VOLUME 3
ISSUE 3
FALL
2025

ISSN 2817-4127 (Print)
ISSN 2817-4135 (Online)

CANADIAN IBD TODAY

Clinical Insights, Perspectives, and Disease Management

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doi.org/10.58931/cibdt.2025.3348

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Is IL-23 the Winner? Lessons from Inflammatory Bowel Disease (IBD) and Psoriasis (PsO)

Jesse Siffledeen, MD

Key Takeaways
Interleukin-23 (IL-23), and the IL-23/Th-17 interaction, plays a pivotal role in the pathogenesis of immune-mediated diseases, such as psoriasis (PsO) and inflammatory bowel disease (IBD). This has led to the development and commercialization of several anti-IL-23 therapies, all demonstrating high efficacy and safety in the management of these conditions.
Anti-IL-23 therapies, have been shown to be amongst the most highly effective treatments in PsO, achieving meaningful and durable treatment response (PASI-90) in over 80 percent of participants in registrational clinical trials, while in IBD the meaningful one-year efficacy, based on the varied definitions of the studies' primary endpoints, is achieved (at most) in just over 50 percent of participants, though rates of achieving remission in Crohn's disease are much lower.
Several ongoing studies examining the role of IL-23 inhibition in specific IBD populations (e.g., perianal Crohn's disease), and studies examining the combination of IL-23 inhibitors with other targeted therapies, capitalizes on the excellent safety and efficacy profile of anti-IL-23, reflecting the long-term importance of these therapies in the IBD treatment landscape.

Introduction

Psoriasis (PsO) and inflammatory bowel disease (IBD) are two immune-medicated inflammatory disorders (IMIDs) that have overlapping pathogenic mechanisms and thus share many advanced treatments for patients with moderate-to-severe disease. Historically, both conditions have faced limitations in the degree to which conventional therapies could promote safe and effective disease control. This landscape has shifted with the introduction and widespread adoption of advanced therapies for IMID management. The first class of advanced therapies, anti-tumour necrosis factor alpha (anti-TNF) agents, nearly doubled the meaningful response to treatment in PsO over that of conventional corticosteroid-sparing therapies (e.g., methotrexate), with comparable results in pivotal studies of anti-TNF therapies over conventional immunosuppressants (e.g., azathioprine) in IBD.[1] Despite these advances, most IBD patients in both clinical studies and real-world settings treated with anti-TNF agents (e.g., adalimumab, infliximab) still fail to achieve long-lasting, durable remission.[1,2]

Interleukin-23 (IL-23), first identified in 2000 as a mediator of inflammation in IMIDs, has since been shown to be a key cytokine in the inflammatory disease process. Overproduction of IL-23 by antigen-presenting cells and other myeloid cells promotes the proliferation of pathogenic T-helper 17 (Th17) cells that produce and secrete other inflammatory mediators, such as IL-17A, IL-17F, TNF-a, and IL-22, while suppressing regulatory T-cell differentiation (an important mediator of immune homeostasis).[1,2] This process, in turn, leads to an amplification of IL-23 production from stromal cells and local myeloid cells, which further drives the inflammatory process. The IL-23/Th17 immune pathway also plays an important role in maintaining gut homeostasis through the production of IL-17A, though overproduction of IL-23 can impair gut barrier function by other mechanisms.[1,2] Both IL-17A and IL-17F mediate inflammatory activity, representing the primary pathogenic mechanism contributing to PsO. IL-23 shares homology with IL-12, another proinflammatory cytokine initially identified in 1989 and implicated in PsO and IBD pathogenesis due to its influence on interferon gamma (IFNg) production and in promoting Th1 activity.[3] These insights led to the development and commercial use of ustekinumab, a monoclonal antibody (MAb) targeting the p40 subunit, shown to be effective in the management of PsO and IBD.

IL-12 and IL-23 are heterodimeric cytokines composed of two distinct subunits. Both share the p40 subunit, while the p19 subunit is specific to IL-23. Although both IL-12 and IL-23 cytokines were initially thought to be involved in the IMID process, preclinical and clinical data has subsequently determined IL-23 overactivity as the primary driver of inflammatory disease activity in PsO, psoriatic arthritis (PsA), and IBD.[1,2] In IBD, for example, genome-wide association studies have identified several single nucleotide polymorphisms in the IL-23 receptor that increase the risk of ulcerative colitis (UC) and Crohn's disease (CD), whereas studies on IL-12 deficiency alone have shown no impact on IBD.[4] These findings have allowed the development and commercialization of several anti-p19-specific MAbs, first approved for PsO and more recently for IBD. Given the central role of IL-23 in mediating these disease conditions, this review examines the efficacy and safety data supporting p19 inhibitor use in PsO and IBD, and their overall impact on disease management.

Impact of p19 Inhibitors in PsO and IBD

Review of Phase 3 Clinical Trials of p19 Inhibitors in Psoriasis: an IL-23-dominant Disease

Consistent with preclinical studies establishing the importance of IL-23/Th17 in PsO, p19 inhibitor therapy has dominated the PsO treatment landscape, outperforming the preceding advanced therapies, such as ustekinumab. PsO disease activity is graded according to the Psoriasis Area and Severity Index (PASI) score, which assesses disease extent and severity on a scale with a maximum score of 72. Clinical trials typically define standard primary outcome measures in PsO as achieving a 75% or 90% reduction in the PASI score (PASI 75 and PASI 90, respectively), allowing for reasonable comparisons of outcomes. Across phase 3 clinical trials, long-term extension studies, and head-to-head comparison studies, p19 inhibitors have consistently demonstrated the highest rates of efficacy. Notably, guselkumab and risankizumab in particular have achieved PASI 75 response rates of 88–91% at week 24, with sustained results through week 48.[1] Guselkumab has further demonstrated superiority over active comparator adalimumab in the pivotal VOYAGE 1 and VOYAGE

2 trials.[5] Similarly, the phase 3 risankizumab studies (UltIMMA-1 and 2) employed ustekinumab as an active comparator, with superiority demonstrated in PASI 90 (75% vs 42% at week 16, respectively, and sustained through week 52 (82% vs 44%, respectively).[6] The subsequent phase 3 ECLIPSE trial has shown that guselkumab was superior to secukinumab (an IL-17 inhibitor) in achieving PASI 90 at week 48 (84% vs 70%, respectively).[7] A recent systematic review and network meta-analysis of phase 3 therapeutic trials further demonstrated numerical superiority of p19 inhibitors over other available advanced therapies, namely IL-17 inhibitors ixekizumab and secukinumab, when adjusted for placebo group response, across PASI 75, 90 and 100 at week 28.[8] Throughout these trials, systematic reviews and network meta-analyses, no new safety signals have been reported, consistent with the targeted nature of IL-23 inhibition and its role in promoting regulatory T-cell function.

These p19 inhibitors have also been shown to provide a durable and long-lasting response over other classes of treatment for PsO. A systematic review and meta-analysis of electronic health records, registries, and pharmacy/claims data assessing drug survival of IL-17 and IL-23 inhibitors for PsO demonstrated high persistence rates for all agents assessed, with guselkumab and risankizumab consistently outperforming secukinumab and ixekizumab, at each annual checkpoint over 5 years of assessment.[9]

In addition, prospective and retrospective data also suggests that p19 inhibition may be more effective in the prevention of PsA compared with IL-17 inhibitors and ustekinumab.[10] Indeed, this potential alteration in the natural history of PsO, combined with the superior efficacy of p19 inhibitors, their dominance in head-to-head studies, their impressive durability of response, and their excellent safety profile, reflect the high impact of targeting IL-23 in PsO. Collectively, these features present a compelling argument to consider using IL-23 therapies as a first-line option in the management of this condition.

Review of Pivotal Clinical Trials of p19 Inhibitors in Inflammatory Bowel Disease

The importance of IL-23 inhibition in CD was first highlighted by the success of ustekinumab, which achieved statistically significant efficacy in its pivotal phase 3 CD registrational studies (UNITI 1, UNITI 2, IM-UNITI) (**Table 1**).[11] Additionally, ustekinumab exhibited an impressive safety profile, with no increase in adverse events, serious adverse events, malignancies, or infections above that of placebo therapy. More recently, the importance of IL-23 inhibition in CD was demonstrated in a head-to-head non-inferiority study of ustekinumab compared to adalimumab in an advanced therapy-naïve CD population (SEAVUE trial).[12] After 52 weeks of open-label therapy, 65% of participants on ustekinumab achieved the primary endpoint of clinical remission (CDAI <150), while 42% achieved an endoscopic response (defined as a reduction in the simple endoscopic score [SES-CD] by at least 50% from baseline, SES-CD ≤3, or SES-CD 0 for those starting with an SES-CD of 3). While these outcomes were statistically non-inferior to those in the adalimumab cohort, ustekinumab showed slightly higher numerical results. Similarly, ustekinumab has demonstrated both efficacy and safety in the phase 3 UC program (UNIFI), resulting in its approval for UC in 2019 (**Table 1**).[13]

Since the UNITI and UNIFI trials, clinical endpoints in IBD studies have evolved to incorporate more objective parameters to assess treatment efficacy. The recent approvals of three p19 inhibitors (guselkumab, risankizumab, and mirikizumab) for the management of CD, UC, or both, are based on strong and objective results from phase 3 registrational trials. Yet, targeting of the p19 subunit in IBD has not produced treatment responses as robust as those observed in PsO. While no clear explanation can account for such a difference, it is likely that PsO is primarily driven by the IL-23/Th17 axis, while the pathogenesis of IBD may be more heterogeneous, involving additional immune pathways beyond IL-23. Results of the phase 3 CD trials and their primary endpoints are summarized in **Table 1**.

Crohn's Disease

Risankizumab was the first p19 inhibitor approved for use in CD in 2023, on the basis of its phase 3 intravenous (IV) induction trials (ADVANCE, MOTIVATE) and subcutaneous (SC) maintenance trial (FORTIFY). In ADVANCE, endoscopic response at week 12 was achieved in 40% of patients receiving 600 mg IV risankizumab versus 12% with placebo.[14] Responders to induction were re-randomized for maintenance to placebo, risankizumab 180 mg, or 360 mg every 8 weeks. At week 52 of maintenance, 46.8% of those receiving 360 mg risankizumab

Study Therapy (*ST*)	Intervention Period	Dosing vs Placebo	Study Dur (*wk*)	Primary Endpoint Definition	% Achieving Primary Endpoint			% Achieving Primary Endpoint by Prior ADT-Failure		Clinical Trial
					ST (*N*)	PBO (*N*)	Δ (%)	No Prior ADT (*N*)	Prior ADT (*N*)	
Crohn's disease										
Ustekinumab	Induction	6 mg/kg IV, wk 0	6	Clinical Remission (CDAI <150)	18.5 (249)	9 (247)	9	N/A	18.5 (249) (TNF IR only)	UNITI-1[11]
	Induction	6 mg/kg IV wk 0	6	Clinical Remission (CDAI <150)	34.9 (209)	17.7 (209)	17.2	34.9 (209)	N/A	UNITI-2[11]
	Maintenance (responder re-randomization)	90 mg sc, q 8 wk	44	Clinical remission (CDAI <150) in ustekinumab induction responders	53.1 (132)	35.9 (131)	17.2	62.5 (74)	41.1 (58)	IM-UNITI[11]
Risankizumab	Induction	600 mg IV, wk 0,4,8	12	**1.** Clinical remission (SF/APS) **2.** Endoscopic response (SES-CD decrease by >50%)	43.5 (336) 40.3 (336)	21.7 (175) 12 (175)	21.9 28.3	48 (141) 50 (141)	41 (195) 33 (195)	ADVANCE[14]
	Induction	600 mg IV, at wk 0,4,8	12	**1.** Clinical remission (SF/APS) **2.** Endoscopic response (SES-CD decrease by >50%)	34.6 (191) 28.8 (191)	19.3 (187) 11.2 (187)	15.2 17.6	N/A	All Bio-IR	MOTIVATE[14]
	Maintenance (responder re-randomization)	360 mg sc, q 8 wk	52	**1.** Clinical remission (SF/APS) & **2.** Endoscopic response (SES-CD decrease by >50%)	51.8 (141) 46.5 (141)	39.6 (164) 22 (164)	12.2 24.5	62 (34) 54 (34)	48 (183) 44 (183)	FORTIFY[15]

Study Therapy (*ST*)	Intervention Period	Dosing vs Placebo	Study Dur (*wk*)	Primary Endpoint Definition	% Achieving Primary Endpoint			% Achieving Primary Endpoint by Prior ADT-Failure		Clinical Trial
					ST (*N*)	PBO (*N*)	Δ (*%*)	No Prior ADT (*N*)	Prior ADT (*N*)	
Guselkumab	Induction & Maintenance (Treat-through)	200 mg IV at wk 0,4,8, then 100 mg sc, q 8 wk	48	**1.** Clinical response (CR100) at wk 12 + clinical remission (CDAI<150) at wk 48	49.0 (143) 46.9 (143)	11.8 (76) 12.5 (72)	38.1 34.2	51.7 (116) (pooled results – GALAXI 2+3)		GALAXI 2[17] GALAXI 3[17]
				2. Clinical response at wk 12 + endoscopic response (SES-CD decrease by >50%) at wk 48	39.2 (143) 33.6 (143)	5.3 (76) 5.6 (72)	33.7 27.9	40.5 (116) (pooled results – GALAXI 2+3)		GALAXI 2[17] GALAXI 3[17]
	Induction & Maintenance (Treat-through)	200 mg IV at wk 0,4,8, then 200 mg sc q 4 wk	48	**1.** Clinical response (CR100) at wk 12 + clinical remission (CDAI<150) at wk 48	54.8 (146) 48.0 (150)	11.8 (76) 12.5 (72)	42.8 35.0	54.7 (128) (pooled results – GALAXI 2+3)		GALAXI 2[17] GALAXI 3[17]
				2. Clinical response at wk 12 + endoscopic response (SES-CD decrease by >50%) at wk 48	38.4 (146) 36.0 (150)	5.3 (76) 5.6 (72)	32.9 30.8	43.8 (128) (pooled results – GALAXI 2+3)		GALAXI 2[17] GALAXI 3[17]
Mirikizumab	Induction & Maintenance (Treat-through)	900 mg IV at wk 0,4,8, then 300 mg sc, q 4 wk	52	**1.** Clinical response (SF/APS) at wk 12 + clinical remission (CDAI <150) at wk 52	45.4 (579)	19.6 (199)	25.8	47.3 (298)	43.4 (281)	VIVID-1[18]
				2. Clinical response at wk 12 + endoscopic response (SES-CD decrease by >50%) at wk 52	38.0 (579)	9.0 (199)	28.9	39.3 (298)	36.7 (281)	

Study Therapy (*ST*)	Intervention Period	Dosing vs Placebo	Study Dur (*wk*)	Primary Endpoint Definition	% Achieving Primary Endpoint			% Achieving Primary Endpoint by Prior ADT-Failure		Clinical Trial
					ST (*N*)	PBO (*N*)	Δ (%)	No Prior ADT (*N*)	Prior ADT (*N*)	
Ulcerative colitis										
Ustekinumab	Induction	6 mg/kg IV, wk 0	8	Clinical remission (Mayo score ≤2, no subscore >1)	15.5 (322)	5.3 (319)	10.2	19 (156)	13 (166)	UNIFI[13]
	Maintenance (responder re-randomization)	90 mg sc, q 8 wk	44	Clinical remission (Mayo score ≤2, no subscore >1)	43.8 (176)	24.0 (175)	19.8	48.2 (85)	39.6 (91)	UNIFI[13]
Mirikizumab	Induction	300 mg IV wk 0,4,8	12	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	24.2 (868)	13.3 (294)	10.9	30.6 (507)	15.2 (361)	LUCENT-1[20]
	Maintenance (responder re-randomization)	200 mg sc, q 4 wk	44	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	49.9 (365)	25.1 (179)	24.8	51.9 (237)	46.1 (128)	LUCENT-2[20]
Risankizumab	Induction	1200 mg IV, at wk 0,4,8	12	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	20.3 (650)	6.2 (325)	14.1	29.7 (317)	11.4 (333)	INSPIRE[22]
	Maintenance (responder re-randomization)	360 mg sc q 8 wk	52	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	37.6 (186)	25.1 (183)	12.6	61.7 (47)	29.5 (139)	COMMAND[22]
Guselkumab	Induction	200 mg IV, at wk 0,4,8	12	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	22.6 (421)	7.9 (280)	14.7	31.7 (202)	12.5 (208)	QUASAR[21]
	Maintenance (responder re-randomization)	100 mg sc, q 8 wk	44	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	49.4 (188)	18.9 (190)	30.5	50.4 (105)	40.3 (77)	QUASAR[21]
	Maintenance (responder re-randomization)	200 mg sc, q 4 wk	44	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	51.6 (190)	18.9 (190)	32.7	58.3 (96)	39.8 (88)	QUASAR[21]

Table 1. Efficacy of IL-23 inhibition in Phase 3 registrational trial programs for approved doses in Crohn's disease and ulcerative colitis; *courtesy of Jesse Siffledeen, MD*

Abbreviations: ADT: Advanced Therapy; **aMayo:** adapted Mayo score; **APS:** abdominal pain score; **Bio-IR:** biologic inadequate responder; **CDAI:** (Crohn's Disease Activity Index; **CR100:** clinical response – CDAI reduction by 100 points; **IV:** intravenous; **N:** total number of subjects in the treatment cohort; **PBO:** placebo; **q:** every; **RB:** rectal bleeding score; **sc:** subcutaneous; **SES-CD:** simple endoscopic score for Crohn's disease; **SF:** stool frequency; **Stud Dur:** Study Duration & Endpoint; **wk:** week

demonstrated an endoscopic response (defined as a reduction in the SES-CD of ≥50%) compared to 13% in the placebo withdrawal group.[15] Endoscopic remission (defined as an SES-CD ≤4, a ≥2 point reduction from baseline, and no individual score >1) at week 48 was 39% versus 13%, respectively. The study population was considered a difficult to treat group, with a high mean SES-CD score of 14–14.8. In the ADVANCE trial, 58% of patients had previously demonstrated an inadequate response to at least one advanced therapy, including 22% who had failed ustekinumab; all participants in MOTIVATE were required to have failed at least one biologic agent. Subsequently, the SEQUENCE trial, a head-to-head study of risankizumab versus ustekinumab in CD patients with prior anti-TNF therapy failure showed that the primary endpoint of endoscopic remission at week 48 was significantly superior for risankizumab (32% vs 16%, respectively).[16]

The efficacy of guselkumab in the management of moderate-to-severe CD was assessed in two identical phase 3 trials (GALAXI 2 and GALAXI 3). These treat-through trials included IV induction with guselkumab (200 mg every 4 weeks for three doses) followed by SC maintenance (either 100 mg every 8 weeks or 200 mg every 4 weeks). Comparator arms included ustekinumab (6 mg/kg IV induction, then 90 mg SC every 8 weeks) and placebo. The co-primary endpoints were clinical response at week 12 and clinical remission/endoscopic response at week 48 versus placebo.[17] Endoscopic response at weeks 12 and 48, along with endoscopic remission at week 48, were among several prespecified secondary endpoints, all of which, along with the primary and secondary endpoints, were statistically superior for guselkumab versus placebo. Importantly, guselkumab also demonstrated statistical superiority over ustekinumab for endoscopic response at week 48 (48% and 53% in the 100 mg every 8 weeks and 200 mg every 4 weeks treatment cohorts, respectively, vs 37% in the ustekinumab cohort) and for endoscopic remission (33.2% and 37.2% vs 24.7%).[17] These results are numerically comparable to those observed in the risankizumab phase 3 trials.

The efficacy of mirikizumab in CD was assessed in the VIVID-1 phase 3 clinical trial, which used a treat-through design similar to the GALAXI 2 and GALAXI 3 studies. Participants received mirikizumab 900 mg IV at weeks 0, 4, and 8, followed by 300 mg SC every 4 weeks from week 12 through week 52, or were assigned to comparator arms of ustekinumab (6 mg/kg IV induction, then 90 mg SC every 8 weeks), or placebo.[18] The co-primary endpoints were clinical response at week 12 and clinical remission/endoscopic response at week 48 versus placebo, with endoscopic response and remission at week 52 as prespecified secondary outcome measures. As with guselkumab, mirikizumab demonstrated statistically significant and clinically meaningful improvements versus placebo for both co-primary endpoints and all key secondary endpoints. At week 52, endoscopic response was 48.4% in the mirikizumab cohort versus 9% in the placebo cohort, while endoscopic remission rates were 28.5% versus 4%, respectively.[18] In contrast to the GALAXI studies, however, mirikizumab did not demonstrate statistical superiority over ustekinumab in VIVID-1, reflected in a relatively higher ustekinumab response in VIVID 1, compared with the ustekinumab response in the GALAXI studies (endoscopic response 46.3% at week 52 vs 37.1% at week 48, respectively).[17,18]

Overall, p19 inhibition in CD yields comparable outcomes and demonstrates highly statistically significant improvements over the comparator placebo cohort. However, several shortcomings in these results are evident when they are compared to its dominance of p19 inhibition in PsO. Notably, only half of trial participants achieved a meaningful endoscopic response after one year of treatment, and even fewer achieved remission, highlighting a significant unmet need for more efficacious therapies. Response and remission rates are significantly lower in patients with prior exposure to advanced therapies, and robust data remains lacking for patients with complex phenotypes of CD, such as complex perianal fistulizing CD, which confer significant health and quality of life burden.

Ulcerative Colitis

Mirikizumab was the first p19 inhibitor to be approved for UC, based on results from the phase 3 induction (LUCENT 1) and maintenance (Lucent 2) trials.[19] In LUCENT 1, participants were randomized to receive mirikizumab 300 mg IV, or placebo, at weeks 0, 4, and 8. Treatment responders were then re-randomized in LUCENT 2 to receive mirikizumab 200 mg SC, or placebo, every 4 weeks from week 12 to week 52. The primary endpoint was clinical remission

assessed at week 12 for LUCENT 1 and at week 52 for LUCENT 2, defined by the adapted Mayo score ≤2 (stool-frequency subscore of 0, or a stool-frequency subscore of 1 with a decrease of ≥1 point from baseline, a rectal-bleeding subscore of 0, and an endoscopic subscore of 0 or 1, excluding friability). Clinical remission rates for mirikizumab were 24.2% at week 12 and 49.9% at week 52, compared with 13.3% and 25.1% for placebo, respectively. Several prespecified secondary endpoints were also achieved, including patient-reported outcomes, such as early improvement in bowel urgency. Long-term durability has been demonstrated as well: in the LUCENT-3 extension study, 70% of those in remission at one year remained in remission at 3 years, based on non-responder imputation.[20]

The efficacy of guselkumab in moderate-to-severe UC was demonstrated in the phase 3 QUASAR induction and maintenance trial.[21] During induction, participants received guselkumab 200 mg IV, 400 mg IV, or placebo at weeks 0, 4, and 8. At week 12, responders to guselkumab were re-randomized to receive maintenance therapy with guselkumab 100 mg every 8 weeks, 200 mg every 4 weeks, or placebo, for 44 weeks. The primary outcome was clinical remission, assessed by the adapted Mayo score at week 12 (for induction) and at the end of the 44-week maintenance period. All primary and secondary endpoints were met for both induction and maintenance outcomes. At week 12, 54% of participants receiving guselkumab 200 mg achieved clinical remission, compared with 25% in the placebo cohort. During maintenance, 45% of participants receiving 100 mg every 8 weeks and 50% of participants receiving 200 mg every 4 weeks achieved clinical remission, compared with 18% among those re-randomized to placebo therapy.

The efficacy of risankizumab in UC was demonstrated in the phase 3 induction (INSPIRE) and maintenance (COMMAND) trials.[22] During induction, participants received risankizumab 1200 mg IV or placebo at weeks 0, 4, and 8. At week 12, responders to risankizumab were re-randomized to maintenance therapy with risankizumab 180 mg or 360 mg every 8 weeks, or placebo, for 52 weeks. The primary endpoint was clinical remission, assessed by the adapted Mayo score at week 12 (induction) and after 52 weeks of maintenance. All primary and prespecified secondary endpoints were met in both the induction and maintenance studies. These included novel patient-reported outcomes such as bowel urgency, fecal incontinence, fatigue scores, and reduced hospitalization at week 12. During induction, clinical remission was achieved in 20% of participants receiving risankizumab, compared with 6% of the placebo cohort. After 52 weeks of maintenance, remission rates were 40% and 38% for participants receiving risankizumab 180 mg and 360 mg every 8 weeks, respectively, compared with 31% of those in the placebo withdrawal cohort.[22]

The p19 inhibitor class exhibits exceptional safety, with no associated severe adverse events such as increased risk of serious infections, hospitalization, cardiovascular events, malignancies, death, or other adverse events of interest (i.e., opportunistic infections) identified. With this safety profile in mind, several ongoing clinical trials are investigating combinations of p19 inhibitors with other targeted therapies. In support of this approach, the phase 2 VEGA study examined the combination guselkumab plus golimumab (an anti-TNF agent) versus either agent alone for induction of remission in UC. Combination therapy showed a statistically significant advantage over guselkumab monotherapy in achieving clinical remission at week 12 (by adapted Mayo Score), and this benefit was maintained after switching to guselkumab monotherapy for an additional 24 weeks (48% vs 31% at week 38).[23] Importantly, tissue transcriptomic profiles revealed a synergistic effect of combination therapy with regards to downregulation of proinflammatory cytokine gene expression and upregulation of genes promoting epithelial normalization.[24] Guselkumab and golimumab are currently under investigation for induction and maintenance of remission in phase 2 trials for CD (DUET-CD) and UC (DUET-UC). These studies use primary endpoints aligned with those of the GALAXI and QUASAR studies, respectively, at 48 weeks of treatment. Both studies have completed enrolment.

Is IL-23 the Clear Winner in IBD?

Collectively, these phase 3 registrational studies of IL-23 inhibitors in UC and CD highlight a strong class effect in achieving both response and remission, along with superiority in head-to-head evaluations. Coupled with their established safety profile, reduced hospitalizations, and improvements in quality-of-life measures, p19 inhibitors clearly stand out amongst the currently

available advanced therapeutic options for patients. This has further been reinforced in network meta-analyses of phase 3 registrational studies, which place risankizumab, for example, as among the most effective agents for inducing UC remission and potentially superior in patients naïve to advanced therapies. However, any conclusions regarding comparative efficacy from network meta-analyses are limited by the heterogeneity in trial designs and endpoint definitions across phase 3 trials in CD and UC.[25] Looking ahead, the future is bright for these therapies, with several active and pending pivotal trials targeting IL-23 inhibition, either as monotherapy, or in combination with other targeted therapies.

Despite these positive features, questions do remain amongst clinicians on how to choose between the three anti-IL-23 therapies currently available for CD and UC, while other limitations to IL-23 inhibition in IBD prevent it from achieving broad dominance in the field. These therapies have not been able to surpass the therapeutic ceiling for objective endoscopic disease remission, which remains below 40% in registrational trials for both UC and CD. Additionally, evidence supporting IL-23 therapy in special IBD populations is limited, such as patients with concomitant IMID not driven by the IL-23/Th17 pathway, patients with severe hospitalized UC, and those with complex perianal fistulizing CD. Ongoing clinical studies aim to address these limitations. For example, the efficacy and safety of guselkumab in fistulizing, perianal CD is currently being evaluated in the phase 3 placebo-controlled FUZION trial, with the primary outcome of fistula remission (closure) at week 24.[26] In addition, an ambitious head-to-head trial of risankizumab vs guselkumab is being planned, to identify differences in the efficacy of these therapies in CD. Moreover, excitement continues to grow regarding combination advanced therapy strategies that include p19 inhibition, which may achieve much higher rates of objective resolution of inflammation in IBD than is currently observed with monotherapies or immune targeting approaches. This broad research activity, taken together with robust safety data and a wide therapeutic index, IL-23 inhibitors are poised to increase their impact in the management of IBD.

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Financial Disclosures

J.S.: Consulting fees: Janssen, AbbVie, Takeda, Pendopharm, Fresenius Kabi, BioJamp, Bristol Myers Squibb, Amgen, McKesson, Pfizer, Celltrion, Ferring, and Eli Lilly; **Speaker fees:** Janssen, AbbVie, Takeda, Fresenius Kabi, BioJamp, Bristol Myers Squibb, Amgen, Pfizer, Ferring, Lupin Pharma, Celltrion, and Eli Lilly

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doi.org/10.58931/cibdt.2025.3349

Pregnancy in Inflammatory Bowel Disease (IBD)

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Key Takeaways
Preconception assessment and counselling is recommended for women with IBD who are contemplating pregnancy, ideally occurring at least 3 to 6 months prior to attempts at conception
Most IBD therapies are recommended to be continued throughout pregnancy and lactation to minimize the potential detrimental impact of active disease on infant and maternal outcomes
Consideration of aspirin commencement for preterm preeclampsia prevention is recommended, prior to 16 weeks gestation, in women with IBD, especially if additional risks for preeclampsia development
Infants exposed to biologics in utero can receive inactive vaccines and Rotavirus live vaccine per schedule.

Introduction

Inflammatory Bowel Disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), currently affects nearly 1% of the Canadian population, with the incidence rising most rapidly among the pediatric age group, while the prevalence is highest in the young adult age group.[1] Many patients will be managing their IBD during their formative years of life, such as when they are starting relationships, potentially planning families, or experiencing pregnancy. We summarize the most recent recommendations from the Global Consensus Statement on the Management of Pregnancy in Inflammatory Bowel Disease from 2024,[2] highlighting key updates since the 2016 Canadian Toronto Consensus Guidelines.[3] Guidelines such as the Global Consensus Statement provide practical tips for all clinicians to incorporate into their clinical practice, helping them to comfortably manage IBD during pregnancy.

Global Consensus Statement on the Management of Pregnancy in IBD

What is the Global Consensus?

Given the ever-changing landscape of IBD management, including IBD therapies, several regional health care system-specific guidelines have been created for the management of IBD during pregnancy. The Helmsley PIANO Expert Global Consensus provides evidence-based recommendations to health care providers regarding caring for women with IBD from fertility through pregnancy, delivery, and considerations for their offspring. Where sufficient data was available, the consensus utilized the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology based on a thorough literature review. For areas with insufficient data for GRADE, expert consensus was achieved through RAND (Research And Development) panel voting in May 2024.

A) Hereditability and Preconception Considerations

The consensus has highlighted that preconception counselling reduces the risk of disease relapse during pregnancy and lowers the risk of a low-birth-weight infant, most likely due to improving patient knowledge and optimizing disease control. For those who require contraception, including for the indication of allowing time to optimize disease control, the consensus advised long-acting reversible contraception over estrogen-containing contraceptives.

B) Fertility and Assisted Reproductive Treatments

Women with IBD may experience decreased fertility compared to women without IBD, particularly if they have active IBD or a

history of Ileal Pouch Anal Anastomosis (IPAA). The consensus has suggested that assisted reproductive technology (ART) may have similar effectiveness in women with IBD compared to women without IBD, as measured by live birth rates. In addition, the consensus suggests that women with IBD who have undergone pelvic surgery for IBD show comparable in vitro fertilization (IVF) effectiveness compared to women with IBD without such surgical history. Therefore, if fertility challenges persist despite adequate control of their IBD, a referral to a fertility specialist familiar with IBD and its therapies should be offered to the patient. It is also important to understand that current evidence does not show an increased risk of disease flare associated with oocyte retrieval procedures.

C) Pregnancy

The consensus has classified pregnancies for women with IBD as high risk for complications given the increased risk for adverse pregnancy outcomes and the need for more intense monitoring of the mother and fetus. Pregnant women with IBD are at increased risk for adverse maternal outcomes, and the consensus suggests prescribing low dose aspirin (162 mg) starting at 12–16 weeks of gestation as a preventive strategy for the development of preterm pre-eclampsia. Although concerns have previously existed regarding the risk of IBD flares from the use of NSAIDs, studies have shown that low dose aspirin during pregnancy does not increase flare risk.

Regarding IBD therapies during pregnancy, the consensus recommends continuing maintenance treatment with 5-ASA, sulfasalazine, and thiopurines, and using corticosteroids when clinically necessary. It was recommended to discontinue methotrexate at least 3 months prior to conception. Contrary to the Toronto Consensus Statements where alterations in third trimester dosing were considered, the consensus advises continuing maintenance anti-tumour necrosis factor (TNF) therapy throughout pregnancy without change in dose or dosing strategy to reduce maternal disease activity and the risk of preterm birth. It also supports continuing maintenance combination therapy with an anti-TNF agent and thiopurine therapy throughout pregnancy. Earlier concerns about increased risks of congenital malformations or infant infections from these therapies has been disputed. Regarding newer advanced therapies, the consensus suggests continuing maintenance therapy with vedolizumab and ustekinumab throughout pregnancy. For anti-interleukin (IL)-23 therapies, data were insufficient to issue a GRADE recommendation; however, the consensus suggests that these therapies could be continued in women with IBD who are pregnant or attempting conception. Finally, regarding small molecules, the expert consensus recommends discontinuing Janus kinase (JAK) inhibitors and sphingosine 1-phosphate (S1P) modulators prior to pregnancy and provides guidance on washout intervals prior to conception. One should also consider the time to segue to another appropriate IBD therapy to maintain disease remission. However, it was acknowledged that some patients with IBD may have refractory disease and may require continuation when “there is no effective alternative therapy to maintain maternal health.”

D) Delivery Planning

Delivery methods have generally varied by obstetrical health care provider, however, most women with IBD are candidates for vaginal delivery. Cesarean section is recommended for women with active perianal CD to prevent worsening of perianal involvement. For women with IBD and prior IPAA it is suggested (conditional recommendation) to undergo cesarean delivery, aimed at reducing the risk of pouch dysfunction from a complicated vaginal delivery.

E) Infant Vaccinations

A notable change in the consensus recommendations compared to the 2017 Toronto Consensus Guidelines is that infants exposed to biologics in utero can receive the live rotavirus vaccine in addition to inactivated vaccines per the standard schedule. This conditional recommendation is based on both retrospective and prospective studies, including the largest and only prospective study on rotavirus vaccination in infants exposed to biologic agents in utero, conducted by the Special Immunization Clinics of Canada, demonstrating this strategy to be low risk.[4]

F) Breastfeeding

Breastfeeding is encouraged for women with IBD whenever possible, as it may provide protective benefits against the development of IBD in the infant, in addition to other general health benefits. Breastfeeding is considered compatible with most IBD therapies, excluding methotrexate. There is limited safety data on JAK inhibitors, and S1P modulators, therefore, breastfeeding should be avoided whilst taking these therapies.

Conclusions

Recommendations for the management of IBD during the reproductive stages of life remains an integral component of the delivery of longitudinal, multi-disciplinary IBD care. As evidence continues to evolve, regular updates to these recommendations are necessary. Accordingly, the release of the Global Consensus Statements on Management of Pregnancy in IBD is exciting, as they offer timely and highly relevant guidance.

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Financial Disclosures

V.W.H: Honoraria (speaking): Abbvie, Amgen, Celltrion, Eli Lilly, Ferring, Fresenius Kabi, Janssen, Lupin, Organon, Pfizer, Takeda; **Honoraria (consulting/advisory board):** Abbvie, BioJAMP, Celltrion, Eli Lilly, Ferring, Fresenius Kabi, Janssen, Organon, Pfizer, Sandoz, Takeda; **Educational grant (to institution):** Abbvie, Celltrion, Janssen, Organon, Pfizer, Takeda, Viatris/Biocon
A-J.W.: Honoraria: Takeda, Janssen, Pfizer, Celltrion, Eli Lilly, CSL Vifor and Abbvie; **Honoraria/grant support:** Ferring and CSL Vifor; **Consultancy provided for:** Abbvie, Takeda, Celltrion, CSL Vifor, Ferring, Johnson and Johnson and Dr Falk Pharma

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doi.org/10.58931/cibdt.2025.3350

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Artificial Intelligence in Inflammatory Bowel Disease (IBD) Diagnostics: Applications and Future Directions

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Key Takeaways
AI can improve the accuracy, objectivity, and reproducibility of IBD disease assessments across multiple disease assessment indices.
Multiple AI models have shown expert-level performance in the assessment of endoscopic and histologic activity in IBD.
The deployment of AI models can help uniformize the quality of disease assessment across academic and community centres alike.
The next steps will involve multimodal AI models. The development of these models, and the fine-tuning of unimodal systems, will require large, diverse datasets and careful governance.

Introduction

Management of inflammatory bowel diseases (IBD) relies on clinical, endoscopic, and histologic indices to assess disease activity and guide treatment. In practice, clinicians integrate multiple datapoints to formulate a treatment plan. Advances in artificial intelligence (AI) provide a unique opportunity to integrate these inputs to deepen both our understanding and assessment of the disease.

The role of disease activity indices is pivotal to the treat-to-target strategy recommended by the STRIDE-II consensus.[1] Yet, commonly used indices often face challenges such as subjectivity, low interobserver reliability, and limited granularity in evaluating severity or phenotypic differences. AI methods can address several of these issues. This brief narrative overview introduces core AI concepts that clinicians are likely to encounter in the future, and discusses key applications spanning clinical, endoscopic, histologic, and multimodal assessments of disease.

Artificial Intelligence – What is It All About?

AI refers to the computerization of tasks that would otherwise require human cognition, such as pattern recognition, problem-solving, and decision-making. Machine learning (ML), a subset of AI, refers to models that learn directly from data rather than being explicitly programmed to do so. Deep learning (DL), a subset of ML, uses *multiple* layers of neural networks to learn complex patterns.

AI models are classically trained in a supervised or unsupervised fashion. In supervised learning, the model learns from labelled data, for example, a model would be shown an image of an ulcer which would be labelled as such in the context of IBD. In unsupervised learning, models identify patterns in the data on their own. The models are trained on one dataset and tested on another. Generalizability refers to how well a model maintains its performance when applied to new data. Key pitfalls in model performance include overfitting (when a model learns from test data but fails to perform on new data), and underfitting (when a model is not exhaustive enough to capture patterns, leading to poor performance on both training and test sets). Overfitting may occur in contexts where the training data differs radically from test data, such as differences in endoscope models, image quality, or patient case mix. To mitigate overfitting, strategies such as using diverse datasets in addition to federated learning, in which models are locally trained and centrally aggregated.

Neural networks (NN) are a class of ML algorithms inspired by the interconnected structure of neurons in the brain. They consist of multiple layers, including an input layer, one or more processing layers, and an output layer. As the NN analyzes data, the strength of the connection between nodes varies to improve the quality of the output. Among NNs, convolutional neural networks (CNNs) are more commonly used for image and video processing and are widely applied in endoscopic tasks such as polyp detection. Natural language processing (NLP) also uses NNs to enable computerized understanding and generation of human language. An application of NLP is the development of large language models (LLMs), which are trained on large data sets to predict and generate language in a conversational manner, such as ChatGPT (OpenAI, San Francisco, USA).

These concepts constitute a brief overview of core AI principles. Together, these methods underlie the IBD applications discussed in this review.

Clinical Disease Activity in IBD – Only Part of the Answer

Clinical indices, such as the Crohn's disease (CD) activity index (CDAI), the Harvey-Bradshaw Index (HBI), and the partial Mayo Score (pMS) are widely used to assess disease activity, yet each contains subjective elements. The CDAI is vulnerable to interobserver reliability, at least partly due to its reliance on subjective evaluation in key items, such as "general well-being,"[2] and it may be markedly affected by recall bias. Although simpler and easier to use, the HBI and pMS are also partly reliant on subjective items. Furthermore, several items within these indices may be confounded by conditions such as irritable bowel syndrome, which overlaps with IBD in 7–25% of patients.[3,4] These limitations highlight a potential role for AI to complement symptom assessment by integrating data from different sources, and by the use of continuous, objective measures.

Outside of a clinic appointment, patients often communicate with their treating physician through phone calls, emails, or via

a patient portal. AI may be used to identify active disease during these interactions. For example, a recent study applied NLP to an IBD online forum and identified 20 surrogate markers of clinical flare derived from patient language.[5] This study highlights the potential for NLP to analyze other patient-generated data sources, such as messages, emails, and patient portal communications. Much time is spent reviewing interim clinical interactions. LLMs have demonstrated the ability to extract patient-reported outcomes from IBD-related clinical data,[6] and AI-based chart review systems can accurately identify extraintestinal manifestations within IBD clinical notes.[7] Similar systems can be used to reduce clinical time spent on chart reviews and effectively highlight relevant between-visit changes. However, an important caveat is input quality: note forwarding, incomplete charting, or lack of quantification all contribute to misclassification and poor accuracy.

An exciting frontier in the clinical assessment of disease activity is the emerging use of wearable health sensors. In a study involving a cohort of 309 patients equipped with consumer wearables, physiological data, including heart rate (HR), resting HR, HR variability, and oxygen saturation, were paired with daily symptom surveys and biochemical markers.[8] ML models were able to predict flares (defined as symptoms *with* corroborating biochemical evidence such as fecal calprotectin, C-reactive protein, and erythrocyte sedimentation rate) up to 49 days before onset. Continuous data collection through wearables may allow early identification of patients at risk of flares, permitting earlier testing and proactive assessments. While physiologic, non-invasive data from wearable devices offers valuable information through ML, the promise for wearable-acquired biochemical data is even greater. Future developments in wearable technology may allow for real-time sensing of biochemical data. A recently developed non-invasive, perspiration-based wearable can measure sweat calprotectin, interleukin-6, and C-reactive protein levels.[9] In the study, the sensor was able to distinguish between patients with endoscopically active versus inactive ulcerative colitis (UC) based on sweat calprotectin levels. As well, perspiration-based measurements of each marker showed moderate to strong correlations with corresponding serum levels. While longitudinal validation is pending, this proof-of-concept suggests an exciting future in which real-time evidence of inflammation can facilitate rapid triage, timely assessments, and treatment modifications.

Such innovations have the potential to shift real-time disease monitoring from a periodic, timepoint based model to a proactive model where changes and discussions can occur prior to the onset of a significant clinical status change.

Endoscopic Assessment in IBD – How We Can Do Better

Endoscopic evaluation of disease activity in IBD largely relies on the Simple Endoscopic Score in CD (SES-CD) and the Mayo Endoscopic Score (MES). The SES-CD evaluates ulcers, affected areas, and stenosis across segments and has shown good inter-rater reliability among central readers in clinical trials.[10] However, its generalizability and uptake in community practice remains uncertain. In contrast, the MES offers a simpler approach but may lack precision, as it relies on subjective thresholds, such as distinguishing mild friability from friability. AI-assisted endoscopic activity assessment models can provide a systematic and reproducible endoscopic disease activity index.

In a study by Gottlieb et al., 795 endoscopic videos from a phase 2 trial of mirikizumab in UC were centrally scored using MES and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) by a single reader and then analyzed with a DL model, which showed strong agreement across both indices.[11] Similarly, Fan et al. trained an AI scoring system model for UC using still images, and tested it on 20 full-length endoscopic videos divided into five segments.[12] The model achieved concordance in 83% of segments with active disease and 100% of segments with inactive disease, and generated colourized colon maps—an intuitive graphical tool representing disease severity. These findings suggest that DL algorithms can identify and distinguish active and inactive disease at an expert-level.

Granularity remains a challenge in UC scoring. In a 2023 study by Kim et al. involving a UC cohort of 492 patients who demonstrated endoscopic improvements from MES 1 to 0, the endoscopic disease activity assessments of gastroenterologists was compared to that of a DL algorithm.[13] Results show the model outperformed the consensus of a group of gastroenterology fellows, providing more accurate results and superior ability to distinguish between MES 0

and 1. Notably, the algorithm maintained its performance level on an external dataset. These findings support the use of AI as an adjunct to improve scoring in UC, and allow for subtle discrimination near clinical thresholds.

In CD, the SES-CD relies on bias-prone assessments, such as ulcer size and affected surface. Marked interobserver variability can be noted in specific subscores, even among expert gastroenterologists.[14] An AI model trained to assess ulceration in CD was shown to have a strong correlation with the total SES-CD score, a moderate but significant correlation with fecal calprotectin levels, and, importantly, superior ability to identify clinical remission compared with SES-CD.[15] For small-bowel assessment, AI applications in video capsule endoscopy have rapidly progressed, outperforming gastroenterologists in both bleeding detection and review times.[16] In IBD, computer-assisted detection of erosions and ulcers has achieved sensitivity and specificity >90%,[17] with good discrimination between superficial and severe ulcers.[18] More recently, an AI-generated score for assessing small-bowel disease severity in CD was found to be strongly correlated to the Lewis Score.[19]

Despite strong results, heterogeneity remains. A recent meta-analysis revealed marked variability in AI accuracy for assessing mucosal healing in UC across datasets,[20] highlighting the need for standardized algorithm training, and extensive external validation.

Histologic Assessment in IBD – AI as the Great Equalizer?

Histologic remission is increasingly recognized as a potential treatment target in IBD, particularly in UC. However, histologic evaluation is labour-intensive, and requires subspecialty expertise, limiting its widespread adoption. Najdawi et al. trained a series of CNNs to identify tissues and cells, generating interpretable outcome features, including cell density and affected tissue areas.[21] From these, 13 features were selected by expert consensus as most predictive of outcomes, demonstrating strong correlation with the Nancy Histological Index, and achieving 97% accuracy in detecting histologic remission. Notably, the model's agreement with gastrointestinal pathologists matched inter-pathologist agreement, indicating expert-level performance.

AI-assisted histologic assessment can also predict outcomes. Using the PICaSSO Histologic Remission Index (PHRI), an AI model was able to predict clinical relapse with similar performance to expert pathologist assessment, with the AI generated results being obtained in as little as 9.8 seconds.[22]

These results illustrate how AI can democratize histologic expertise, especially in community settings where dedicated gastroenterology pathology may be limited.

AI in IBD – Putting It Together

Decision-making in IBD is inherently multimodal, and AI is helpful in interpreting heterogeneous signals. Chen et al. developed a clinical decision support tool that used only complete blood counts to non-invasively predict the extent and severity of colonic inflammation achieving an area under the receiver operating characteristic curve as high as 0.81 when differentiating between extensive colitis and proctitis on external validation data sets.[23] Additional data points can be integrated to assess disease severity with greater certainty and granularity. The integration of multiple disease activity parameters into one index has been recognized as potentially useful, particularly for the purpose of increasing sensitivity to therapeutic response in studies with smaller sample sizes.[24] Multimodal data integration with ML has also been applied to gene expression profiles to predict clinical response to advanced therapies,[25] or to models integrating clinical history and biochemical data to predict 1-year CD-related surgical risk.[26] These efforts highlight the potential of AI in optimizing treatment selection and prognostication.

Using data from a phase 2 trial of mirikizumab in UC, an AI fusion model that combined endoscopic and histologic data inputs outperformed individual single-modality models in predicting histologic remission.[27] This study provides an important proof-of-concept for using AI to integrate multiple disease activity inputs to better predict healing. Future research should explore the application of fusion models in predicting clinical and endoscopic outcomes.

Where Do We Go From Here?

The growing role of AI in IBD holds tremendous promise, but will require collaboration and care in its implementation. First, the use of diversified and multicentric datasets are a priority to protect against overfitting and improve generalizability. *Gastronet-5M*, a publicly available endoscopy dataset compiled from eight Dutch centres using different endoscope systems (Fuji, Olympus, Pentax), illustrates how diversified training datasets can improve model performances across a variety of endoscopy-related tasks.[28]

Second, AI should augment, but not replace, clinical judgment. Recent data has shown a decrease in adenoma detection rates during standard colonoscopies following AI-assisted colonoscopies, suggesting a risk of over-reliance on AI.[29] Maintaining clinicians' skills and autonomy will remain essential.

Third, interdisciplinary collaboration will be essential as IBD research increasingly recognizes the value of transmural assessment, and explores the potential of molecular and genetic markers. Equally, the implementation of AI tools should include community centres, where expertise and patient volumes in IBD may be limited, which will help to standardize care.

Ultimately, the integration of AI into IBD care represents a paradigm shift. When implemented responsibly, these tools will provide a much-needed level of objectivity and reproducibility to disease assessment. The next step will be prospective validation, across large multicentric datasets. AI holds the potential to support gastroenterologists in delivering care that is earlier, more precise, and, importantly, equitable for all patients with IBD.

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Financial Disclosures

A.Z.: None declared.
A.A.: None declared.
E.M.: None declared.
T.B.: None declared.

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doi.org/10.58931/cibdt.2025.3351

Inflammatory Joint Pain in Inflammatory Bowel Disease (IBD) Patients Treated with Anti-Tumour Necrosis Factor (TNF) Therapy:

Differentiating IBD Arthritis, Paradoxical Arthritis, Anti-TNF-induced Lupus, and Serum-Sickness-Like Reactions

Vivek Govardhanam, B.Eng, MD, FRCPC
Catherine Ivory, MD, PhD, FRCPC

Key Takeaways
We propose a mechanism based approach assessing bowel activity, timing of drug exposure and auto-antibody profile to manage arthritis in IBD patients treated with anti-TNF therapy.
Paradoxical arthritis, anti-TNF- induced lupus, and serum-sickness-like reaction can occur with anti-TNF therapy; all require a change in targeted therapy.
Managing arthritis in IBD requires multidisciplinary work between gastroenterologist and rheumatologist to optimize treatment of both manifestations.

Introduction

Musculoskeletal complaints remain the most frequent extra-intestinal manifestation (EIM) of inflammatory bowel disease (IBD), affecting up to one-third of patients over their lifetime and representing a major determinant of impaired quality of life.[1,2] Joint symptoms range from transient arthralgia to severe, erosive arthritis and are a leading cause of functional limitation among individuals with Crohn's disease and ulcerative colitis.

The advent of anti-tumour necrosis factor-alpha (anti-TNF-α) therapy revolutionized IBD management. Landmark infliximab trials in the late 1990s demonstrated not only mucosal healing but also marked improvement in arthritic and dermatologic EIMs.[3] Over time, however, long-term experience revealed paradoxical and autoimmune musculoskeletal phenomena—such as new or worsening arthritis in patients with quiescent bowel disease, occasionally accompanied by lupus-like serology or immune-complex reactions.

For clinicians, differentiating classical enteropathic arthritis from paradoxical inflammation, anti-TNF-induced lupus (ATIL), and serum-sickness-like reactions (SSLR) is essential. Misclassification can lead to premature discontinuation of an effective biologic or inappropriate escalation of therapy. This review provides a summary of current knowledge regarding the epidemiology, mechanisms,

Entity	Gut Activity	Onset Timing	Serology	Typical Pattern / Management
IBD Arthritis	Active	Any time	Seronegative	Large joints ± axial — Treat IBD ± DMARDs[1]
Paradoxical	Remission	Months–years	ANA- / RF- / CCP-	RA/PsA-like — Switch class; DMARD ± biologic[4,10]
ATIL	Remission	Months–years	ANA+, dsDNA+, histone-	Lupus rash / serositis — Stop TNF; supportive[7]
SSLR	Remission	7–14 days post-infusion	ATI+, ↓ C3/C4	Fever, rash, polyarthritis — Steroids; avoid culprit[7]

Table 1. Distinguishing Features of Inflammatory Joint Pain in IBD Patients on Anti-TNF Therapy; *courtesy of Vivek Govardhanam, B.Eng, MD, FRCPC and Catherine Ivory, MD, PhD, FRCPC.*

Abbreviations: ANA: antinuclear antibody; **ATI:** anti-TNF antibodies or anti-infliximab antibodies; **ATIL:** anti-TNF-induced lupus; **CCP:** cyclic citrullinated peptide antibody; **DMARDs:** disease-modifying antirheumatic drugs; **dsDNA:** double-stranded DNA; **IBD:** inflammatory bowel disease; **PsA:** psoriatic arthritis; **RA:** rheumatoid arthritis; **RF:** rheumatoid factor; **SSLR:** serum sickness-like reactions; **TNF:** tumour necrosis factor

diagnosis, and evidence-based management of inflammatory joint pain in IBD patients treated with anti-TNF agents.

Epidemiology and Classification

Population-based registries estimate that 20–30 % of IBD patients experience inflammatory joint symptoms.[1,2] Data from the Swiss IBD Cohort and GETAID registries indicate peripheral arthritis occurs in approximately 13–20% of patients, and axial spondyloarthritis affects 5–10%. The risk is greater in Crohn's disease than in ulcerative colitis, particularly among women, and those with extensive or ileocolonic disease.[2] Clinical features and timing of musculoskeletal symptoms can help differentiate the type of arthritis, and guide subsequent management (**Table 1**).

IBD-associated arthritis can be grouped into three clinical patterns[1]:

1. **Type 1 peripheral arthritis**—acute, asymmetric, oligoarticular <5 joints, predominantly knees and ankles, paralleling intestinal flares.
2. **Type 2 peripheral arthritis**—chronic, symmetrical, polyarticular, involving small joints (hands, wrists), independent of bowel activity.
3. **Axial involvement**—sacroiliitis or ankylosing spondylitis, often associated with HLA-B27 positivity and persisting irrespective of gut inflammation.

Paradoxical arthritis, defined as new inflammatory joint disease during sustained gut remission on anti-TNF therapy, occurs in ~2–10% of treated patients.[4,5] It has been reported with all TNF blockers, most frequently infliximab and adalimumab, and often coexists with paradoxical psoriasis.[5,6]

Anti-TNF–induced lupus (ATIL) develops in <1% of exposed patients.[6,7] The syndrome arises months to years after therapy initiation and is characterized by ANA and anti-double-strand DNA (dsDNA) positivity with mild systemic features.

Serum-sickness–like reaction (SSLR) occurs acutely—typically 7–14 days post-infusion—reflecting immune-complex deposition and complement activation. Its overall incidence is <2%, but risk increases markedly after drug holidays.[8]

Pathophysiology of Joint Manifestations in IBD

IBD-Associated Arthritis — the Gut–Joint Axis

The "gut–joint axis" concept integrates intestinal and articular inflammation through overlapping cytokine networks (TNF-α, interleukin [IL]-23, IL-17) and shared genetic risk alleles (HLA-B27, ERAP1, IL23R).[9] Bacterial antigens such as *Klebsiella pneumoniae* and adherent *E. coli* may translocate across a permeable mucosal barrier, activating Th17-dominant responses that migrate to synovial tissue. Consequently, type 1 arthritis

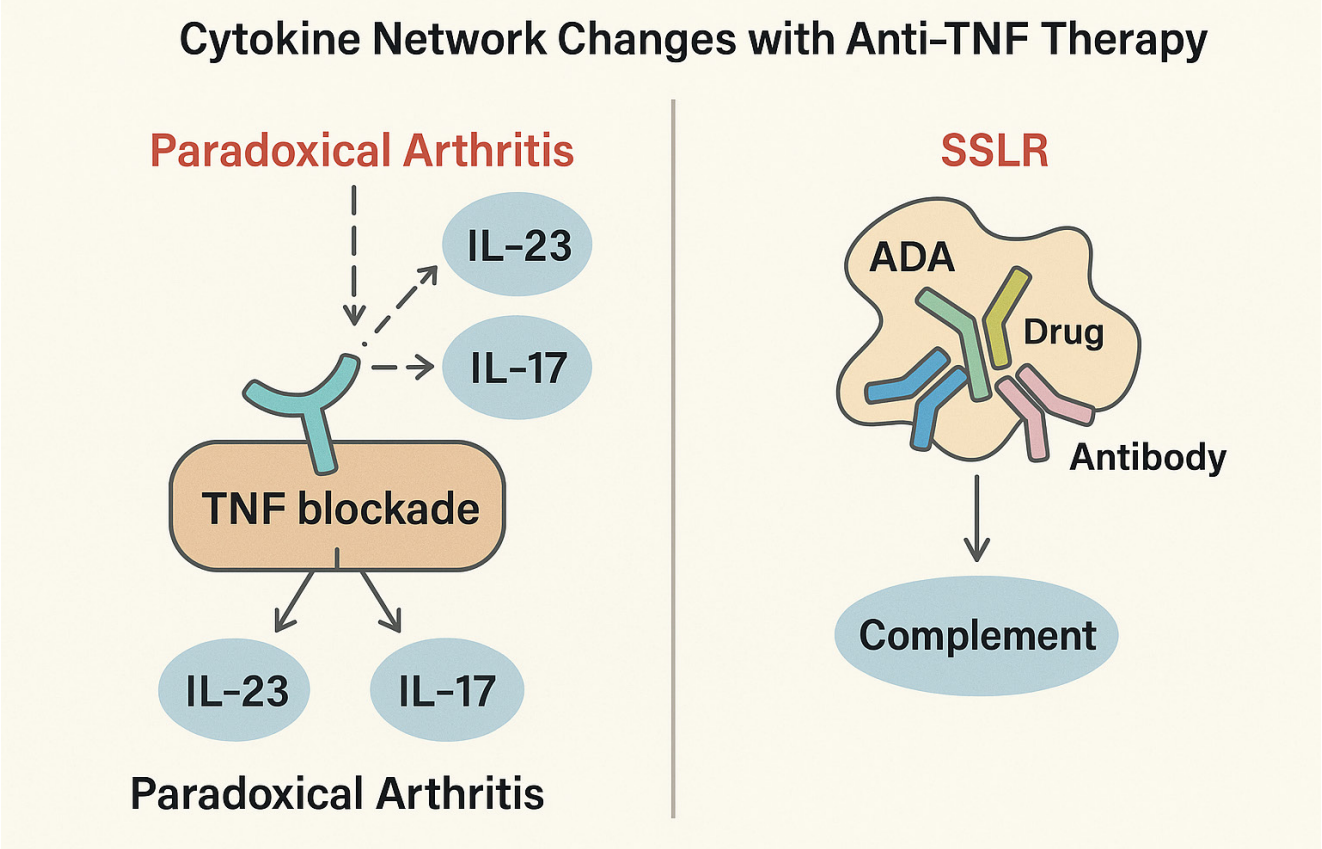

Figure 1. Cytokine network schematic showing tumour necrosis factor (TNF) blockade–induced interleukin (IL)-23/IL-17 and interferon-α up-regulation driving paradoxical arthritis, contrasted with anti-drug antibody (ADA)-mediated immune-complex activation in serum-sickness-like-reaction (SSLR)[6-8,10]; *courtesy of Vivek Govardhanam, B.Eng, MD, FRCPC and Catherine Ivory, MD, PhD, FRCPC.*

mirrors intestinal activity, whereas type 2 and axial disease follow more autonomous courses.

Paradoxical Arthritis under Anti-TNF Therapy

In paradoxical arthritis, TNF blockade disrupts immune equilibrium. Suppression of TNF driven negative feedback leads to compensatory up-regulation of type I interferons and activation of the IL-23/IL-17 axis.[6,9] Histopathologic studies reveal psoriatic-like synovial infiltrates enriched with CD3+, CD20+, and CD68+ cells along with elevated IL-23 expression despite therapeutic drug levels.[10] Importantly, anti-drug antibodies (ADAs) are usually absent, distinguishing this cytokine-rerouting phenomenon from immunogenic "loss of response" (**Figure 1**).

Anti-TNF–Induced Lupus (ATIL)

ATIL arises from autoantibody induction and loss of immune tolerance. Up to 75% of patients on anti-TNF therapy develop new antinuclear antibodies (ANA) and 20–30% develop anti-dsDNA, though only a minority develop drug-induced lupus.[6,7] Unlike classic drug-induced lupus, where anti-histone antibodies predominate, ATIL typically exhibits high-titer ANA (≥1: 320) and dsDNA positivity.[7] Complement activation and immune-complex deposition may contribute to rash, arthritis, and serositis, while severe renal or neurologic involvement remains rare. Among patients with ATIL, cutaneous manifestations are common, reported in approximately 60–70% of cases, but the rash is not uniformly a classic malar rash.[6,7] More frequently, patients develop photosensitive or maculopapular lupus-like eruptions, with malar rash representing only a subset of presentations. Symptoms typically resolve within 2–3 months following discontinuation of therapy.

Serum-Sickness–Like Reaction (SSLR)

SSLR is a type III hypersensitivity reaction. When infliximab is administered intermittently

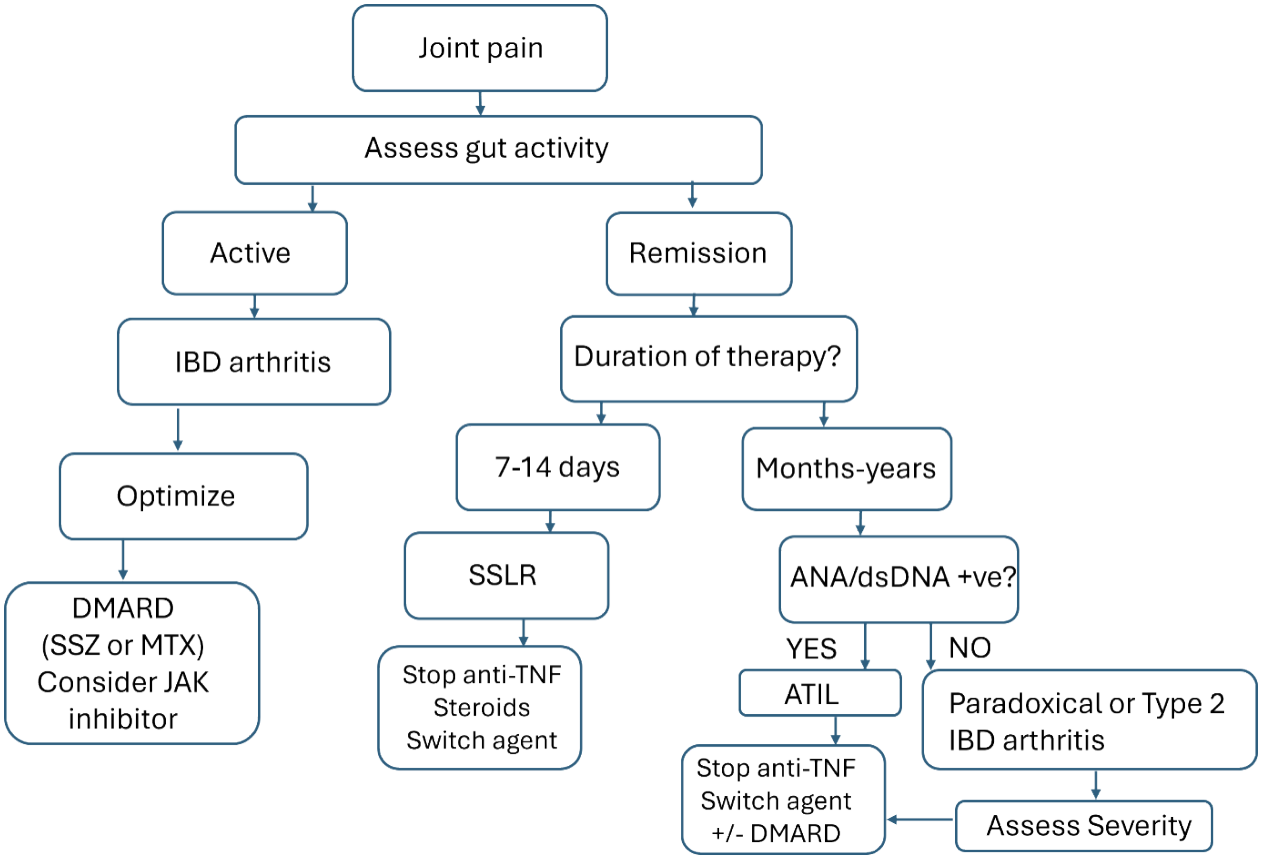

Figure 2. Algorithm for evaluating new arthritis in an anti- tumour necrosis factor (TNF)–treated IBD patient; *courtesy of Vivek Govardhanam, B.Eng, MD, FRCPC and Catherine Ivory, MD, PhD, FRCPC.*

Abbreviations: ANA: antinuclear antibodies; **ATIL:** Anti-TNF- induced lupus; **DMARD:** disease-modifying-anti-rheumatic drugs; **dsDNA:** anti-double-stranded DNA antibodies; **IBD:** inflammatory bowel disease; **JAK:** Janus Kinase inhibitor; **MTX:** methotrexate; **SSLR:** serum-sickness-like-reaction; **SSZ:** sulfasalazine.

or after a long interruption, circulating ADAs form complexes with drug antigen, precipitating complement activation (↓ C3/C4) and cytokine release (**Figure 1**). IgG1-containing immune complexes deposit in small vessels and synovia, causing fever, urticarial or morbilliform rash, and polyarthritis.[8] The reaction subsides rapidly with corticosteroid therapy once the drug is discontinued.

Diagnostic Approach

A systematic evaluation of bowel activity, symptom chronology, serology, and imaging is essential (**Figure 2**).

1. **Assess intestinal activity:** Active gut disease indicates IBD-related arthritis; new arthritis with mucosal remission suggests paradoxical or autoimmune etiology.[1,4]
2. **Timing:**
   - Acute onset (7–14 days post-infusion) → SSLR.[8]
   - Chronic onset (months–years) → paradoxical arthritis or ATIL.[6,7]
3. **Serology:**
   - ANA +/dsDNA + → ATIL.[7]
   - anti-TNF antibodies or anti-infliximab antibodies (ATI) +/low complement → SSLR.[8]
   - ANA −/rheumatoid factor (RF) −/ cyclic citrullinated peptide antibody (CCP) → Paradoxical arthritis.[4,10]

4. **Drug levels:**
   - Therapeutic trough with inflammation → paradoxical disease.
   - Low trough/high ADA → immunogenicity or SSLR.[8]
5. **Imaging:** Musculoskeletal ultrasound detects early synovitis and enthesitis; MRI of sacroiliac joints identifies bone-marrow edema in axial disease.[11,12]
6. **Arthrocentesis:** Exclude sepsis or crystalline arthritis in monoarticular presentations.[13]

General Considerations

Joint pain may not always indicate inflammatory disease. Assessing joint symptoms for active synovitis via ultrasound assessment or MRI can help distinguish osteoarthritis from concomitant fibromyalgia.[11,12] It is important to identify inflammatory arthritis, as it may necessitate adjustments in immunosuppressive therapy. Patients with psoriatic arthritis have an increased risk of gout,[13] which is also inflammatory but does not require changes to IBD therapy. In cases of acute monoarthritis, arthrocentesis is imperative to rule out septic arthritis, particularly in immunocompromised individuals.[14]

Management Strategies

IBD-Associated Arthritis

The primary goal is restoration of bowel remission, which often improves joint symptoms in type 1 IBD-associated arthritis.[1,2] For persistent peripheral arthritis, add sulfasalazine (2–3 g/day) or methotrexate (15–25 mg/week) as steroid-sparing DMARDs.[15] Anti-TNF therapy remains the first-line treatment for axial spondyloarthritis.[1] Short courses of COX-2-selective NSAIDs can be used safely in patients with quiescent bowel disease.[16] Corticosteroids may serve as bridge therapy during induction or when transitioning between biologics.

Paradoxical Arthritis

Disease severity often dictates management[4,10]:

- **Mild:** Add a DMARD (methotrexate or sulfasalazine).
- **Moderate–severe:** Discontinue the TNF inhibitor and switch to a different therapy.
  - **Ustekinumab (IL-12/23 blockade)** has shown improvement in articular symptoms in case series and registry data.[10]
  - **Vedolizumab**, though gut-selective, may allow joint inflammation to subside after TNF withdrawal.
- **Additional advanced therapies** such as JAK inhibitors, S1P receptor modulators and IL-23 inhibitors may be considered in selected cases, though data remain limited.
- **TNF-to-TNF switching** is seldom effective because paradoxical inflammation is considered a class-wide phenomenon.[5]

Anti-TNF–Induced Lupus (ATIL)

Immediate drug cessation is essential.[7] Symptomatic treatment may include NSAIDs, hydroxychloroquine, or low-dose corticosteroids. Lupus manifestations resolve within 6–12 weeks. If ongoing biologic therapy is required, consider switching to an alternate biologic therapy with a different mechanism of action; re-challenging with another TNF agent carries a small but measurable recurrence risk.[7]

Serum-Sickness–Like Reaction (SSLR)

Initiate systemic corticosteroids (0.5–1 mg/kg/day prednisone equivalent) and supportive care.[8] Symptoms typically abate within 48–72 hours. The offending drug should be permanently discontinued and documented as an allergy. For subsequent treatment, consider fully human antibodies (e.g., adalimumab, golimumab) or a non-TNF biologic.[8,17]

Emerging Therapies

JAK inhibitors (tofacitinib, upadacitinib, filgotinib) block multiple cytokine pathways downstream of TNF and IL-23 signalling. Phase 3 trials in ulcerative colitis and real-world data demonstrate their efficacy in managing concomitant arthropathy.[17,18] JAK inhibitors also carry on-label indications for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, thus addressing both bowel and joint inflammation in most cases. Their oral administration and systemic activity make them particularly attractive for patients with overlapping gut and joint inflammation, although careful

monitoring for infection and thromboembolic risk is required.

Conclusion

Inflammatory joint pain in IBD patients treated with anti-TNF therapy spans a continuum from classical bowel-driven arthritis to paradoxical and autoimmune syndromes. Recognizing the temporal relationship to drug exposure, bowel activity, and antibody profile is critical for appropriate management.

A mechanism-based approach, including treating gut inflammation for enteropathic arthritis, targeting alternative cytokine pathways for paradoxical disease, and discontinuing TNF blockade for ATIL or SSLR, achieves optimal outcomes while preserving intestinal remission. Multidisciplinary coordination among gastroenterology, rheumatology, and dermatology should be the standard for managing these complex immune intersections.

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Financial Disclosures

V.G.: None declared.
C.I.: Consultant/Speaker fees: AstraZeneca, AbbVie, GSK, JAMP

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