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Optimizing the Risk-benefit Conversation with Inflammatory Bowel Disease Patients

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Key Takeaways:

Contextualize Treatment Options Against the Risk of No Treatment:

A primary driver of therapeutic hesitancy is a disproportionate fear of medication side effects. Clinicians must counter this by clearly articulating the severe and often certain morbidity associated with untreated intestinal inflammation.

Leverage the Safety Profile of Selective Pathways:

The expansion of the therapeutic armamentarium allows for more personalized efficacy and safety considerations. Factor this in when helping patients choose appropriate treatment options (ie. Treatments that will treat extra-intestinal manifestations; treatments with impeccable safety profiles for those patients exceptionally anxious over side effects).

Utilize Structured Communication Models:

Effective communication is the cornerstone of the therapeutic alliance, yet many patients report that treatment discussions are often brief and lack depth. Adopting a structured framework can ensure a collaborative rather than directive process.

Address the Disconnect in Treatment Goals:

There is a significant disconnect between what clinicians measure and what patients experience. While doctors focus on objective markers like fecal calprotectin and endoscopic findings, patients are often most burdened by bowel urgency. Centring the risk-benefit conversation on the restoration of social and professional functioning—rather than just laboratory targets—can meaningfully improve patient satisfaction and long-term treatment adherence.

Introduction

The landscape of inflammatory bowel disease (IBD) management in Canada has undergone a significant transformation over the past decade, transitioning from a reactive approach focused on symptom suppression to a proactive, target-driven paradigm.[1] As of 2026, gastroenterologists are equipped with an unprecedented therapeutic armamentarium. This expansion introduces significant complexity into the shared decision-making process. The challenge lies in articulating the profound clinical benefits of advanced therapies while providing a nuanced, evidence-based contextualization of rare but serious risks. Contemporary IBD care therefore requires clinicians to act not only as prescribers but a sophisticated communicators capable of bridging the gap between objective clinical targets and the subjective priorities of each patient.

Articulating the Risks of Untreated Inflammatory Bowel Disease

A critical component of any risk-benefit discussion of advanced therapies is a clear explanation of the risks associated with untreated IBD. Therapeutic hesitancy, often driven by a patient's disproportionate fear of medication-related side effects, must be countered with an evidence-based discussion of the morbidity associated with uncontrolled intestinal inflammation.[2]

The natural history of Crohn's Disease (CD) indicates that approximately one third of patients' progress from an inflammatory phenotype to stricturing or penetrating complications within 5 years, with nearly half doing so over a 20-year period, based on population-based cohort data. This disease progression can result in bowel obstructions, often necessitating surgical resection. Furthermore, penetrating disease behaviour may lead to the formation of abscesses and fistulas.[3]

The risk of surgery remains a pivotal concern, with approximately 50% of IBD patients requiring at least one surgical intervention over their lifetime.[1] In moderate-to-severe CD, delaying initiation of advanced therapy is associated with significantly increased odds of undergoing surgery.[1] Conversely, early biologic intervention, initiated soon after diagnosis of CD has been shown to modify the disease course for up to 6 years, and can prevent hospitalization, the need for surgery, and disease progression as evidenced by the PROFILE Extend study.[4] Failure to control inflammation can also lead to short bowel syndrome following multiple resections, potentially even requiring long-term parenteral nutrition.

In ulcerative colitis (UC), the risks of untreated disease are often centred on the integrity of the colonic mucosa. Severe, uncontrolled inflammation can lead to opportunistic infections involving *Clostrioides difficile* and cytomegalovirus, or, toxic megacolon, thereby increasing the risk of perforation and sepsis. Patients with extensive, poorly controlled colitis are also at risk for severe rectal bleeding, which can lead to life-threatening anemia and the need for emergency colectomy.[5]

Patients with colonic IBD face an increased risk of colorectal cancer (CRC), which can be as much as fourfold higher than that of the general population if inflammation is not controlled. Achieving mucosal healing is currently recognized as a pivotal strategy for cancer prevention, as the risk of CRC is directly proportional to the duration and severity of the inflammatory burden.[6]

Recent research has illuminated the systemic consequences of chronic intestinal inflammation, including its role in atherosclerosis and increasing cardiovascular risk. IBD patients exhibit a significantly higher incidence of heart failure (37% increase) and atrial fibrillation, particularly during disease flares.[7] Furthermore, untreated disease is associated with metabolic disturbances and bone mineral density loss.

Anti-Tumour Necrosis Factor Therapies: Risks and Benefits

Anti-tumour necrosis factor (TNF) therapies remain among the most widely used advanced treatment options for patients supported by their long-standing record of efficacy and the availability of cost-effective biosimilars.

The primary clinical benefit of anti-TNF therapy is the induction and maintenance of deep remission. In CD, infliximab has demonstrated its ability to maintain clinical remission in 39% of patients with moderate-to-severe disease, compared to 21% in the placebo group, with approximately 50% achieving endoscopic remission by one year versus only 7.1% with placebo.[8] In UC, infliximab has shown a clinical response rate of 69% at week 8, versus 37% in the placebo group, and achieved mucosal healing in approximately 60% of patients during maintenance

therapy, compared to only 30% among placebo-treated patients.[9]

A critical benefit of anti-TNF therapy, specifically infliximab, is its status as the "gold standard" for managing fistulizing CD. Infliximab has shown complete fistula closure in 36% of patients at week 54, compared to 19% in the placebo group.[10] Beyond fistula control, achieving mucosal healing at one year with anti-TNF agents has been shown to be a potent predictor of reduced risks of colectomy and hospitalization in patients with IBD.[11] Lastly, the exceptional safety profile of anti-TNF therapy during pregnancy and breastfeeding supports their use as an attractive option for appropriate patients.[12]

The safety profile of anti-TNF therapies is defined primarily by a moderately increased risk of serious and opportunistic infections. These agents can reactivate latent infections, most notably tuberculosis and hepatitis B. Reports from some cohorts indicate tuberculosis reactivation rates of up to 6.4% among patients receiving anti-TNF therapy, reinforcing the need for screening for latent infections before treatment initiation.[13]

Malignancy risk, particularly lymphoma, remains a prominent concern for patients considering anti-TNF therapy. Current evidence suggests that anti-TNF monotherapy carries a low absolute risk of lymphoma, estimated at 0.41 cases per 1,000 person-years. However, the risk is substantially increased when these agents are used in combination with thiopurines (azathioprine or 6-mercaptopurine), with an adjusted hazard ratio (HR) of 6.11 (95% confidence interval [CI], 3.46–10.8).[14] Patients should also be monitored for non-melanoma skin cancers and for non-malignant complications including drug-induced lupus or demyelinating disease.

Vedolizumab: Risks and Benefits

Vedolizumab represents a significant advancement in therapy by offering a gut-selective mechanism of action, with its clinical utility best demonstrated in UC. In the landmark VARSITY trial, vedolizumab has shown superiority over adalimumab in achieving clinical remission at week 52 (31.3% vs 22.5%; p=0.006). Vedolizumab was also shown to achieve significantly higher rates of endoscopic improvement compared to adalimumab (39.7% vs 27.7%; p=0.0005).[15] These results have positioned vedolizumab as a favourable advanced therapy for moderate-to-severe UC.

In CD, real-world data indicate that vedolizumab is associated with favourable long-term effectiveness and treatment persistence. At one-year, clinical remission rates are approximately 39.4% (95% CI, 33.9–45.1), with mucosal healing rates of 40.6% (95% CI, 34.2–47.3).[16] Vedolizumab has also shown benefit in patients with draining fistulas, providing an alternative for those who fail or cannot tolerate anti-TNF agents.[17]

The gut-selective nature of vedolizumab results in a safety profile that may make it the most favourable among advanced therapies. Data from large-scale studies, including the VARSITY trial, have demonstrated low overall rates of adverse events (AEs) and serious infections, consistent with its minimal impact on systemic immune surveillance.[15]

Common side effects are generally mild and include nasopharyngitis, headache, and arthralgia. Rare reports of hepatic injury have been noted, though they are infrequent and typically reversible upon discontinuation. Infusion-related reactions occur in approximately 4% of patients and are usually manageable with standard infusion protocols.[18]

Ustekinumab: Risks and Benefits

Ustekinumab is a human monoclonal antibody that targets the shared p40 subunit of both interleukin (IL)-12 and IL-23. A distinguishing clinical feature of ustekinumab is its durability and efficacy in treatment-experienced patients. In CD, real-world data indicate that amongst those who have failed anti-TNF therapy, 46% (at 8 week interval dosing of ustekinumab) of patients achieved steroid-free remission at one year.[19] In UC, the pivotal UNIFI trial demonstrated that ustekinumab was significantly more effective than placebo in inducing and maintaining clinical remission and endoscopic healing. Notably, approximately 55% of patients in the UNIFI maintenance study remained in clinical remission through nearly 4 years of therapy.[20]

Ustekinumab is widely regarded as having an exceptional safety profile. Evidence from large-scale clinical trials and real-world cohorts show significantly lower rates of serious infections compared to anti-TNF therapies. Long-term monitoring has also shown no increased risk of lymphoma or other malignancies compared to the general population. Common AEs are typically mild, including nasopharyngitis, upper respiratory

tract infections, headache, and arthralgia.[21] While patients are screened for latent tuberculosis before initiation, the risk of reactivation is considered lower than that observed with anti-TNF agents.

IL-23 Inhibition: Risks and Benefits

Risankizumab, mirikizumab, and guselkumab selectively target the p19 subunit unique to IL-23, thereby blocking the pathogenic Th17 pathway while sparing the IL-12 pathway that contributes to host defence against intracellular pathogens and tumour surveillance.[22]

Emerging evidence suggests that this selective blockade of IL-23—sparing the IL-12 pathway—offers distinct therapeutic advantages in both efficacy and safety.[23] As a therapeutic class, p19 inhibitors have demonstrated robust efficacy to induce and maintain clinical remission, promote deep mucosal healing, and improve patient-reported outcomes while maintaining a favourable safety profile compared to prior biologics and small molecules.[24]

The risankizumab clinical program has established its role in both bio-naive and bio-experienced patients. In the ADVANCE and MOTIVATE Crohn's disease induction trials, risankizumab showed significant superiority over placebo in achieving clinical remission and endoscopic response at week 12. A subsequent meta-analysis of these trials confirms a strong treatment effect, with an odds ratio of 4.11 (95% CI, 2.9–5.9; $p<0.001$) for achieving endoscopic remission, highlighting its potency in inducing mucosal healing.[25]

The VIVID-1 trial evaluated mirikizumab in patients with CD, including a cohort exposed to ustekinumab. Mirikizumab achieved significantly superior clinical remission rates compared to placebo (45.4% vs 19.6%) and achieved endoscopic response rates comparable to ustekinumab in the active-comparator arm. Notably, mirikizumab was associated with a high rate of corticosteroid-free clinical remission, a critical long-term goal for CD management.[26]

Guselkumab demonstrated superiority over ustekinumab in achieving endoscopic remission in patients with CD.[27] More recently, the GRAVITI and ASTRO studies explored a fully subcutaneous induction regimen for guselkumab in IBD, demonstrating that subcutaneous delivery could achieve clinical and endoscopic outcomes comparable to traditional intravenous induction. This flexibility in route of administration represents a significant benefit for patient independence and healthcare resource utilization.[28,29]

In UC, the IL-23 pathway is a central mediator of neutrophilic infiltration and epithelial barrier destruction. Selective p19 inhibitors have shown a unique ability not only to resolve symptoms but also to achieve histologic normalization, a target increasingly linked to reduced risks of hospitalization and colectomy.[30]

As a therapeutic class, IL-23 p19 inhibitors are among the safest advanced therapies currently available for IBD.[31] Their use avoids the potential risks associated with anti-TNF agents (e.g., serious infections, tuberculosis reactivation, and demyelinating disease) and Janus Kinase (JAK) inhibitors (e.g., major adverse cardiovascular events (MACE), venous thromboembolism, and herpes zoster [shingles]).

Across phase 3 trials, the overall incidence of AEs with p19 inhibitors has been comparable to placebo. Serious infections are rare, occurring at rates of approximately 1.1% to 1.5% per 100 patient-years, which is not significantly higher relative to placebo groups. The most common AEs are typically mild and include nasopharyngitis, headache, and injection-site reactions.[32]

Janus Kinase Inhibitors: Risks and Benefits

JAK inhibitors are orally administered small molecule therapies that block intracellular signalling of multiple pro-inflammatory cytokines. Their rapid onset and high efficacy in refractory disease position them as a critical tool, particularly for patients who prefer oral therapy or who have failed multiple advanced therapies.

Tofacitinib provides an exceptionally rapid onset of symptomatic response. It is highly effective in inducing remission among UC patients, even those who are refractory to anti-TNF therapies.[33] A significant side effect is a dose-dependent increase in the risk of herpes zoster, accordingly, vaccination with the recombinant zoster vaccine is highly recommended before starting therapy. Tofacitinib has also been associated with increases in serum lipid levels (low density lipoprotein and high density lipoprotein cholesterol),[33] although this has not been definitively linked to increased cardiovascular events in IBD populations.

Upadacitinib is a preferentially selective JAK1 inhibitor approved for the treatment of both CD

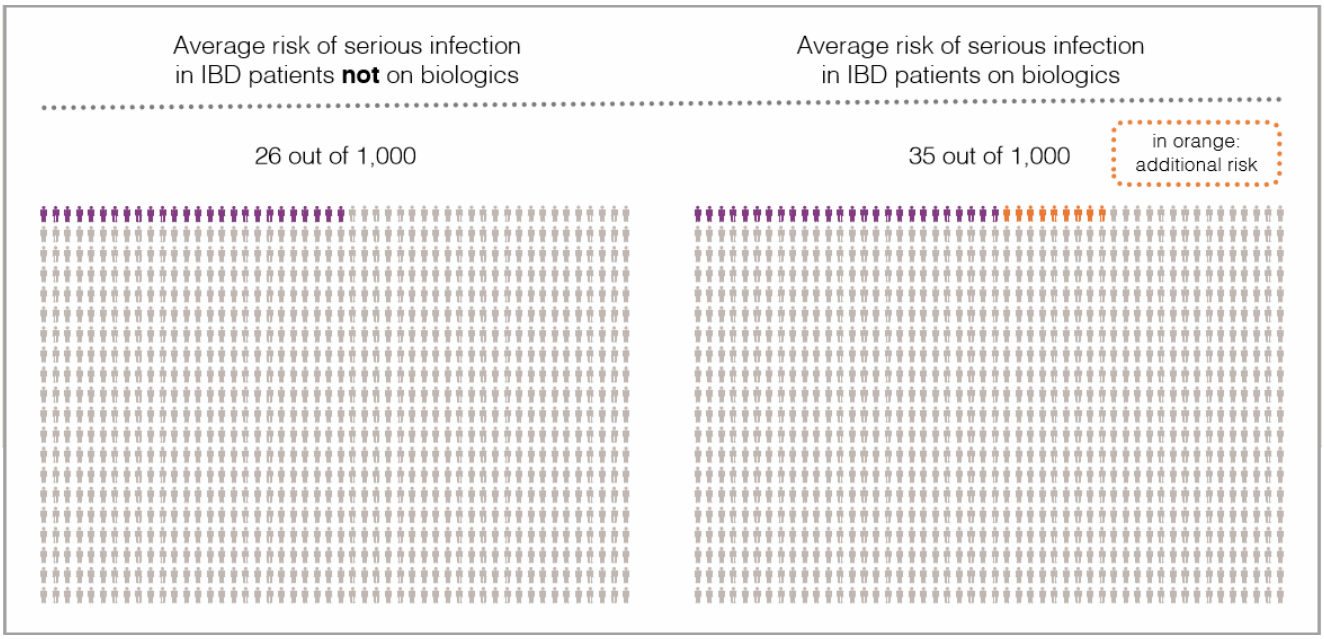

Figure 1. Average risk of serious infection in inflammatory bowel disease (IBD) patients.[43]

and UC. Real-world meta-analyses have shown that upadacitinib is effective at achieving clinical remission at week 8 in 69% of patients with highly refractory UC.[34] In addition, observational data in difficult-to-treat CD patients demonstrate clinical remission rates of approximately 50% at week 12.[35]

The safety profile of upadacitinib is consistent with the JAK inhibitor class, with reported increased risks of acne, herpes zoster, and elevated creatine phosphokinase.[36] While it carries the class-wide "Black-Box Warning," recent data suggests its high selectivity may mitigate some off-target risks.[37]

The safety discussion of JAK inhibitors has been shaped by the ORAL Surveillance study, which reported a higher incidence of MACE and venous thromboembolism (VTE) with tofacitinib compared to TNF inhibitors.[38] However, these findings require careful contextualization, as the study population was enriched for rheumatoid arthritis patients and the observed risks have not been consistently replicated in the IBD population. In contrast, a recent systematic review and meta-analysis that included 42 head-to-head studies and over 813,000 patients found no meaningful difference in the risk of MACE, serious infections, or malignancy between JAK inhibitors and anti-TNF therapies across the general population. While a slightly higher risk of VTE was observed (HR 1.26, 95% CI, 1.03–1.54; p=0.03), this was pronounced in rheumatoid arthritis patients, with no significant increase in VTE risk detected among IBD patients compared to those receiving anti-TNF therapies.[39]

Sphingosine 1-Phosphate Receptor Modulators: Risks and Benefits

Sphingosine 1-Phosphate (S1P) receptor modulators offer a novel mechanism for UC by binding to S1P receptors on lymphocytes and preventing their egress from lymph nodes, thereby limiting lymphocyte trafficking to the inflamed gut. Ozanimod and etrasimod have been indicated for use in moderate-to-severe UC.

Ozanimod was the first S1P receptor modulator approved for the treatment of moderate-to-severe UC. In a clinical trial, ozanimod demonstrated higher clinical remission rates at week 52 compared with placebo (37% vs 18.5%).[40] Ozanimod requires a 7-day dose titration to mitigate the risk of transient bradycardia. It has a long half-life, with lymphocyte counts returning to the normal range only 1–3 months after treatment discontinuation. Rare AEs include macular edema and liver enzyme elevations.[40]

Etrasimod is the second selective S1P modulator approved for use in UC and has shown superior clinical remission rates compared to placebo (32% vs 6.7%).[41] Unlike ozanimod,

etrasimod does not require a titration period and has a much shorter half-life, with absolute lymphocyte counts typically recovering within 1–2 weeks of discontinuing therapy. Reported adverse effects include minor transient bradycardia, rare atrioventricular block, and macular edema.

As a therapeutic class, S1P therapies are considered exceptionally safe. A meta-analysis published in late 2025 analyzed data from six phase 3 randomized controlled trials involving 1,744 IBD patients. While overall AEs were slightly higher than placebo (risk ratio 1.18, 95% CI 1.07–1.30; p=0.001), there were no significant differences in the risk of serious infections, cardiac events, or mortality.[42]

Evidence-Based Strategies for Risk and Benefit Communication

Effective communication is the cornerstone of the therapeutic alliance in IBD. It would come as no surprise to many clinicians that many patients report that conversations about treatment are limited in depth and brief. To optimize patient outcomes and adherence, adopting a structured communication framework represents a practical and effective strategy.

Structured Frameworks: The Three-Talk Model and BRAN

1. ***The Three-Talk Model:*** This model ensures the decision is a collaborative process rather than a directive one. The model includes three deliberate stages.
   - **Team Talk:** Establishes that the clinician and patient are working together toward a common goal.
   - **Option Talk:** Compares the benefits and risks of different alternatives using clear, understandable language.
   - **Decision Talk:** Culminates in selecting a treatment choice based on the patient's personal values and preferences.
2. ***The BRAN Framework:*** Provides a simple mnemonic to ensure all critical facets of a treatment discussion are addressed:
   - **B**enefits: What are the specific gains?
   - **R**isks: What are the potential harms, and how rare are they?
   - **A**lternatives: What other medications or surgical options are available?
   - **N**othing: What happens if we do not treat the inflammation?

Visual Communication Strategies

Visual aids are highly effective in facilitating these discussions. Tools such as Paling palettes allow clinicians to visually display the high likelihood of therapeutic success versus the extreme rarity of serious harm. Online tools such as IBD&me[43] provide individualized three-year risk visualizations, which can help patients grasp the long-term impact of their therapeutic choices.

A significant disconnect persists in IBD care: while clinicians focus on objective disease markers such as C-reactive protein and endoscopic findings, patients report that they are burdened by bowel urgency.[44] This urgency leads to significant social withdrawal and embarrassment, yet it is often overlooked during routine appointments. Notably, nearly 40% of patients with moderate-to-severe IBD report wearing protective pads or diapers due to the fear of incontinence. Directly addressing these quality-of-life concerns and centring the benefit-risk conversation on the restoration of social and professional functioning can meaningfully improve patient satisfaction and treatment adherence.

The management of IBD in 2026 demands more than clinical expertise alone; it requires a sustained commitment to evidence-based shared decision-making. By applying structured communication frameworks and clearly conveying the high likelihood of success with contemporary treatments versus the severe, certain risks of uncontrolled inflammation, gastroenterologist can empower patients to regain control of their lives. Ultimately, success is defined by the restoration of quality-of-life, achieved through a robust therapeutic alliance and a shared understanding of the diverse therapeutic landscape.

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