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# The 5 Most Clinically Impactful Papers Published in 2024 and Beyond

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*This past year saw the publication of a number of highly influential papers that have had immediate impacts on how we care for patients with Inflammatory bowel disease (IBD). In this review, I have selected five articles detailing studies published since the beginning of 2024 that have already directly impacted how I manage the care of people living with IBD. These articles are essential reading for all Canadian physicians treating IBD.*

## Earlier Anti-tumour Necrosis Factor (TNF) Exposure Leads to Better Long-Term Outcomes in Crohn's Disease: (PROFILE)

Biological therapies, starting with the emergence of anti-TNF based therapies in the early 2000s, have revolutionized the care of Crohn's disease (CD). These therapies were far superior to existing therapies for promoting clinical remission, inducing mucosal healing, preventing CD related hospitalizations and surgeries, and reducing the need for corticosteroids. Over the following two decades, multiple other biologic agents and targeted immunomodulatory therapies with diverse mechanisms of action were approved. However, even the best therapies only induce clinical remission in 60–75% of patients at best, along with endoscopic remission rates reaching just 40–50% at 1 year.[1,2]

Previous observational studies have suggested that patients with CD who access anti-TNF therapies earlier in the course of their disease have higher rates of clinical response and remission.[3] This is based on the model that persistent uncontrolled inflammation in CD may promote the development of fibrosis and the development of complications such as strictures and fistulas, which often require surgical management. A recent meta-analysis of clinical trials showed that persons who received biologic therapies within 18 months of diagnosis were 33% more likely to have clinical remission at the end of induction, compared with patients whose first exposure to biologics occurred more than 18 months following diagnosis.[3] Additionally, a

Canadian analysis also showed persons who used anti-TNF agents within 2 years of diagnosis were 50% less likely to require surgical management in the subsequent 5 years.[4] However, early access to anti-TNF agents has also been limited due to their high cost compared to other therapies. Furthermore, most Canadians are treated using a step-up model, where biologic agents are only provided when there is a failure of traditional immunomodulators and/or proof of corticosteroid dependence. It is also less clear whether there are greater benefits to even earlier treatment with biologic therapies, which is what the PROFILE study aimed to assess.

In the PROFILE study,[5] patients with newly diagnosed CD were given a 2-week course of 40 mg/day of prednisone. Following this, they were randomized into two groups: to receive either infliximab and an immunomodulator, or to just have their corticosteroids tapered. In the event of relapse, the latter group first received an immunomodulator, and then infliximab if a second relapse occurred. In the early infliximab arm, patients received their first dose a median of 11 days following diagnosis. Patients who received initial infliximab with an immunomodulator achieved an almost 80% rate of sustained clinical remission and a 67% rate of mucosal healing at 1 year, compared to 15% and 44% rates of sustained remission and mucosal healing in the step-up group. The requirement for hospitalization and surgical intervention was also significantly lower in the early infliximab group. To date, no other study assessing the impact of an advanced therapy in CD has shown equivalently high rates of sustained clinical remission or mucosal healing.

There are a few barriers to implementing these findings into immediate clinical practice. First, many patients with CD will follow a more benign course. Therefore, implementing universal early biologic treatment to all persons diagnosed with CD will lead to significant over-treatment.[6] It is also unclear if these findings can be generalized to other advanced therapies. The falling price of anti-TNFs in the biologic era should facilitate earlier treatment for those patients who are deemed to be at high risk. At this time, I have been selectively treating newly diagnosed CD patients with biologic therapies if they have indicators of severe activity (extensive involvement, deep ulcerations, or evidence of penetrating/fistulizing disease). In addition, I rapidly reassess patients early in the course of disease to look for signs of endoscopic progression.

## Risankizumab is Superior to Ustekinumab for Crohn's Disease Patients Losing Response to First Line Anti-TNFs (SEQUENCE)

Until recently, anti-TNF agents were the most commonly used first line agents in CD. A recent real-world study showed that over one-quarter of patients were not using the anti-TNF agent prescribed to them within 12 months of initiation, and approximately one-half had discontinued anti-TNF therapy within 3 years of initiation.[7] Therefore, a significant proportion of anti-TNF users will have indications for rescue therapies. Ustekinumab, an interleukin (IL)12/23 inhibitor, became the second line agent of choice for persons with CD. Observational data has suggested that ustekinumab is superior to vedolizumab for patients who had lost response to anti-TNF therapy.[8] It is believed that most of the anti-inflammatory activity of ustekinumab is mediated through its inhibition of IL-23, whereas IL-12 inhibition may actually be pro-inflammatory.[9] There may be additional benefits of using therapies which selectively target the binding of IL-23 to its receptor while leaving IL-12 unaffected.

Risankizumab was the first IL-23 selective inhibitor approved for the induction and maintenance of remission in persons with moderate-to-severe CD.[10] In fact, it had already been shown to be superior to ustekinumab for patients with plaque psoriasis. The SEQUENCE study sought to evaluate whether risankizumab might be preferred to ustekinumab as a rescue therapy for patients who have lost response to first line anti-TNF therapy.[11]

In this open-label randomized trial, persons who had a clinical and endoscopic relapse of their CD while on an anti-TNF agent were randomized to receive either the standard dose of risankizumab or the standard dose of ustekinumab, with no allowance made for further dose adjustments. Both primary outcomes were met, with risankizumab users having superior outcomes to those given ustekinumab for both clinical remission at week 24 (55% vs. 40%, $p<0.001$), and at endoscopic remission at week 48 (32% vs. 16%, $p<0.001$), respectively. It is less clear whether IL-23 inhibitors outperform ustekinumab as a first line therapy. Studies evaluating the IL-23 inhibitors mirikizumab and guselkumab have shown discordant results. One of the limitations of the

SEQUENCE study is that dose-escalation was not permitted in the protocol, which is a common rescue therapy for patients receiving the standard dose ustekinumab, in spite of the limited evidence for its efficacy. As well, this study was unblinded, meaning patients who were aware that they were receiving ustekinumab may have been more likely to report subjective symptoms suggestive of clinical relapse. However, objective measures favoured risankizumab, with risankizumab users experiencing greater declines in C-reactive protein (CRP) and fecal calprotectin.

In my practice, I now use IL-23 inhibitors for nearly all Crohn's patients where I previously would have preferred ustekinumab. This is because it is unlikely that IL-23 inhibitors are inferior to ustekinumab, and they are more difficult to access in Canada than biosimilar ustekinumab. Although there are no studies comparing IL-23 inhibitors to ustekinumab in ulcerative colitis, I am also preferentially using IL-23 inhibitors over ustekinumab in ulcerative colitis, based on the same reasoning, in spite of the absence of head-to-head comparisons.

## Vedolizumab is Effective in Preventing Post-Operative Recurrence in Crohn's Disease – The REPREVIO Study

Approximately 20–40% of patients with ileal or ileocolonic CD have required a surgical resection due to the presence of medical therapy-resistant complications within 5 years of diagnosis, though the incidence of requiring surgery has been decreasing over time.[12,13] Following the creation of a surgical reanastomosis, up to 15% of persons will require a repeat surgical intervention within 10 years due to recurrent CD at or proximal to the anastomosis.[12] Endoscopic evidence of recurrence can be observed in 37% of persons within 6 months following a surgical resection and reanastomosis.[14] Additionally, early endoscopic recurrence is strongly predictive of clinical recurrence and the need for surgical interventions.[15] Therefore, there has been considerable focus on how to best reduce the risk of early post-operative recurrence as a strategy to reduce long-term symptom burden and the risk of complications.

Anti-TNF therapies, when provided within 4 weeks following a surgical reanastomosis, have been shown to significantly reduce the risk of endoscopic post-operative recurrence for up to 2 years following the surgical date.[16] However, not all patients will be suitable candidates for anti-TNF therapy in the post-operative setting, either because of previous non-response or loss of response to anti-TNF therapies, the development of autoantibodies to anti-TNF therapies, or being at higher risk of complications.[17] Until the publication of REPREVIO, there was no randomized controlled trial level evidence supporting the use of any other class of agents in this setting, although observational data have suggested some benefit of vedolizumab and ustekinumab.

In the REPREVIO study,[18] patients who had undergone an ileal or ileocolonic resection and reanastomosis were randomized to receive intravenous vedolizumab every 8 weeks or a placebo, starting within 4 weeks of their surgery date. The primary outcome was the difference in the Rutgeerts score at week 26 following the first dose. A total of 62.8% of patients had a history of prior anti-TNF exposure at baseline. Those who received vedolizumab were significantly less likely to have severe endoscopic recurrence (Rutgeerts Grade 2b or greater) than those receiving placebo (23.3% vs. 62.2%, p=0.004), respectively. These results are comparable to the rates of endoscopic recurrence observed in the PREVENT study that evaluated infliximab for prevention of post-operative recurrence in CD, although patients were followed for up to 2 years.

Following this study, while I still prefer anti-TNFs over vedolizumab for induction of remission for ileal and/or ileocolonic CD, I am increasingly opting for vedolizumab over anti-TNFs to prevent post-operative recurrence. Vedolizumab has the advantage of a favourable safety profile, with a lower risk of antibody formation. For patients with a history of anti-TNF exposure, vedolizumab becomes an even more obvious first choice over other classes of advanced targeted therapies. However, longer term follow-up of patients in REPREVIO will be helpful in determining whether vedolizumab should replace anti-TNFs as the agent of choice for post-operative prophylaxis in treatment naïve patients.

## Neither Accelerated nor Intensified Dosing of Anti-TNFs are More Effective than Standard Dosing in Patients with Acute Severe Ulcerative Colitis – PREDICT-UC

Acute severe ulcerative colitis (ASUC), defined as having symptoms of colitis severe enough to require hospitalization, occurs in approximately 22% of patients with UC within 5 years of their date of diagnosis per year.[19] Even in the modern era, 15% of patients admitted with ASUC will require colectomy either during the index hospitalization or within 1 year of discharge.[20] While intravenous corticosteroids remain the standard first line therapy for ASUC, approximately 35% of patients will not respond to this therapy in the first 72 hours.[21] For these patients, administration of infliximab at a dose of 5 mg/kg is the most common rescue strategy. This approach has been shown to result in clinically meaningful improvement of ASUC in 50% of cases.[22] However, this implies that a significant proportion of patients will fail to respond to this rescue therapy. One of the mechanisms that may contribute to anti-TNF non-response is the impact that severe colonic and systemic inflammation has on the pharmacokinetics of infliximab. This inflammation can lead to increased fecal losses of infliximab and result in the drug being bound more rapidly by higher levels of circulating TNF.[23] One strategy that has emerged to counter this issue involves providing higher doses of infliximab or providing additional doses of infliximab in advance of the usual 2 week interval. While accelerated dosing of infliximab has been shown to be superior to standard dosing in observational trials,[24] there has not been a dedicated trial to compare different infliximab based treatment modalities until this past year.

In the PREDCT-UC study,[25] patients with ASUC who did not respond to corticosteroids within 72 hours were initially randomized to receive either 5 mg/kg or 10 mg/kg of intravenous infliximab. Those who received 5 mg/kg were further randomized to receive either an accelerated infliximab regimen (5 mg/kg at weeks 1 and 3) or standard dosing (5 mg/kg at weeks 2 and 6). Those receiving 10 mg/kg at the onset received an additional 10 mg/kg at week 1 and then 5 mg/kg at week 6. Salvage doses of infliximab were allowed for non-responders.

No difference was observed for the primary outcome of clinical response at day 7 following the initial 5 mg/kg versus 10 mg/kg dose of infliximab (61% vs. 65%, p=0.62). In addition, no differences were observed in colectomy rates by day 90 or in the incidence of serious adverse events. There was a trend toward improved outcomes for the higher 10 mg/kg dose of infliximab for those with CRP >50 and/or serum albumin <25g/L at baseline. No differences were observed between the standard, accelerated, and intensive dosing schedules when participants were followed for up to 90 days. This study concluded that there were no statistically significant differences between the dosing regimens.

While this study was officially negative, it does not close the door entirely on the decision to use higher initial dosing and/or earlier rescue therapy at high doses for people admitted with ASUC. In my practice, I will likely continue to administer higher initial doses of infliximab to those patients who exhibit clinical indicators of high levels of inflammation and poor prognosis. These indicators include low albumin levels, very high CRP levels, very extensive disease observed on imaging and endoscopy, and comorbidities that would increase the risk of death or complications should a colectomy be necessary. Future studies looking at the role of pharmacokinetic monitoring with rapid therapeutic decision making may provide more guidance on rational anti-TNF dosing in ASUC,[26] whereas other studies evaluating the efficacy for early Janus kinase-inhibitors for ASUC may render many of the finer points of anti-TNF based ASUC therapy obsolete.[27]

## Histologic Remission is Associated with Increased Fertility in Women with IBD

IBD affects men and women in approximately equal numbers. Since it is a disease frequently diagnosed in adolescence and early adulthood, it affects women at a time when it can impact fertility and fecundity. It is well established that women with IBD have lower fertility rates than non-IBD controls,[28] and the factors which may negatively impact fertility in IBD may be related to the disease itself (severity of inflammation), its treatments (medications and surgical factors) as well as sociobehavioural considerations.

Among women with IBD, active IBD at the time of conception has been shown to be strongly associated with decreased fertility.[29] Although the definition of what constitutes “active IBD”

has never been precisely defined, women with "active IBD" can include those with severe ongoing inflammation and impactful constitutional symptoms and systemic effects, but could also include women with milder levels of inflammation with systemic stability, and those with no symptoms but ongoing endoscopic or histologic activity. No studies conducted before this year have been able to discriminate the effects of systemic inflammation from the more subtle levels of inflammation confined to the bowel. Current Canadian guidelines recommend that women who are trying to conceive should aim to bring their IBD into remission to maximize their chances to attain a successful conception and pregnancy. However, it has never explicitly defined whether that meant that the treatment target should be clinical remission, endoscopic remission, or deep histologic remission.[30]

Mårild et al.[31] used data from the national registry of all Swedish women with IBD. This registry contained data from histologic assessments performed over the course of IBD. Women with biopsies showing histologic inflammation were assumed to have ongoing inflammation for the subsequent 12 months following the date of the biopsies. All other periods without histologic inflammation were assumed to be times of histologic quiescence. Clinical disease activity was determined according to health care utilization data, including hospitalizations, use of corticosteroids, or the initiation of a new immunomodulatory or biologic therapy. This dataset was then linked to the Swedish birth registry to calculate live birth rates during periods of both clinical and histologic activity, which were offset by 9 months to allow for the duration of a pregnancy. Adjusted fertility ratios were calculated, excluding periods of contraceptive use from the analysis.

In a study involving 15,600 women of child-bearing potential, fertility rates were significantly decreased during periods of inflammation compared to times of presumed remission (adjusted fertility rate ratio [aFRR] 0.90; 95% confidence interval [CI] 0.81–0.99). Clinically active IBD was also associated with decreased fertility, consistent with other studies (aFRR 0.76; 95% CI 0.72–0.79). Importantly, among women with clinically quiescent disease, fertility was significantly decreased during periods of presumed histologic activity (aFRR 0.85; 95% CI 0.73–0.98), suggesting that it is not merely systemic or severe inflammation that is responsible for decreased fertility (i.e., the level that would be seen in patients requiring hospitalization, corticosteroids, or new immunotherapies).

This study has significant limitations given the nature of the data source. It lacks data on actual clinical activity, making it more reasonable to consider histologic activity as a proxy for combined clinical and endoscopic activity at a level below the threshold of hospitalization, corticosteroids, or major changes in therapy. In my practice, I inform patients that even if they are feeling well, ongoing disease activity may affect their likelihood of successful conception. I recognize that many women seeking to become pregnant may have some apprehension about initiating or maximizing drug therapies. For women struggling to conceive, I adopt a more aggressive approach to achieve endoscopic remission, especially for women who are considering assisted reproductive technologies to facilitate conception.

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