for guselkumab and risankizumab in UC have also recently been reported.[46]

Antagonism of IL23p19 has several advantages. First, the safety profile of this class of therapy is supported across multiple indications. Second, these agents are highly effective for some IMIDs, particularly in psoriasis where this class of therapy induces and maintains complete skin clearance.[47] Both risankizumab and guselkumab have also been demonstrated to be effective for the treatment of psoriatic arthritis.[48,49] Third, these agents are effective in both CD and UC, and effectively achieve endoscopic endpoints that represent the long-term treatment target in IBD. However, it should also be considered that p19 antagonism is not an effective mechanism for patients with axial spondyloarthritis and is not approved for rheumatoid arthritis.[8]

Gut-selective Mechanisms in Patients with IMIDs

Vedolizumab is a gut-selective α4β7 integrin antagonist approved for the treatment of both moderate-to-severe CD and UC.[50,51] The unique mechanism of vedolizumab interrupts the trafficking of gut-targeted lymphocytes by blocking the interaction between integrin receptors and the mucosal addressin cell-adhesion molecule (MAdCAM)-1 on gut endothelium. This mechanism has specific advantages for the IBD population. First, targeting a critical component of IBD pathophysiology is associated with substantial efficacy, particularly in patients with early CD and UC. In a head-to-head clinical trial vedolizumab was shown to be more effective than adalimumab for inducing and maintaining clinical, endoscopic and histologic remission in UC.[21] Vedolizumab is also effective in subgroups of patients with IBD, including those with perianal CD and chronic antibiotic-resistant pouchitis.[52,53] This efficacy has been paired with a remarkable safety profile. Patients treated with vedolizumab are generally not considered to be systemically immunosuppressed because of the mechanism of action, and in long-term follow-up there has not been a signal for infection or malignancy.[54]

One obvious potential downside to the use of vedolizumab as a gut-selective therapy is that it may not be effective for patients with other IMIDs or EIMs. However, this is quite controversial. In a post-hoc analysis of the registrational GEMINI vedolizumab program, Feagan et al showed that vedolizumab was associated with a reduced likelihood of new or worsening joint symptoms in CD patients. This finding has been corroborated in several observational cohorts, where up to half of patients with IBD-related arthralgia experienced improvement with vedolizumab treatment.[55,56] It is hypothesized that this may relate to reduction in luminal inflammation with subsequent control of EIMs that are linked to active IBD.

Should vedolizumab be avoided in patients with EIMs? This is a challenging clinical scenario. Given its safety profile, vedolizumab remains an important therapeutic option in IBD, especially in elderly or comorbid patients. It is often a preferred treatment option for patients given that it can be administered subcutaneously or intravenously and is gut selective. While generally not a first-line choice for patients with concomitant EIMs, many patients may still choose vedolizumab in this setting and in these situations. It is worth evaluating both gut and joint activity after at least 3-6 months of treatment. In some cases, combination therapy with another immunosuppressant may be required if luminal control is achieved but there remain active IMIDs or EIMs. There has also been increasing interest in using combination treatment approaches, including dual biologic or advanced therapies.[57] These scenarios often use vedolizumab as an "anchoring" therapy given its favourable safety, although the long-term cost-effectiveness and sustainability of such a strategy requires further assessment.

Finally, two additional oral small molecule sphingosine-1-phosphate receptor modulators, ozanimod and etrasimod, have been approved for the treatment of UC.[58,59] These agents interrupt lymphocyte trafficking by blocking the egress of activated lymphocytes out of lymph nodes. Etrasimod is currently under development for the treatment of atopic dermatitis but its efficacy for other non-GI inflammatory manifestations is unclear.

Conclusion

The management of complex patients with IBD with concomitant IMIDs or EIMs requires thoughtful consideration of medical therapy, often in collaboration with multidisciplinary partners. The "right" choice of treatment should consider the patient and disease profile, individual patient preferences, and shared pathological mechanisms of disease. The subsequent monitoring of treatment response and treat-to-target approaches must also capture GI, rheumatologic and other end-organ targets. In the past several years, multiple novel classes of treatment have

been approved for IBD, many of which have broad-spectrum effects and can be effective for both IBD and other rheumatologic indications. However, the advantages and disadvantages of these new options should be balanced against the potential of existing therapies for treating patients with complex disease manifestations.

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Disclosures:

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