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References: 1. Data on file (Formulary). July 23, 2024. AbbVie Corporation. **2.** SKYRIZI Product Monograph. AbbVie Corporation. **3.** Data on file (First & Only). January 10, 2024. AbbVie Corporation. **4.** Peyrin-Biroulet L, et al. Risankizumab versus ustekinumab for moderate-to-severe Crohn's disease. *N Engl J Med*. 2024;391(3):213–223.

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The 5 Most Clinically Impactful Papers Published in 2024 and Beyond

Laura E. Targownik, MD

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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Using Immunosuppressive Therapies to Treat Inflammatory Bowel Diseases (IBD) in the Post-Cancer Setting

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Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD), and ulcerative colitis (UC), are chronic immune-mediated inflammatory disorders (IMID) affecting both intestinal and extraintestinal organs. Chronic intestinal inflammation causes multifocal DNA damage,[1-3] increasing the risks of intestinal cancers.[4,5] While the widespread use of effective biologic and small molecule therapies and intensified immune modulating (IM) regimens in recent years may have contributed toward declining colorectal cancer risks,[6] these treatments could have introduced unexpected cancer risks in organs not directly affected by IBD due to reduced immune surveillance. Among individuals with IBD, the use of thiopurines has been frequently associated with risks of lymphoma,[7-9] non-melanoma skin cancer (NMSC),[10-12] and cervical cancer.[13] Several large studies have also reported increased risks of lymphoma,[8] and melanoma[14,15] associated with anti-tumour necrosis factor alpha (anti-TNF) therapies, although other studies have not shown these associations.[16] A randomized controlled trial (RCT) in elderly individuals with rheumatoid arthritis (RA) and cardiovascular risk factors reported a slightly increased all-cause cancer risk with the non-selective Janus kinase inhibitor (JAKi), tofacitinib.[17] Other immunosuppressive (IS) therapies, including methotrexate, anti-interleukin (IL)-12/23 or anti-IL-23 therapies,[18-20] anti-α4β7 integrin therapy,[21,22] JAK-1-selective inhibitors (upadacitinib),[23,24] and sphingosine-1-phosphate receptor agonists,[25-27] have not been associated with increased cancer risks to date. However, some of these newer therapies have only been available for a few years.

Given the low absolute risk of treatment-related cancers, controlling underlying IBD with IS therapies is typically prioritized to improve quality of life and reduce IBD-related complications. However, the decision to start or continue IS therapy in individuals with current or prior malignancy is more complex, as immune surveillance may be more crucial for these patients. Clinical trials generally exclude patients with a cancer history, which limits the available evidence on cancer recurrence risks associated with specific therapies. Additionally, some cytotoxic chemotherapy regimens can control IBD for prolonged periods,[28] suggesting that additional immunomodulation may be unnecessary, and potentially harmful, during cancer treatment. Conversely, hormonal, radiation, and immune checkpoint inhibitor therapies have been associated with increased risks of IBD flares.[29,30] Therefore, a careful and collaborative approach with oncologists is essential for the optimal management of IBD patients diagnosed with cancer.

Recently, the European Crohn's and Colitis Organization (ECCO)[31] and the American Gastroenterological Association (AGA)[32] released practice recommendations regarding the use of IS therapies in individuals with IBD in the post-cancer setting. This review summarizes the evidence regarding cancer risks associated with specific IBD therapies in this context and presents a management approach based on both scientific and practical considerations.

Methotrexate and Thiopurines

Methotrexate (MTX) and thiopurines (azathioprine and 6-mercaptopurine) are anti-metabolites that act as non-selective IM by interfering with DNA synthesis.[33,34] A meta-analysis of 16 studies, including 11,702 individuals with IMIDs (IBD, RA, psoriasis), and 3,706 with IBD, followed for an average of 3 years post-cancer diagnosis, found no significant increase in new or recurrent non-dermatological cancers among patients continuing IM vs. anti-TNF therapy or no IM therapy (36.2, 33.8, and 37.5 per 1000 patient years [PY], respectively). However, there was a slight increase in the rate of new or recurrent skin cancers among those who continued immunosuppression compared to those who discontinued it (71.6 vs 50.8/1000 PY).[35] A retrospective study of 54,919 IBD patients with prior basal cell carcinoma (BCC) found that thiopurine use was associated with an increased risk of BCC recurrence compared to 5-ASA therapy (adjusted hazard ratio [aHR] 1.65, 95% confidence interval [CI] 1.24–2.19).[36]

Based on the limited data, ECCO concluded that there is insufficient evidence regarding the safety of methotrexate use following a cancer diagnosis. Both ECCO[31] and AGA[32] suggested discontinuing thiopurine therapy in patients with active malignancy and considering alternatives in individuals with a history of lymphoma, NMSC, or cervical cancer.

Anti-TNF Therapy

Anti-tumour Necrosis Factor (TNF) therapies (infliximab, adalimumab, golimumab, certolizumab) were the first biologic treatments introduced for CD and UC. Despite concerns about inhibiting a cytokine involved in tumour clearance, anti-TNF therapies have generally not been associated with increased cancer risks,[16] except for a few isolated reports relating to lymphoma[8] and melanoma.[14,15]

In the aforementioned meta-analysis of 16 studies, no increase in cancer recurrence was observed in IBD patients who remained on anti-TNF therapy compared to those who discontinued IM agents.[35] Another retrospective study of 463 IBD patients diagnosed with cancer found no increase in new or recurrent cancer in those who continued or were newly started on anti-TNF therapy, compared to those who did not receive IM agents over a 6.2-year median follow-up.[37] Additionally, a multicentre retrospective cohort of 538 IBD patients with a history of non-digestive cancers found no difference in the incident cancer-free survival rates between patients treated with anti-TNF therapy or vedolizumab over a median follow-up of 55 months.[38] Furthermore, a population-based study of 25,758 IMID patients from Denmark found no significant increase in cancer rates among IBD patients on anti-TNF therapy (30.3/1000 PY) compared to those not on therapy (34.4/1000 PY).[39]

Based on the above, ECCO suggests that anti-TNF therapy may be used in patients with current or prior cancer, although data on specific cancer types are lacking.[31] In contrast, the AGA recommends stopping anti-TNF therapy indefinitely for patients with a history of melanoma or hematologic cancers but continuing it for patients with other cancer types.[32]

Vedolizumab

Vedolizumab, a gut-selective α4β7 integrin inhibitor, has shown an excellent overall safety profile in treating UC and CD.[40] Follow-up data from clinical trials have not indicated an increased risk of malignancy with vedolizumab.[21] A retrospective study of 538 IBD patients with non-digestive cancers found no difference in cancer-free survival rates between patients treated with anti-TNF therapy or vedolizumab compared to those not receiving IM therapy.[38] Additionally, another study of 463 IBD patients with a history of cancer found that vedolizumab was associated with a lower rate of new or recurrent cancers (2.2/1000) compared to anti-TNF therapy (4.2/1000) and no IM effects (5.6/1000).[37]

ECCO[31] and AGA[32] recommend continuing vedolizumab in the post-cancer setting. However, decisions made during active cancer, particularly gastrointestinal cancers, should be individualized due to the lack of evidence.

Anti-IL12/23 and Anti-IL23

Anti-IL-12/23 antibodies (ustekinumab) and anti-IL-23-specific (rizankizumab, mirikizumab, guselkumab) antibodies have shown efficacy and have an excellent safety profile in treating UC and CD.[18,41,42] Long-term registry data from psoriasis and psoriatic arthritis have not demonstrated an increased risk of malignancy with these agents.[20,29] A retrospective study of 341 IBD patients with a cancer history found no significant difference

in cancer incidence between those treated with ustekinumab and those treated with anti-TNF therapy (aHR 5.23, 95% CI 0.96–28.41) or no IM therapy (aHR 0.88, 95% CI 0.25–3.03) over a median follow-up of 5.4 PY.[43] Data on anti-IL-23 therapies is limited, as these agents have only recently become available for IBD.

Based on the limited data, ECCO recommends continuing anti-IL12/23 therapy in patients with a history of malignancy but makes no specific recommendations for its use during active malignancy.[31] Similarly, AGA recommends not changing anti-IL12/23 or anti-IL23 therapy in patients with prior cancer.[32]

Other Therapies

JAKi and sphingosine-1-phosphate receptor agonists are becoming more common in IBD management. To date, no studies have evaluated the cancer risks associated with these therapies in the post-cancer setting. ECCO and AGA currently do not recommend changing these therapies for patients with active or prior cancer.

Cancer Recurrence Risks Across Multiple IS Therapies

A prospective cohort study of 405 IBD patients with a prior cancer diagnosis found no association between IM use at the time of study entry and the risk of new or recurrent cancers.[44] Similarly, a large registry study (SAPPHIRE) of 305 IBD patients with a history of cancer found no significant difference in cancer recurrence between those who received IM therapy (2.58/100 PY) and those who did not (4.78/100 PY) (aHR 1.41, 95% CI, 0.69–2.90) over a median follow-up of 4.8 years.[45]

Two meta-analyses involving IMID patients (11,702 and 3,266 patients, respectively) have also shown no statistical difference in cancer recurrence risks based on the timing of IM therapy (IM therapy started within versus more than 5 or 6 years from the index cancer diagnosis (33.6 vs 32.9/1000 PY for IM, p=0.86, and 43.7 vs 21.0/1000 PY for anti-TNF, p=0.43).[35] Similarly, the rates were 22 vs 48/1000 PY for IM and 32 vs 32/1000 PY for anti-TNF, (p>0.1 for all).[46]

Recommendations for IBD Treatment in the Post-Cancer Setting

In the post-cancer setting, the decision to initiate or continue IM therapy should consider the relative risks of cancer recurrence versus IBD relapse. The early post-cancer setting (within 5 years of cancer diagnosis) is generally considered a more critical period for cancer recurrence, although two meta-analyses found no significant difference in cancer recurrence based on whether IM therapy was started within 6 years or more than 6 years after cancer diagnosis.[35,46]

In some situations, managing IBD may be as important, if not more so, than the cancer recurrence risk, particularly for those with complicated IBD phenotypes (e.g., penetrating or extensive small bowel CD, complex perianal fistulizing CD, or severe pancolitis) or those with palliative cancer who prioritize quality of life. Furthermore, the type of cancer and cancer treatment regimen play a significant role in determining the appropriate IM therapy, necessitating a collaborative approach with oncologists.

The Penn Classification system, which was developed to describe rates of cancer recurrence in solid organ transplant recipients, can help guide the management of IM in post-cancer IBD patients. It is important to recognize that the IM regimens used in the post-transplant setting differ from those used in IBD. According to this system, low-risk cancers (e.g., lymphoma, thyroid, cervical, and testicular cancers) have less than a 10% chance of recurrence, while intermediate-risk cancers (e.g., uterine, breast, prostate, lung, and gastrointestinal cancers) have an 11–25% recurrence risk, and high-risk cancers (e.g., bladder, renal, melanoma, NMSC, sarcoma, multiple myeloma) have over a 25% recurrence risk.[47]

Based on the available evidence, we recommend avoiding thiopurines in individuals with lymphoma, NMSC, or cervical cancer, and to withhold them for at least 5 years after alternate cancer diagnoses. Given the limited utility of thiopurines in managing IBD, their continued use should be carefully considered on a case-by-case basis. Anti-TNF therapy should be withheld for up to 5 years after a lymphoma or

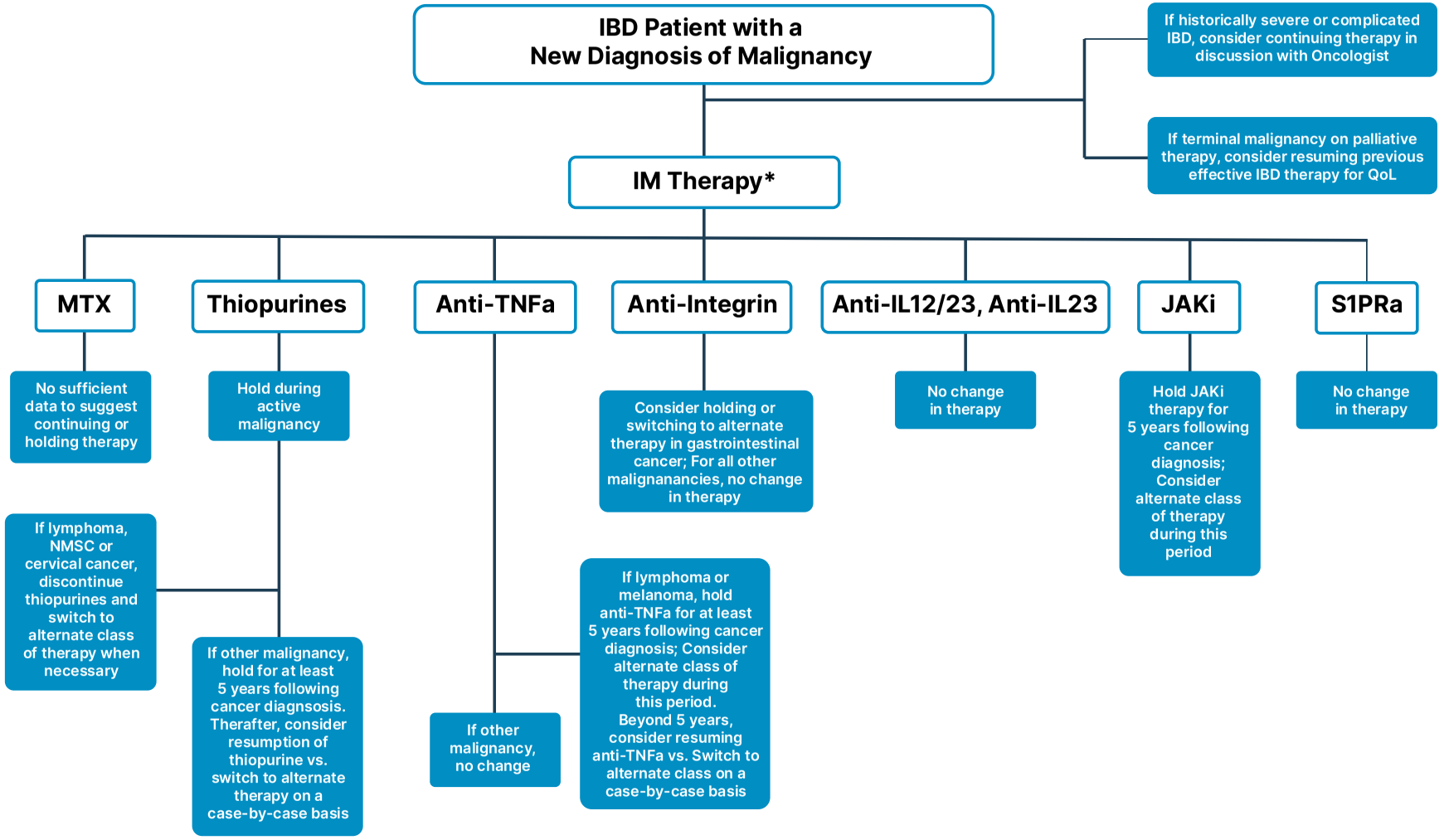

Figure 1. Putative care pathway to manage immunosuppressive therapies following cancer diagnosis in individuals with IBD; *courtesy of Rana Kandel, MD and Sanjay K. Murthy, MD, MSc, FRCPC.*

Abbreviations: IBD: inflammatory bowel diseases, **IL:** interleukin, **IM:** Immunomodulating, **JAKI:** Janus kinase inhibitors, **NMSC:** Non-Melanoma Skin Cancer, **MTX:** Methotrexate, **QoL:** quality of life, **S1PRa:** Sphingosine-1-Phosphate Receptor agonists, **TNF:** anti-tumour Necrosis Factor.

melanoma diagnosis, and alternative therapies, such as anti-IL-23 or anti-integrin therapy, may be considered for these patients if necessary. Given the potential for increased risk of cancer in IMID patients treated with non-selective JAKi, we suggest withholding this class of treatment for up to 5 years following a cancer diagnosis. The decision to resume or switch to alternate therapy should be considered on an individual basis. This recommendation differs from ECCO and AGA but is in line with that of other groups.[48] We also suggest reassessing anti-integrin therapy in patients who develop gastrointestinal malignancies. For all other IM classes, there is no compelling data to suggest holding or switching therapy. However, holding therapy may be reasonable in patients receiving cytotoxic chemotherapy expected to control systemic inflammation or in those with a prior cancer that has a moderate to high risk of recurrence (**Figure 1**).

Conclusion

With a growing armamentarium of IBD therapies, their increasing use at higher doses and earlier in the disease course, and an IBD population that is living longer, gastroenterologists will encounter an increasing number of IBD patients with active or prior cancer. We have summarized the available evidence and proposed a management approach in this setting to guide shared decision-making in practice. However, it is important to note that nearly all the existing data are based on observational studies and the number of large studies in the post-cancer setting, particularly for newer agents, is limited. As such, optimal management in this area requires a collaborative, dynamic approach, with no "set in stone" solutions. Future large multi-centre studies evaluating specific cancer risks associated with specific therapies are required to better guide IBD treatment in this setting.

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Inflammatory Bowel Disease in the Elderly

Seth R. Shaffer, MD, MS

Introduction

The incidence of inflammatory bowel disease (IBD) among the elderly in Canada has increased from 1 out of 160 seniors in 2018, to 1 out of 88 seniors in 2023, representing 1.14% of the senior population.[1] It is thought that more than one-third of all IBD patients will be over 60 years of age in the next decade.[2] The prevalence is expected to increase due to a combination of new diagnoses as well as the aging of younger people already living with IBD.

Elderly persons with IBD face unique challenges that younger people with IBD often do not, such as co-existing comorbidities, frailty, polypharmacy, and an increased risk of infections and cancer. While the therapeutic management of elderly persons with IBD is similar to that of younger people with IBD, it requires careful consideration of many different factors, and special attention is needed when weighing the risks and benefits of medical therapy.

Clinical Presentation

Elderly-onset Crohn's disease (CD) is more frequent in females, while elderly-onset ulcerative colitis (UC) is more common in males.[3,4]

Elderly persons with IBD can present with different symptoms compared to younger people with IBD. In UC, weight loss is more commonly reported, while rectal bleeding and abdominal pain are less commonly reported.[3] Left sided disease is the most common presentation. Additionally, the cumulative 5-year risk of surgery is 7.8%, which is similar to that of adults with IBD.[5] Compared with younger individuals with CD, elderly people are more likely to have isolated colonic disease, as well as fibrostenosis, while penetrating or perianal disease is rare.[5,6] Rectal bleeding, diarrhea, abdominal pain, and weight loss are all less common.[3] The cumulative 5-year risk of surgery for those over the age of 60 with CD is 22.6%.[5] Rates of primary sclerosing cholangitis and dermatologic manifestations of IBD are similar between elderly persons and younger adults,

with elderly persons having higher rates of ocular manifestations of IBD, and lower rates of arthritis.[7]

In addition, the risk of post-operative mortality is higher in elderly persons with IBD compared to younger people, with rates of 6.1% versus 0.7% in UC and 4.2% versus 0.3% in CD. The risk of non-fatal post-operative complications is similarly higher for elderly people with both CD and UC.[8]

It is important to consider other causes of intestinal inflammation in elderly people, as the differential diagnosis can be broad. This includes conditions such as infectious colitis, microscopic colitis, ischemic colitis, segmental colitis associated with diverticulosis, radiation colitis, and malignancy.[9] For this reason, elderly people can often be misdiagnosed,[10] which can lead to delays in receiving appropriate treatment.

Comorbidities in the Elderly

Persons with IBD are at an increased risk of developing osteoporosis, a risk that cannot be solely attributed to corticosteroid use.[11] A population-based study in Manitoba showed that people over the age of 65 years with IBD have an increased risk of cerebrovascular disease (hazard ratio [HR] 1.19, 95% confidence interval [CI] 1.01–1.40), cardiac disease (HR 1.24, 95% CI 1.07–1.43), peripheral vascular disease (HR 1.36, 95% CI 1.14–1.62), cancer (HR 1.21, 95% CI 1.04–1.40), and other comorbidities.[12] A large US study assessing a nationwide database found that persons with IBD over the age of 65 are more likely to be hospitalized with serious infections and cardiovascular complications compared to individuals aged 40–64 and those younger than 40.[13]

Disease Related Complications

Ananthakrishnan et al. showed that older persons with IBD (65 years or older) who are hospitalized for their condition have an increased mortality compared to those with IBD aged 19–64 years (odds ratio [OR] 3.91, 95% CI 2.50–6.11). This mortality risk is even higher when compared to just those aged 19–35 years (OR 17.42, 95% CI 8.92–33.99).[14] A large US cohort study found that the risk of herpes zoster was higher in those with IBD treated with 5-ASA only compared to persons without IBD (adjusted HR [aHR] 1.72, 95% CI 1.51–1.96). Within the IBD cohort, age was identified as a risk factor for becoming infected.[15] A retrospective study that included[13] hospitals in Hong Kong showed that elderly-onset persons with IBD have a higher risk of developing herpes zoster (OR 2.42, 95% CI 1.22–4.80), cytomegalovirus colitis (OR 3.07, 95% CI 1.92–4.89), all-cancer development (OR 2.97, 95% CI 1.84–4.79), and IBD-related hospitalizations (OR 1.14, 95% CI 1.09–1.20) compared with those with adult-onset IBD.[6]

Access to Care

It has been reported that technology literacy decreases with age,[16] making it difficult for elderly persons with IBD to access their gastroenterologist, particularly as more health care providers have been incorporating virtual care into their practices since the COVID-19 pandemic. Additionally, research has shown that elderly persons with IBD who are treated by a gastroenterologist, or are part of a network with more gastroenterologists, experience better outcomes. These patients are more likely to be prescribed a biologic or immunomodulator compared with those who are not treated by a gastroenterologist.[17]

Frailty

Frailty describes a state where one has a decreased physiologic reserve in response to a stressor, which is often not related to chronologic age, but more to biologic age. Although frailty can theoretically occur at any age, it is more common in the elderly. Frailty has been shown to be related to low-grade inflammation with elevated levels of c-reactive protein (CRP), tumor-necrosis factor-alpha (TNF-alpha), and interleukin-6.[18] It has been shown that fecal calprotectin levels can be elevated in various diseases such as ischemic colitis, neoplasm, and even diverticulitis, as well as with certain therapies such as non-steroidal anti-inflammatory drugs and proton pump inhibitors.[19] Since these are more common in the elderly, biomarkers such as CRP and fecal calprotectin may be less specific for disease activity in the elderly with IBD. Studies reveal that frailty is present in 5–33% of persons with IBD,[20-22] and is more common in older persons with IBD compared to those without IBD.[23] The presence of frailty in persons with IBD is associated with an increase in adverse outcomes, including prolonged hospitalization, readmission to hospital

for IBD, and mortality.[22,24] One study also showed that the presence of pre-treatment frailty was associated with an increased risk of infections in those receiving immunomodulators and anti-TNF therapy.[25]

Polypharmacy

Polypharmacy, often defined as the use of 5 or more medications, is a concern in the elderly, as it can lead to non-adherence with IBD therapies. In people 65 years or older, polypharmacy has been associated with adverse outcomes including drug interactions, falls, urinary incontinence, and cognitive decline.[26] In addition, it poses a risk of flaring in those with IBD (OR 4.0, 95% CI 1.66–1.92).[27] A study of senior persons with IBD showed that each individual had on average 9 prescribed medications, and 40% of them had a potential drug interaction involving one of their IBD therapies.[28] A retrospective study of persons with IBD aged 60 years or older showed that almost three-quarters of the patients experienced polypharmacy. Severe polypharmacy, defined as taking 10 or more medications, was associated with an increased risk of hospitalization (aHR 2.16, 95% CI 1.37–3.43).[29]

Deficits

Geriatric deficits are more common in elderly persons with IBD, and those with active disease are more likely to have deficits compared to those without.[30] The same study also found that elderly persons who were diagnosed with IBD at age 60 or later are more likely to experience cognitive impairment, reduced handgrip strength, and slower gait speed. These deficits are also associated with a lower health-related quality of life.

Treatment and Safety

While therapeutic efficacy for elderly persons with IBD is mostly similar to that of younger patients, there are potential complicating factors to consider. These include increased risks of infection and malignancy, and the potential for drug-drug interactions.

Corticosteroids remain effective for induction therapy and for rapidly improving symptoms in persons with IBD. A systematic review and meta-analysis showed that the use of corticosteroids in persons with IBD over 60 years of age is similar to their use in those younger than age 60, however, the study also showed that the use of immunomodulators and biologics is lower among elderly persons with IBD.[5]

Oral 5-ASA therapies are an effective and safe therapy for inducing and maintaining remission for mild-to-moderate UC, and despite its lack of evidence for their use in CD, they remain widely used.[3] Thiopurines continue to be effective treatments for both UC and CD. A cohort study following elderly persons with IBD has shown that one-fifth of patients were exposed to thiopurines within 5 years of their diagnosis.[31] Thiopurine use, however, can increase the risk of infections,[32] non-melanoma skin cancers in persons over 65,[33] and lymphoproliferative disorders in those over 50.[34] In elderly patients with IBD who start a thiopurine over 60, they are at an increased risk of adverse events including infections, neoplasms, and hematologic abnormalities compared to those who are less than 50 who start a thiopurine.[35]

Anti-TNF therapies remain an important option for elderly persons with IBD, especially for those who are hospitalized, steroid dependent, or steroid refractory. However, the evidence for anti-TNF efficacy in older people with IBD is conflicting. Some studies show that elderly persons have a lower persistence with anti-TNF therapy and are more likely to experience treatment failure.[36,37] Alternatively, analyses from randomized trials show no difference between the older cohort (60 years old and older) compared with the younger cohort (younger than 60) in terms of inducing and maintaining remission.[38] A pooled analysis from randomized trials assessing anti-TNF found an increased risk of adverse events in people aged over 60 years with UC. However, age was a more significant predictor of these adverse events than the anti-TNF therapy.[38] Persons over 60 with immune-mediated inflammatory diseases who were on biologics had an increased risk of infection compared to both older people not on biologics and younger persons on biologics.[39] One study showed that combination therapy involving anti-TNF and a thiopurine in persons over 60 was associated with an increased risk of herpes zoster infection.[15] However, another study observed no difference in infection risk for those over 60 years on combination therapy compared to those receiving conventional treatment.[40]

Vedolizumab, a gut-specific monoclonal antibody, is effective in the elderly, with an efficacy comparable to younger persons.[41,42]

In a retrospective cohort of persons over 60 assessing vedolizumab and anti-TNF therapy, vedolizumab was discontinued less frequently (25.9% versus 51.9%), and had higher endoscopic remission rates (65.7% versus 45.2%).[43] Vedolizumab is effective in the elderly, and is equally as effective and safe as ustekinumab in elderly persons with CD.[44,45] A retrospective study in Italy showed a higher persistence on vedolizumab in non-elderly persons with UC compared with people over 65 years-old, but this was not seen with CD, although they did not control for prior anti-TNF exposure.[46] Vedolizumab has a lower risk of infectious complications and is considered safe for elderly patients.[47]

Ustekinumab, an anti-IL12/23 antibody, has comparable effectiveness across all age groups.[48] One study showed that rates of mucosal healing were similar in the older (65 years and older) and younger (<65 years) cohorts.[49] It is also considered safe for elderly patients, with no increased risk of infectious complications.[50]

Newer anti-IL23 antibody treatments are also considered equally effective and safe among all age groups, including elderly patients, with no increased risk of infections or malignancy.[51,52]

Advanced oral therapies, including Janus kinase inhibitors (JAKi) (tofacitinib and upadacitinib) and oral S1P receptor modulators (ozanimod and etrasimod), have emerged as therapeutic options in recent years. Clinical trial data assessing etrasimod in UC have shown that outcomes are similar across all age groups, including those over 60.[53] Additionally, safety outcomes are similar across all age groups with no increased risk of infection.[53,54] Tofacitinib has been shown to be effective in treating UC across all age groups. However, age was a significant predictor for herpes zoster infection, malignancies excluding non-melanoma skin cancers (NMSC), and NMSC.[55] Small studies have shown upadacitinib to be effective in older people with UC,[56] and it is also indicated in the treatment of CD. The safety profile of upadacitinib in the elderly is thought to be comparable to younger people[49], though there is an increased risk of herpes zoster infection with JAKi treatment and this risk increases with age.[57] Hence, it is imperative that persons with IBD be vaccinated against herpes zoster regardless of their therapy, but especially if they are starting treatment with a JAKi.

Conclusion

The prevalence of IBD in elderly persons is only increasing, presenting unique challenges for their management. When treating elderly persons with IBD, one must be cognizant of age, comorbidities, polypharmacy, frailty, and access to care. Anti-TNF therapies are potentially associated with an increased risk of infection, therefore, biologics with improved side effect profiles should be considered when appropriate. Owing to the complex medical needs of elderly persons with IBD, a multidisciplinary approach is essential to provide comprehensive care.

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Obesity in Inflammatory Bowel Disease (IBD): Recognizing a Critical Modifier In Modern Disease Management

Joëlle St-Pierre, MD, PhD

Introduction: A Shifting Landscape in IBD And Obesity

The notion of obesity as a disease remains controversial. A recent consensus from the *Lancet Diabetes & Endocrinology Commission* reframes obesity by distinguishing between "preclinical obesity," defined as a state of excess adiposity with preserved organ function, and "clinical obesity," defined as a chronic, systemic illness caused by excess adiposity and characterized by measurable dysfunction in organ systems or limitations in daily living activities.[1] This distinction provides a medically meaningful basis to identify when obesity constitutes a disease in its own right.

Historically, inflammatory bowel disease (IBD) was associated with undernutrition and weight loss, a reflection of both disease activity and malabsorption. However, with shifting demographics, improved therapeutic options, and global lifestyle changes, obesity has emerged as an increasingly relevant coexisting condition in patients with IBD. While the current prevalence of overweight and obesity among Canadians with IBD remains unknown, population-level data from Statistics Canada show that 35.8% of adults in urban centers are classified as overweight, and 29.0% as obese.[2]

This epidemiologic shift has important clinical ramifications. Obesity contributes to systemic inflammation and is associated with increased healthcare utilization and reduced quality of life (QoL), which are burdens already faced by patients with IBD. The intersection of these two chronic conditions introduces complex challenges for disease management,

health outcomes, and healthcare systems. This review explores the clinical impact of obesity in patients with IBD, including its influence on disease phenotype, treatment response, surgical outcomes, and QoL.

Measuring Obesity in IBD: Moving Beyond BMI

While body mass index (BMI) remains the most common clinical tool for classifying overweight (BMI ≥25 kg/m^2) and obesity (BMI ≥30 kg/m^2), it fails to distinguish between lean and fat mass or account for fat distribution and adipose tissue function. In a meta-analysis comparing anthropometric tools to imaging standards, BMI showed low sensitivity (51.4% in women, 49.6% in men) albeit high specificity (95.4% and 97.3%, respectively) for detecting obesity.[3] Waist circumference and waist-to-height ratio had similar limitations, with modest sensitivity and variable specificity.

In IBD, visceral adipose tissue (VAT), and specifically mesenteric adipose tissue (MAT), is emerging as a critical player in disease biology. Mesenteric fat is known to expand in inflammation, a phenomenon known as "creeping fat." This "creeping fat," first described by Crohn himself,[4] has been associated with stricturing phenotypes and may predict postoperative recurrence.[5-7] MAT lies adjacent to inflamed bowel, making it more than a systemic marker of adiposity; it may actively drive local inflammation by producing cytokines such as interleukin (IL)-6, tumour necrosis factor (TNF)-α, and leptin that amplify intestinal inflammation.[7] Yet MAT and VAT remain largely invisible when relying on BMI.

Imaging tools such as dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), computed tomography (CT) and point-of-care ultrasound offer more granular insight into adipose tissue distribution and composition. Though not yet standard in routine care, they are increasingly used in research. Future studies should prioritize validating these direct measures of adiposity as clinical biomarkers to improve prognostication and guide personalized management in IBD. Many of these assessments could be incorporated into clinical practice using imaging-based tools such as point-of-care ultrasound, which is increasingly utilized for bedside evaluation in IBD.

Clinical Consequences of Obesity in IBD

Impact on Disease Phenotype

Obesity appears to influence disease phenotype. In ulcerative colitis (UC), obesity has been linked to more extensive disease, particularly pancolitis.[8] In Crohn's disease (CD), paradoxically, higher BMI has been linked to a lower risk of penetrating or fistulizing complications in some cohorts.[9] However, increased MAT in CD has been associated with transmural inflammation, stricturing phenotypes, and postoperative recurrence.[6] This further supports the hypothesis that body composition rather than body size may better define disease phenotype, highlighting the need for imaging-based adiposity measures.

Obesity and IBD-related Complications

The relationship between obesity and IBD-related complications is complex. Several large cohort studies have found no association between obesity and increased steroid use, adverse events, emergency visits, hospitalization, or IBD-related surgery.[10-14] In UC, patients with obesity were found to have a lower proportion of years with chronic active disease, were less likely to be prescribed anti-TNF therapy, and had lower rates of hospitalization or surgery.[8,15]

Conversely, other studies have shown that higher BMI is associated with persistent disease activity, relapse, and a higher risk of colectomy.[16] In patients with IBD and Clostridioides difficile infection, obesity is associated with longer hospital stays, increased colectomy rates, and increased healthcare costs.[17]

Obesity and Response to Therapy

Despite theoretical concerns that obesity may attenuate response to therapy through altered pharmacokinetics and a pro-inflammatory cytokine milieu, current evidence remains mixed. In a large multicenter cohort of over 3,000 biologic-treated patients with IBD, obesity was not associated with an increased risk of hospitalization, surgery, or serious infections within one year of biologic initiation (including TNF antagonists, vedolizumab, and ustekinumab).[13] Similarly, a pooled individual

participant data analysis from randomized clinical trials of infliximab (ACCENT-I/II, SONIC, ACT-1/2) found no association between obesity and rates of clinical or endoscopic outcomes in either CD or UC.[10]

In contrast, a study of infliximab-treated patients with CD has shown that higher VAT was independently associated with a reduced likelihood of mucosal healing after induction therapy.[18] A large real-world study using the TriNetX database has demonstrated that obesity was significantly associated with higher risks of therapy failure across multiple advanced therapies in UC, including TNF antagonists, vedolizumab, ustekinumab, and Janus kinase (JAK) inhibitors.[19] These patients had higher rates of corticosteroid use, therapy switching, and colectomy within two years compared to propensity-matched non-obese controls (adjusted hazard ratios [HR]s ranged from 1.26 to 1.38 depending on therapy).[19]

Evidence for small molecule therapies remains limited. In a post hoc analysis of OCTAVE, BMI did not affect treatment efficacy or safety in patients with UC, with similar remission and response rates across BMI categories.[20] Further studies are needed to disentangle the roles of pharmacokinetic variability and obesity-related pathophysiology. Future work should integrate clinical outcomes with mechanistic measures such as VAT distribution, adipokine profiles, and drug levels to optimize therapy in this population.

Surgical Risk and Outcomes in Patients with IBD and Obesity

Obesity is increasingly recognized as a contributor to adverse surgical outcomes in patients with IBD. A meta-analysis of over 12,000 patients has shown that obesity was associated with increased risks of overall postoperative complications (odds ratio [OR] 1.45, 95% confidence interval [CI] 1.15–1.84), infectious complications (OR 1.48, 95% CI 1.17–1.88), and conversion to laparotomy (OR 1.90, 95% CI 1.32–2.72).[21] Beyond BMI, body fat distribution also appears to influence outcomes. A high subcutaneous-to-visceral fat ratio was independently associated with postoperative infectious complications in CD (OR 2.01, 95% CI 1.20–3.19).[22] In addition, patients with excessive visceral fat area had more than twice the risk of endoscopic recurrence at 18 months following surgery (relative risk [RR] 2.1, 95% CI 1.5–3.0).[23]

These findings have led to growing interest in the mesentery as a surgical target in CD. Extended mesenteric resection, which involves the removal of affected mesenteric fat along with the bowel segment, has been proposed as a strategy to reduce disease recurrence. A recent meta-analysis of 4,358 patients has found that extended mesenteric resection significantly reduced surgical recurrence compared to mesenteric preservation (OR 4.94, 95% CI 2.22–10.97; I^2 = 0%) without increasing postoperative morbidity or length of hospital stay.[24] Together, these data support incorporating visceral adiposity assessment into preoperative planning and suggest that targeting mesenteric disease may help reduce postoperative complications and recurrence in IBD surgery.

Obesity and Metabolic Comorbidities in IBD

Obesity, while not the sole defining feature of metabolic syndrome (MetS), is a central component. Its rising prevalence in the global population has prompted growing interest in associated metabolic comorbidities in patients with IBD, including MetS, type 2 diabetes mellitus (T2DM), and metabolic dysfunction-associated steatotic liver disease (MASLD).

A recent meta-analysis estimated the pooled prevalence of MetS in patients with IBD to be 19.4% (95% CI 15.1–23.8%), with significantly higher rates in UC compared to CD (38.2% vs. 13.6%).[25] In a large prospective cohort, the prevalence of T2DM among patients with IBD was approximately 5%, and its presence was associated with greater systemic inflammation, worse clinical disease activity, lower QoL, and increased healthcare utilization.[26] In a meta-analysis including over 14,000 patients with IBD, the global pooled prevalence of MASLD in patients with IBD was 30.7%, nearly twice the odds compared to healthy controls (OR 1.96, 95% CI 1.13–3.41).[27] Moreover, 13.6% of patients with IBD and MASLD had advanced liver fibrosis. Higher BMI was significantly associated with increased risk of MASLD in patients with IBD, with a pooled adjusted odds ratio of 1.27 (95% CI 1.22–1.32), reinforcing the contribution of obesity to hepatic comorbidity in this population.

Given the prevalence of these conditions in IBD and their strong association with obesity, routine screening for metabolic comorbidities should be considered in patients with IBD and elevated adiposity to identify high-risk

Domain	Key Findings	Clinical Implications	Research Gaps
Assessment of Obesity	BMI poorly reflects fat distribution and adipose function. VAT and MAT are more strongly linked to IBD outcomes.	Clinicians should consider tools that reflect adiposity, such as imaging-based tools, rather than rely on BMI alone.	Validation of VAT/MAT measures as biomarkers. Need for definition of clinical thresholds for risk stratification.
Disease Phenotype	Obesity is linked to more extensive UC. MAT is associated with stricturing CD.	VAT/MAT imaging may help refine IBD phenotyping and prognosis.	Need for prospective studies linking fat distribution to disease behaviour and histology.
IBD-Related Complications	Findings are mixed: some show no effect; others report higher relapse or colectomy risk.	Consider individual body composition and comorbidities when evaluating prognosis.	Harmonize definitions and stratify by fat distribution and metabolic profiles in future studies.
Response to Therapy	Obesity may attenuate the response to biologics, but JAK inhibitors appear to be weight-neutral.	Account for adiposity when selecting or optimizing therapies.	Study pharmacokinetic mechanisms; integrate adiposity and drug levels in treatment-response models.
Surgical Outcomes	Obesity and VAT increase the risk of complications and post-op recurrence.	Use VAT assessment in pre-op planning; consider mesenteric resection in select CD cases.	Prospective trials evaluating mesenteric resection vs. preservation and its long-term outcomes.
Metabolic Comorbidities	MetS, T2DM, and MASLD are more prevalent in patients with IBD and obesity.	Screen for metabolic diseases in patients with elevated adiposity.	Determine the impact of metabolic disease control on IBD outcomes.
Quality of Life	Obesity and VAT are associated with worse patient-centered outcomes; lifestyle modification is beneficial.	Address body composition and lifestyle in routine care.	Longitudinal studies on the QoL impact of weight loss and body composition changes.

Table 1. Summary of Key Findings, Clinical Implications, and Research Gaps Related to Obesity in IBD; *courtesy of Joëlle St-Pierre, MD, PhD.*

Abbreviations: IBD: Inflammatory bowel disease, **UC:** ulcerative Colitis, **CD:** Crohn's disease, **BMI:** body mass index, **VAT:** visceral adipose tissue, **MAT:** mesenteric adipose tissue, **MetS:** metabolic syndrome, **MASLD:** metabolic dysfunction-associated steatotic Liver Disease, **T2DM:** type 2 diabetes mellitus, **QoL:** quality of life

individuals and optimize both IBD and metabolic clinical outcomes.

Obesity and QoL: Patient-Centred Outcomes

Emerging evidence suggests that both obesity and related metabolic comorbidities negatively impact patient-reported outcomes. In a prospective cohort, patients with IBD and T2DM had significantly lower QoL scores based on the Short Inflammatory Bowel Disease Questionnaire (SIBDQ); (49.3 vs. 54.8; P <0.001), higher disease activity and increased healthcare use.[26] A large longitudinal cohort study from the IBD Partners cohort found that obesity was independently associated with inferior patient-reported outcomes across multiple domains, including anxiety, depression, fatigue, pain interference, and social function. These effects were evident in both UC and CD, with exposure-response relationships and longitudinal worsening observed in patients with class II/III obesity.[16]

In a prospective cohort of patients with CD, a higher visceral-to-subcutaneous fat ratio, but not BMI, was independently associated with lower SIBDQ scores over 24 months, particularly in patients with ileal disease.[5] In a cross-sectional

study of 688 patients with IBD, those with an active or healthy lifestyle (Mediterranean diet plus physical activity) had significantly higher IBDQ-9 scores.[28] Inactivity and poor dietary adherence were also independently associated with obesity, MASLD, MetS, and T2DM. Finally, Guardado et al. reported that surgical resection led to significant SIBDQ improvements across all BMI groups, with no pre- or postoperative QoL differences by BMI, suggesting obesity does not preclude postoperative QoL improvement.[29] Overall, these findings underscore the need for future studies that move beyond traditional clinical endpoints to understand better how obesity, visceral adiposity, and lifestyle factors affect QoL, which is an increasingly recognized and key target in the holistic management of IBD.

Clinical Practice Implications and Research Priorities

Obesity is an increasingly common coexisting condition in patients with IBD, influencing disease phenotype, treatment response, surgical risk, metabolic health, and QoL. These domains, summarized in **Table 1**, reflect a growing body of evidence highlighting the need for a more nuanced and proactive approach to care. For example, providers should move beyond BMI, incorporating image-based assessments of visceral adiposity to better stratify risk and guide management, though broader implementation in practice remains a future goal.

Therapeutic decisions should consider how obesity modifies drug response. Obesity may reduce the effectiveness of biologic therapies, while JAK inhibitors appear to maintain efficacy across weight categories. Routine screening for cardiovascular disease, diabetes, and MASLD should be incorporated into the standard of care for patients with IBD with excess adiposity. Multidisciplinary care, through collaboration with dietitians, psychologists, endocrinologists, and hepatologists, may help address the complex needs of this population and optimize both gastrointestinal and metabolic outcomes.

Despite progress, critical gaps remain. Future research should clarify the mechanistic links between adiposity and intestinal inflammation. Longitudinal studies are needed to assess the impact of obesity and its management on IBD-specific outcomes. Comparative effectiveness studies evaluating medical (e.g., glucagon-like peptide-1 receptor agonists), surgical, and lifestyle interventions across diverse IBD populations are needed. Finally, as weight management therapies become more widely used, consensus guidelines are urgently needed to support their safe and effective integration into IBD care.

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Is There Still a Role for Proactive Therapeutic Drug Monitoring (TDM) in Inflammatory Bowel Disease (IBD): A Review of the Literature

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Introduction

The management of biologic medications in inflammatory bowel disease (IBD) is complex due to the inter- and intra-individual variability in pharmacokinetics and pharmacodynamics. There exist important differences in drug uptake and metabolism depending on a variety of factors including dosing intervals, route of administration, gender, body weight, albumin levels, inflammation, immunogenicity, genetic variation and other concurrent therapies.[1] Males and individuals with higher body weight exhibit increased drug clearance, and certain biologics are more immunogenic than others. Moreover, the presence of a high inflammatory state, as demonstrated by elevated CRP levels and low albumin levels, also increase drug clearance and are associated with worse clinical outcomes.[2,3]

Therapeutic drug monitoring (TDM) can be useful in titrating certain biologic medications in IBD patients. By measuring drug levels and screening for antibody formation, TDM allows physicians to evaluate and optimize response to medications. Using these values, physicians can determine whether patients are sub-optimally dosed and can benefit from a reinduction or dose escalation, or whether these patients have begun developing immune responses to these medications.[4-7]

Reactive and Proactive TDM

There are 2 strategies for the use of TDM in clinical practice. The first strategy is reactive, whereby TDM is used in patients with active clinical, biochemical and endoscopic inflammation. This strategy allows physicians to understand whether active inflammation can be attributed to sub-therapeutic drug levels, anti-drug antibodies, or a pharmacodynamic treatment failure, where patients have optimal drug concentrations. There is a general consensus that a reactive TDM strategy is useful in patients on anti-tumor necrosis factor (anti-TNF) medications and that regular proactive monitoring of disease activity is the standard of care in IBD patients starting biologic medications[8] (**Figure 1a**). The American Gastroenterological Association's (AGA) clinical guidelines recommend reactive TDM in IBD patients on anti-TNF medications, though this recommendation is based off low-quality evidence.[9] Suggested therapeutic TDM thresholds in clinical practice (expert opinion) are outlined in **Table 1**, but clinical judgement should be exercised when using these thresholds.

The utility of a reactive strategy for patients on non-anti-TNF biologics is less clear. However, there is data demonstrating an exposure response relationship in patients on ustekinumab (UST)[10] and vedolizumab (VDZ) [10,11] and that dose escalation may be helpful for patients with a loss of response to help recapture remission.[12,13] Given

Drug	Suggested Trough Concentration (*ug/mL*)
Infliximab	≥10–15
Adalimumab	≥15
Golimumab	≥3

Table 1. Therapeutic TDM levels in anti-TNF agents; *courtesy of Davide De Marco, MD and Waqqas Afif, MD, M.Sc. (Epi), FRCPC.*

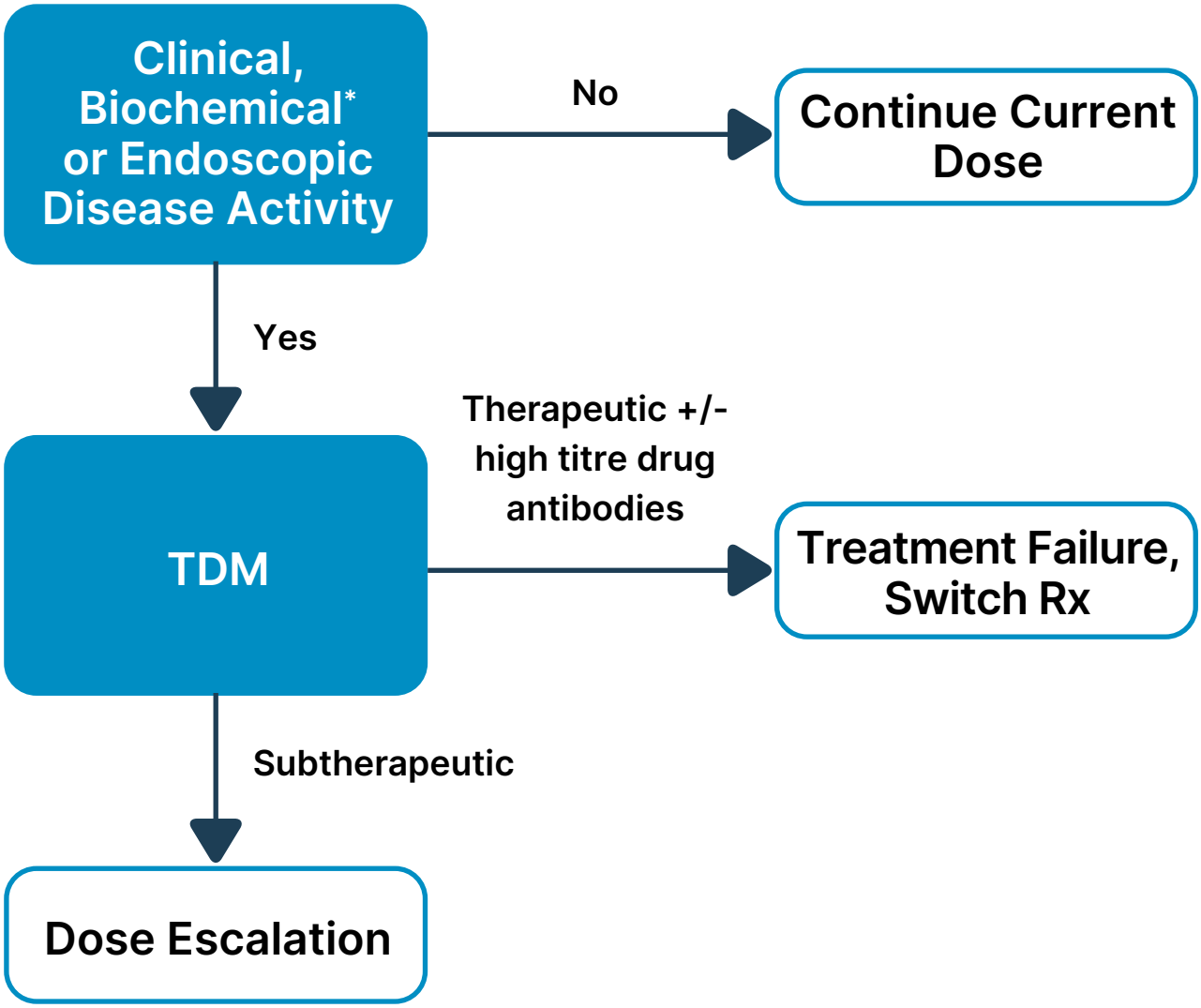

Figure 1a. Reactive TDM strategy; *courtesy of Davide De Marco, MD and Waqqas Afif, MD, M.Sc. (Epi), FRCPC.*

*Fcal q3–4, months in first year of Rx followed by yearly.

the low rates of immunogenicity of UST, VDZ, and newer Interleukin (IL)-23 biologics (<5%) and the absence of clear cut-offs where dose escalation would not be useful, the utility of reactive TDM for UST and VDZ remains unclear. Although TDM assays for UST and VDZ are readily available, their use in routine clinical care is likely not indicated given the available data. TDM is likely not necessary for oral small molecules such as Janus Kinase inhibitors (tofacitinib and upadicitinib) and the sphingosine-1-phosphatase receptor modulators (ozanimod and etrasimod). These oral molecules have stable pharmacokinetics and no immunogenicity, which makes their dose effect more predictable.[14-21]

On the other hand, a proactive strategy employs TDM during induction or maintenance, irrespective of the presence of symptoms or objective inflammation, to help guide decisions on drug dosing. It has been proposed that this strategy may allow drug serum concentrations to be optimized which may prevent suboptimal drug concentrations and antibody formation. It has also been proposed that this strategy may help prevent the development of active inflammation in patients who are in remission.[22,23] Most of the data for a proactive TDM approach pertains to patients on anti-TNF medications, which will be the main topic of discussion for this review.

Proactive TDM with Anti-TNF Medications

Anti-TNFs, such as infliximab (IFX), adalimumab (ADAL) and golimumab, are commonly used agents for the induction and maintenance of clinical remission in both CD and UC.[24-27] While these medications achieve 52-week clinical remission rates of 35–40% (26, 28, 29), 30% of patients are primary non-responders and an additional 50% will eventually experience a loss of response.[11,30] There is a well-documented exposure-response relationship amongst IBD patients on anti-TNF therapies.[31-35] ACT I/II trials in UC and the ACCENT I trials in CD respectively demonstrated post-induction IFX trough levels of >5.1 ug/mL and >3.4 ug/mL at 14 weeks, respectively, as predictive of prolonged clinical response.[29,34,36]

Anti-TNF therapy alone without concomitant use of an immunomodulator (monotherapy) is associated with an increased risk of immunogenicity. A recent study by Battat et al, which included 63,176 patients, found that 23.6% of patients who were treated with IFX and 19.6% of those treated with ADAL developed anti-drug antibodies.[37] Additionally, the PANTS study which included 955 IFX patients and 295 ADAL patients, found that suboptimal drug concentrations at week 14 predicted immunogenicity.[4] Given this data a proactive TDM approach can be considered to prevent treatment failure in the context of biologic monotherapy. This approach allows for dose optimization via increasing the dose or frequency during or immediately after induction.

The TAXIT randomized control trial (RCT), which included 263 IBD patients with stable responses to maintenance infliximab therapy, randomized patients to dose adjustments based on clinical features or on TDM levels (target trough 3–7 ug/mL). While no statistically significant difference was observed in achieving remission based on the 2 treatment strategies, a statistically significant decrease was noted in disease relapse among patients with concentration-based dosing compared to clinical dosing (7% vs 17% p=.018).[38] The TAILORIX RCT, which included 122 biologic naïve CD patients, showed no statistically significant difference between clinically driven dose escalation when compared to TDM driven dose escalation. However, it is important to note that most patients were not able to achieve therapeutic drug concentrations (sustained IFX level >3ug/mL in only 47% and 46% of the intensification groups and 60% in the control group).[39] Conversely, the PAILOT RCT, a randomized control trial of 78 children with CD found that patients who were randomized to the proactive group were more likely to achieve corticosteroid remission at 72 weeks compared to the reactive group (82% vs 48%, p=.002).[40]

A meta-analysis of 9 RCTs on proactive TDM found that there was no difference in the risk of failing to maintain clinical remission in patients who underwent proactive TDM when compared to conventional management (38% vs 42%, risk ratio [RR] 0.96; confidence interval [CI] 0.81–1.13).[23] Similarly, a meta-analysis by Sethi et al.,[22] consisting of 26 studies –9 of which were RCTs–sought to better understand the role of proactive TDM compared to standard of care (SOC) or reactive TDM. Amongst these studies, 8 explored proactive TDM for clinical remission or response. The proactive arm included 704 patients, and the SOC included 632 patients. No significant difference was noted between the two arms (RR 1.07, 95% CI 0.97–1.18, p=0.19).[22] However, sub analyses of studies comparing 793 proactive patients to 525 reactive patients, revealed that the proactive group was less likely to experience treatment failure (RR 0.46, 95% CI 0.21–0.98) and had lower hospitalization rates (RR 0.33, 95% CI 0.21–0.54). Conversely, there were no statistically significant differences between proactive and reactive TDM in the need for surgical interventions (RR 0.54, 95% CI 0.17–1.77, p=0.31). Ongoing prospective RCT's are further investigating the role of proactive TDM testing in patients with IBD.

Proactive TDM with Non Anti-TNF Medications

There is limited data available on the use of proactive TDM in patients receiving newer biologic medications such as UST, VDZ and newer IL-23 medications. A retrospective analysis of 436 Crohn's patients showed that induction and post-induction levels did not correspond to biochemical normalization.[41] Conversely, a recent single centre cohort of 94 IBD patients found those who underwent at least 1 proactive TDM were more likely to achieve drug persistence on multivariate analysis (hazard ratio [HR] 14.3, p<0.001).[42] The recently published ENTERPRET study showed that for patients with

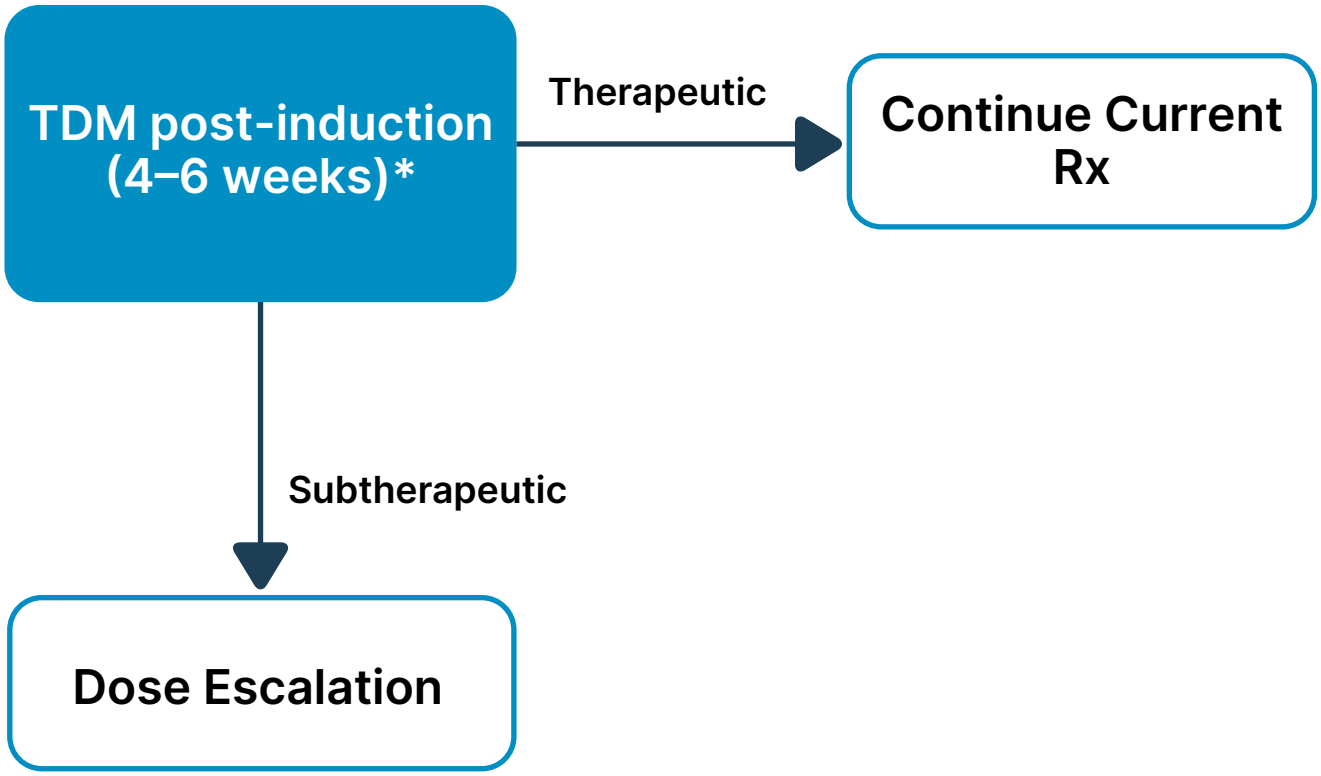

Figure 1b. Proactive TDM strategy; *courtesy of Davide De Marco, MD and Waqqas Afif, MD, M.Sc. (Epi), FRCPC.*

*Preferred in patients with low albumin, HLA-DQA1*05, large inflammatory burden, or multiple failed biologics.

early non-response and high drug clearance (low drug concentrations), dose optimization was of no benefit.[43] For UST, a recent single centre retrospective cohort study of 83 patients on SC UST found that those who underwent a single proactive TDM had higher drug persistence and fewer IBD-related hospitalizations.[44] Given these limited data, proactive VDZ and UST TDM cannot be recommended in routine clinical care.

Proactive TDM in the Clinical Setting

Based on the current evidence, routine proactive monitoring with anti-TNF medications cannot be recommended. But proactive monitoring is important in patients with increased clearance and/or an increased risk of immunogenicity (e.g., those with low albumin, high inflammatory burden, HLA-DQA1*05 haplotype, or anti-TNF exposed) to ensure adequate drug concentrations and treatment success[5,6,11,45] (**Figure 1b**). Proactive TDM may play an important role in these patient populations, as higher trough levels have been shown to decrease non-immunogenic treatment failure and may also lower the risk of neutralizing antibody formation.[46] We would recommend a proactive TDM assay in these patients be done at week 6 for IFX targeting levels of >10 ug/ml and at week 4 for ADAL, targeting concentrations >5 ug/ml.[39,40] Finally, while not within the scope of this review, clinicians can consider using proactive TDM with anti-TNF medications in the setting of dose de-escalation and when considering withdrawal of concurrent immunosuppression with methotrexate or thiopurines.

Conclusion

In conclusion, the use of TDM in the management of IBD provides a valuable tool for optimizing biologic therapy, specifically with anti-TNF medications. Reactive TDM is well-supported in guiding clinical decision-making during disease flares. While proactive TDM cannot be routinely recommended, it shows potential benefits in reducing immunogenicity and maintaining drug persistence in high risk patient populations on anti-TNF medications. The routine use of reactive or proactive TDM for non-anti-TNF biologics or small molecules is not supported at this time.

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