

A User's Guide to De-escalating Immunomodulator and Biologic Therapy in Inflammatory Bowel Disease



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De-escalation of immunomodulators and biologic agents in inflammatory bowel disease is frequently discussed with patients and must weigh the risk of continued medical therapy with the risk of disease recurrence. Risk factors for disease flare after withdrawal of inflammatory bowel disease medications such as disease activity at de-escalation, disease prognostic features, and prior course of disease have been identified predominately in retrospective studies, allowing for risk stratification of patients. This review evaluates the published literature regarding therapeutic de-escalation and provides a framework for physicians to apply this to clinical practice. Prospective trials are underway and planned, which should provide further insight into this treatment paradigm and better inform patient selection for this strategy.

Key words: Crohn's Disease; Ulcerative Colitis; Deescalation; Withdrawal; Cessation; Treatment Discontinuation.

Inflammatory bowel disease (IBD) treatment strategies have shifted toward a treat-to-target approach characterized by achieving mucosal healing and clinical remission.¹ Growing evidence demonstrates that obtaining deep remission results in superior outcomes, with recent large trials demonstrating the superiority of tight disease control and early therapeutic escalation.^{2–5} The advantage of combination biologic and immunomodulator (IM) therapy, including azathioprine, mercaptopurine, and methotrexate, supports the paradigm of early disease management and the use of dual agents to increase treatment success.⁶ Growing application of this approach will result in an increasing number of patients being treated more aggressively and earlier in their disease course. Physicians and patients often grapple weighing the risks and benefits of continuing with this treatment approach once remission is obtained compared with de-escalating medical therapy. While patient preference and willingness to de-escalate differs by region, this topic is frequently broached in clinical practice.⁷ Multiple reviews have been published on the topic, summarizing the available evidence.^{8–10} However, despite its clinical importance, there are significant limitations surrounding its practice,

with few randomized or prospective studies, no data on biologics outside of anti-tumor necrosis factor (anti-TNF) agents, and limited information in ulcerative colitis (UC). Acknowledging these constraints, the goal of this review is to provide an overview of the evidence for de-escalation of IM and biologic agents in IBD as well as provide a guide for applying these principles in clinical practice.

How Do We Decide in Whom to De-escalate?

The first step when considering de-escalating medical therapy in IBD involves an evaluation of risk factors for relapse in the context of ongoing treatment risks. Risk factors for disease relapse after de-escalation can be divided into 4 groups and characterized based on the type of de-escalation strategy employed as well as disease type: (1) disease activity at de-escalation, (2) disease prognostic features, (3) prior course of disease, and (4) other features.⁹ Patient factors predisposing to medication related adverse events should likewise be evaluated.¹¹

IM Monotherapy De-escalation

In Crohn's disease (CD) patients considering thiopurine monotherapy de-escalation, active disease at the time of drug withdrawal is strongly associated with relapse. Surrogate risk factors include elevated C-reactive protein (CRP) (≥ 20 mg/L; risk ratio [RR], 16.90), low hemoglobin (≤ 12 g/dl; hazard ratio [HR], 4.80), and an elevated white blood cell count (WBC) ($\geq 6.6 \times 10^9$ /L; HR, 3.75).^{12–14} In addition, CD features associated with poor disease prognosis increase the likelihood of

Abbreviations used in this paper: anti-TNF, anti-tumor necrosis factor; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IBD, inflammatory bowel disease; IM, immunomodulator; MR, magnetic resonance; RR, risk ratio; UC, ulcerative colitis; WBC, white blood cell count.



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reoccurrence when IMs are stopped. These include ileal disease location, young age (≤ 31 years; RR, 2.70), and perianal disease at diagnosis (HR, 2.24).^{9,15,16} The patients' prior disease course and trajectory inform the difficulty in achieving remission, with risk factors including being corticosteroid-free for ≥ 50 months (RR, 5.20), a history of prior complications (HR, 1.74), need for higher IM doses (HR, 2.20), and a duration of remission < 4 years (RR, 4.00).^{9,12,15,16} Other factors, including male sex and interestingly absence of smoking, have been associated with increased risk of subsequent flare.^{16,17}

In UC, disease activity at the time of de-escalation is important, with biologic absence of disease (HR, 0.004) strongly associated with sustained remission, while an elevated WBC count (HR, 1.44) is associated with future flare.^{14,18} Factors reflecting poor prognosis, including young age (HR for each additional year, 0.95) and extensive disease (pancolitis; HR, 5.01) predict relapse.^{18,19} Disease course is similarly important, with a lack of ongoing remission (HR, 2.35) and number of relapses on IM therapy (HR, 1.30), as well as time between diagnosis and initiation of therapy (HR, 1.01), all impacting the risk of disease recurrence.^{18,20} Finally, shorter duration of IM therapy (3–6 months vs 48 months; HR, 2.78) is an important risk factor, underscoring the importance of the length of time in remission and therefore its stability.^{14,19,20}

IM De-escalation From Combination Therapy

Limited predictors have been identified when withdrawing an IM from anti-TNF combination therapy in CD. Relating to disease activity, a CRP > 5 mg/L, which is associated with subsequent need for biologic escalation (HR, 2.65), and a need for IBD-related surgeries (HR, 11.43) are associated with worse outcomes.^{9,21} Factors reflecting poor disease prognosis include young age at diagnosis (< 16 years compared with > 40 years; HR, 4.55).^{9,22} Other features impacting relapse include duration of combination therapy < 6 months (HR, 5.68) and combination therapy with methotrexate, as compared with azathioprine (HR, 3.37).^{9,22} Relating to the impact of IM withdrawal on the pharmacokinetics of biologic agents, a high infliximab level (> 5 $\mu\text{g/mL}$) at the time of de-escalation is protective against relapse (HR, 0.36).^{9,21}

De-escalation of Anti-TNF Therapy

Studies assessing anti-TNF de-escalation include a range of subjects on combination therapy with IM, confounding their general applicability.⁹ Predictors of relapse after anti-TNF withdrawal predominately relate to underlying disease activity. In CD, low hemoglobin (< 14.5 g/dl; HR, 6.00), increased WBC count ($> 6 \times 10^9/\text{L}$, 2.4), endoscopic disease activity (HR, 2.3), elevated CRP (≥ 5 ; HR, 3.20), elevated fecal calprotectin (> 50 $\mu\text{g/g}$; HR,

3.04), and wall thickening on magnetic resonance (MR) enterography ($P = .015$) are associated with increased rates of relapse.^{23–26} Factors relating to disease prognosis or previous disease course are associated with increased relapse rates, including smoking (HR, 1.91), perianal disease (HR, 1.72), ileocolonic disease location (OR 3.18), and young age at diagnosis (< 22 years; HR, 2.24).^{25,27,28} Shorter periods of anti-TNF use and increased time before starting anti-TNF therapy were associated with relapse.^{9,29} Factors relating to prior disease course play a role highlighting an increased risk of recurrence in those with previously hard to control disease, including need for dose intensification of anti-TNF therapy before de-escalating (HR, 12.96), prior surgeries (HR, 11.43), steroid use when starting anti-TNF therapy (OR 3.43), or prior failure of IM therapy (HR, 1.78).^{21,28,30} High infliximab trough levels (> 2 mg/L) are associated with an increased risk of relapse, likely reflecting that subjects in remission with low drug levels do not require the anti-TNF agent to maintain their remission.²⁴ Unfortunately, there are limited studies evaluating withdrawal of anti-TNF therapy in UC, with only prior exposure to anti-TNF agents predictive of relapse.^{9,31}

Risk Factors With Drug Continuation

Excess risk of infection exists with the combination of immunosuppressive drugs. Adjusted HRs for serious infectious risks for thiopurine monotherapy, anti-TNF agent monotherapy, and thiopurines in combination with anti-TNF agents are 1.3 (95% confidence interval [CI], 1.2–1.4), 1.6 (95% CI, 1.0–2.6), and 2.8 (95% CI, 2.4–3.2), respectively.^{11,32} An increased risk of infection has been linked to patient age and should be considered when deciding whether therapy should be continued in specific age groups. Increasing age is a risk factor for serious and opportunistic infections with ongoing medical therapy.^{33,34} Patients 65 years of age and older have a 2- to 3-fold increased risk of infection compared with those patients younger than 65 years of age.^{32,35} Infectious risk in this age group was highlighted by Lynn et al,³⁶ with an annual incidence of serious infection of 2.7% for thiopurine monotherapy, 5.3% for anti-TNF agents, and 5.1% for combination therapy. Likewise, specific age groups are associated with excess cancer risk. While thiopurine exposure is associated an increased risk of lymphoma, this is most pronounced in those patients older than 50 years of age, or in men younger than 30 years of age.³⁷ Caution must be taken with long durations of thiopurine treatment in these age groups, with most cases of lymphoma occurring after 1 year of therapy.³⁷ Thiopurine exposure also increases the risk of urinary tract cancers in older men.³⁸ Additionally, while rare, there is a risk of hepatosplenic T cell lymphoma with thiopurine use, occurring most commonly in men younger than 35 years of age on at least 2 years of therapy.³⁹

How Does This Translate into Clinical Practice?

It can be daunting to incorporate the myriad of prognostic factors (Table 1) into the de-escalation discussion with a patient, given differing risk factors based on disease state and withdrawal strategy. Clear and easy to understand communication with the patient, utilizing an individualized shared decision-making strategy should be employed. To help guide physicians through this process, we have devised a stepwise approach to incorporate the general concepts outlined above (Figure 1). Given the strong association between disease activity and flare, we make it clear to the patient that objective disease remission must be obtained before considering a de-escalation strategy.⁹ A complete blood count, erythrocyte sedimentation rate, and CRP assess hemoglobin, WBC count, and inflammatory parameters associated with relapse, as highlighted in the Infliximab diSconTinuuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressors trial, in which hemoglobin ≤ 12.5 g/dL and a WBC count $\geq 5.0 \times 10^9/L$ were risk factors for major complications after infliximab withdrawal.^{24,40} Stool assessment for fecal calprotectin provides a noninvasive means to assess intestinal inflammation early in the de-escalation discussion, with values <56 mg/kg identifying subjects more likely to remain in stable remission, and portending a lower rate of relapse.⁴¹

Abnormalities in laboratory values warrant evaluation, followed by a colonoscopy and computed tomography or MR enterography, in subjects with small bowel CD, to confirm endoscopic remission and the absence of inflammation. De-escalation should not be pursued in the absence of endoscopic healing. In UC, achieving histologic remission predicts lower rates of steroid use, hospitalization, and relapse compared with endoscopic remission alone, and represents an evolving more stringent endpoint that could be considered before medication withdrawal.^{42–44}

In patients achieving endoscopic remission, we discuss prognostic factors for relapse and highlight that they are associated with a worse CD or UC course, dictate early and aggressive medical therapy, and pose an increased risk of flare with deescalation.⁹ An individualized approach is paramount as some features, such as perianal CD, strongly factor against de-escalation in discussions with patients.⁴⁵ However, others, such as young age and male sex, associated with hepatosplenic T cell lymphoma risk, may conversely influence the initial decision to de-escalate, and therefore must be weighed differently.³⁹

The patient's prior disease course provides insight into the aggressiveness of his or her IBD and the difficulty in achieving remission. Prior relapses while on therapy increase the likelihood of relapse once therapy is stopped, with the length of time and durability of remission factoring into the de-escalation discussion.¹⁹ If

Table 1. Factors Associated With Risk of Inflammatory Bowel Disease Flare According to Medication Withdrawal Strategy and Disease Type

	Crohn's disease	Ulcerative colitis
Stopping IM monotherapy	Elevated CRP Low hemoglobin Elevated WBC count Ileal disease location Young age Perianal disease Steroid-free ≥ 50 mo Prior complications High IM dose Remission <4 y Male sex Absence of smoking	Biologically active disease Elevated WBC count Young age Extensive disease Lack of remission Number of relapses on IM Time from diagnosis to therapy Short IM duration
Stopping IM from combination	Elevated CRP IBD-related surgeries Young age at diagnosis Combination <6 mo Combination with MTX vs AZA	
Stopping anti-TNF agents	Infliximab level ≤ 5 $\mu\text{g/mL}$ Low hemoglobin Elevated WBC count Endoscopic disease Activity Elevated CRP Elevated fecal calprotectin Wall thickening on MRE Smoking Perianal disease Ileocolonic disease location Young age at diagnosis Short treatment duration Time to start of anti-TNF agent Prior surgeries Steroid at anti-TNF agent start Prior failure of IM therapy Infliximab level >2 mg/L	Exposure to anti-TNF agents

anti-TNF, anti-tumor necrosis factor; AZA, azathioprine; CRP, C-reactive protein; IM, immunomodulator; MRE, magnetic resonance enterography; MTX, methotrexate; WBC, white blood cell.

higher doses of IM monotherapy were needed to achieve remission or the patient has been on either monotherapy or combination therapy, for a short period of time, a discussion about further monitoring may be prudent to establish the patient's disease trajectory. Not only is consideration for complications such as prior surgery prognostic of the need for subsequent surgery, but also if future operations may lead to short bowel, nutritional deficits, or other surgical morbidities, this would strongly argue against employing medication withdrawal.⁴⁶

Last, biologic drug levels should be checked. Infliximab trough levels should be 6 $\mu\text{g/mL}$ or greater before withdrawing an IM, and optimized if needed, while lower levels predict a better disease course with infliximab monotherapy withdrawal.^{21,47} Studies de-escalating

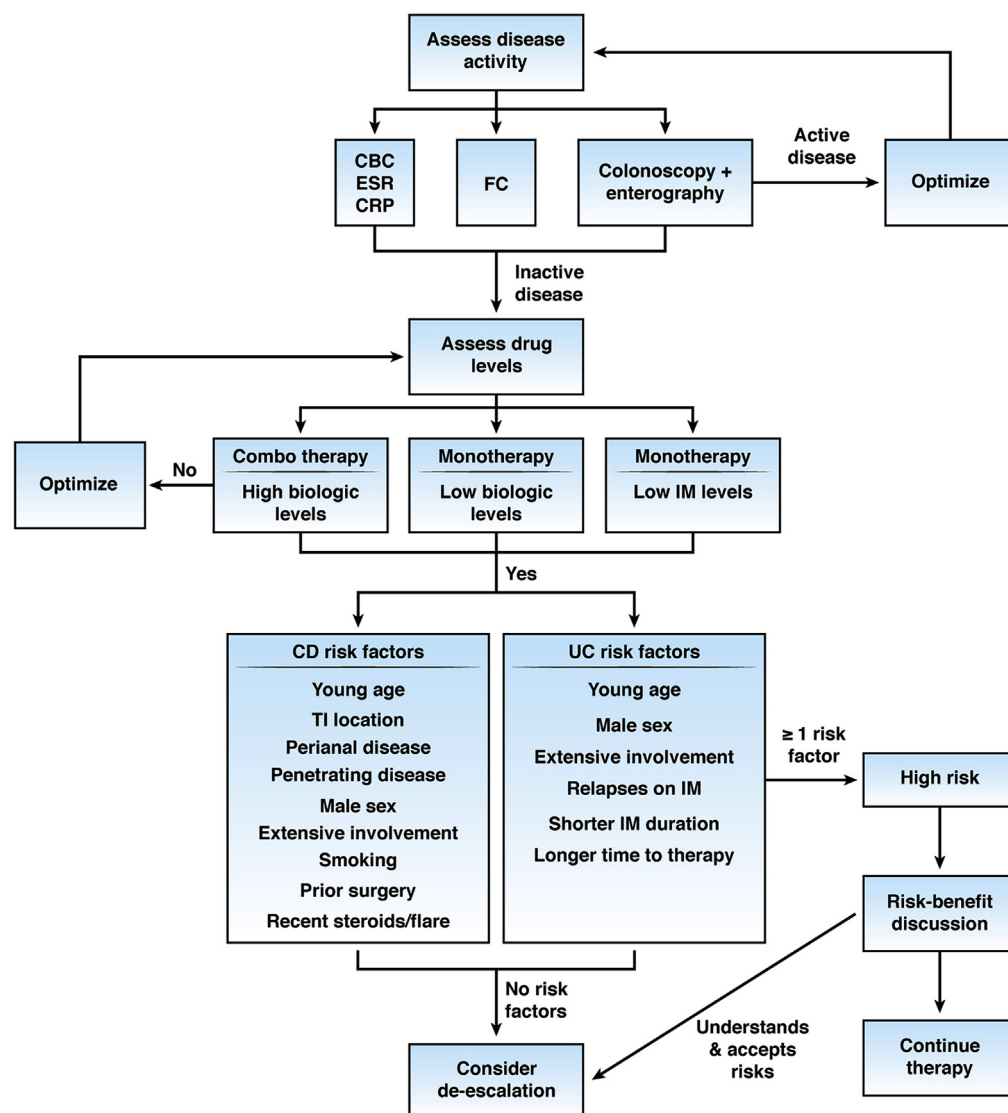


Figure 1. Clinical algorithm to assess patient suitability and risk for de-escalation of IM or biologic therapy. CBC, complete blood count; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; TI, terminal ileum.

other biologic agents are lacking, as well as the benefit of combination therapy over monotherapy. However, by extension, drug levels can be checked for these agents before de-escalation, to assure adequate dosing before IM withdrawal. Further studies are needed to guide this approach.

We Decide to De-escalate: What Can Happen?

Stopping IM Monotherapy

There are 4 randomized controlled trials that have evaluated the impact of withdrawing IM monotherapy in CD. O'Donoghue et al⁴⁸ randomized 51 subjects with CD, treated with at least 6 months of azathioprine, to either continue or stop therapy. Relapse occurred in 5% of subjects continuing azathioprine, compared with 41% in the control group ($P < .01$).⁴⁸ Vilien et al⁴⁹ found that 85% of patients with inactive CD who continued azathioprine remained in remission, compared with 47%

who stopped it ($P = .043$). Those on a higher dose of azathioprine (>1.6 mg/kg/d) had a more pronounced difference, with 89% vs 33% maintaining remission ($P = .017$).⁴⁹ Lemann et al¹² randomized subjects with CD in remission for ≥ 42 months to continue azathioprine or placebo. A total of 8% of those continuing azathioprine, compared with 21% in the placebo group, relapsed at 18 months. Wenzl et al¹⁵ found that 15% of individuals in remission for at least 4 years and who continued azathioprine relapsed within 2 years, compared with 31% of those randomized to placebo. One randomized controlled trial in UC found that those in remission at the start of the trial and randomized to continue azathioprine had a 36% relapse rate at 1 year compared with 59% of those taking placebo (HR, 0.5; 95% CI, 0.25–1.0).¹⁹ Fraser et al⁵⁰ retrospectively reviewed 70 patients with IBD taking methotrexate. With a mean treatment duration of 17.1 months and remission rates of 62% at 3 months, they found that the chance of staying in remission was 42%, 21%, and 16% at 6, 12, and 18 months, respectively.⁵⁰

Stopping an IM From Combination Therapy

A recent Cochrane review evaluated the impact of withdrawing IM from combination therapy with biologic agents, demonstrating that 49% ($n = 27$ of 55) of patients who withdrew azathioprine, compared with 48% ($n = 27$ of 56) of those continuing the combination, experienced clinical relapse (pooled RR, 1.02; $P = .92$).¹⁰ One of these pooled studies, by Van Assche et al,⁵¹ found no difference in endoscopic healing rates at 24 months (61% vs 64%) in CD patients treated with at least 6 months of combination therapy and randomized to continue or stop combination therapy. However, there does appear to be an increased risk of relapse over time. Fischer et al²² retrospectively followed patients for a median duration of 62.5 months after de-escalation, finding that 72.1% required rescue therapy, compared with flare rates of 38% and 27% in 2 retrospective studies following patients for 34 and 14 months, respectively.^{21,52}

While relapse rates do not appear to be affected by IM withdrawal from combination therapy, there may be an impact on the pharmacokinetic profile of biologic agents, particularly anti-TNF therapy. The impact of IM withdrawal on anti-TNF kinetics was demonstrated by Roblin et al⁵³ and showed a significant reduction of infliximab trough levels at 1 year in those who stopped azathioprine ($P = .02$), while those who continued it had no change in levels over time ($P = .9$). Similar results were found by Van Assche et al⁵¹ in a randomized prospective study ($P < .0001$) in patients with CD. The impact of withdrawal of IM on non-anti-TNF agents still needs further evaluation.

Stopping Biologic Therapy

The STORI trial provides robust prospective data regarding relapse rates after anti-TNF withdrawal. A total of 115 patients with CD were treated for at least 1 year with infliximab and an antimetabolite and were in corticosteroid remission for at least 6 months. Subjects stopped infliximab and were followed for at least 1 year. A total of 43.9% and 52.2% of subjects relapsed over 1 year and 2 years, respectively.²⁴ In the long-term follow-up of this cohort, only 21.6% of patients did not restart a biologic or have a major complication 7 years after infliximab withdrawal.⁴⁰ Retrospective studies have confirmed similarly high rates of relapse with biologic withdrawal. Steenholdt et al⁵⁴ performed an observational retrospective study, finding that only 40% of subjects with UC and 12% of subjects with CD at 4.5 and 10 years of follow-up, respectively, remained in remission. A large retrospective multicenter study including 1055 patients with CD and UC in deep remission demonstrated relapse rates of 19% per patient year, with the incidence rate of relapse being 19% and 17% per patient-year in CD and UC patients, respectively.⁵⁵ A

systematic review and meta-analysis by Gisbert et al⁵⁶ included 27 studies, and they found that 44% of those patients with CD and 38% of those with UC relapsed after anti-TNF discontinuation. They found a relapse rate of 40% in patients with CD and 28% in patients with UC at 1 year, concluding that approximately one-third of patients with IBD in remission will relapse 1 year after discontinuation.⁵⁶ It is important to note that the use of IM varied significantly between studies.

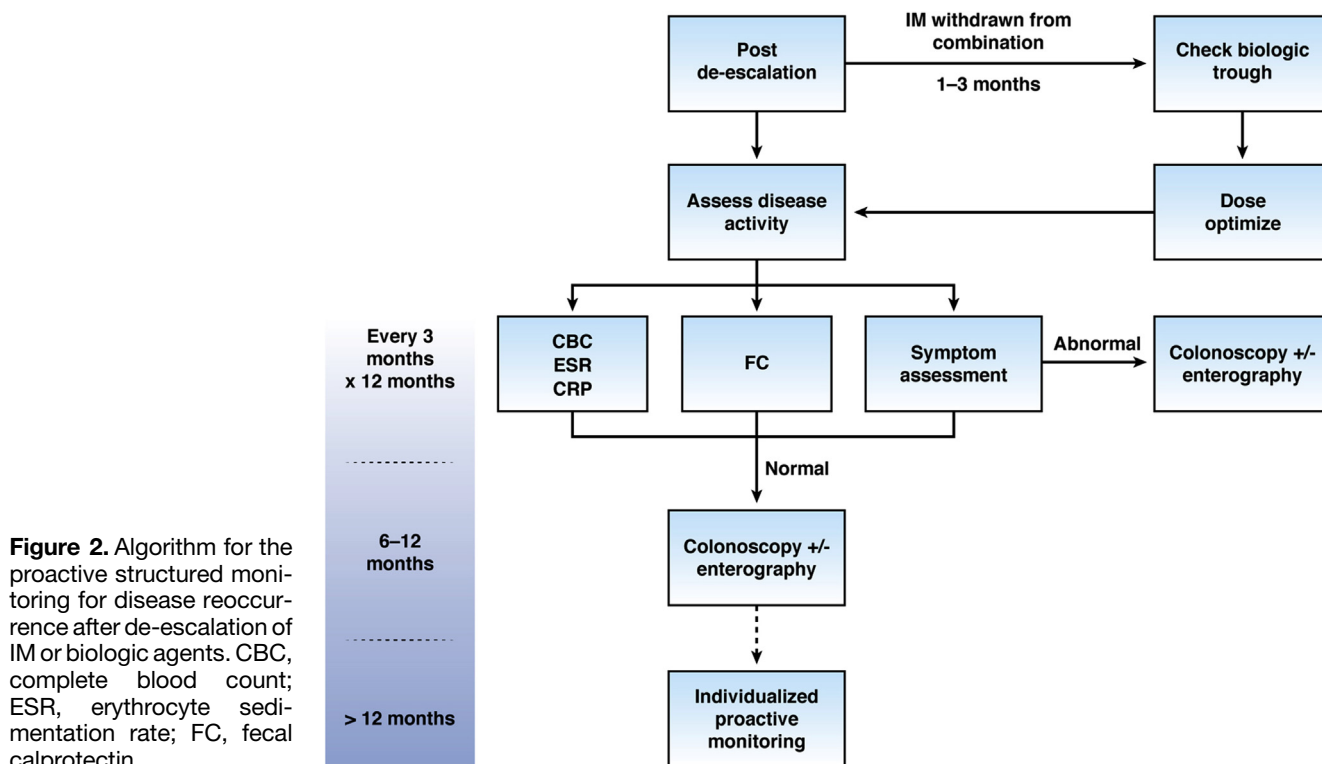
How to Translate This to Your Patient

The previous information should be presented in an easy-to-digest format for patients. Patients with CD on IM monotherapy can be informed that they have approximately a 30%–50% risk of having a disease flare within 2 years of stopping therapy. While the data for UC are limited, a rate of relapse up to 60% can be anticipated, largely in line with the data in CD. Patients who are on combination therapy with an IM and an anti-TNF agent likely have either no increase or only a slight increase in risk of flare upon IM withdrawal. When assessing other anti-TNF agents or biologics, precise drug levels are not available, though we suggest assuring drug levels above cutoffs for optimal remission rates before IM withdrawal. However, trough levels may be more indicative of the clinical situation, with a causative association not proven. Patients with CD and UC who consider stopping biologic agents should be counseled on a 40%–50% risk of relapse over the following 2 years, that will further increase over time.

It is important to frame this discussion by highlighting any risk factors for disease recurrence that may be present and its relative impact on risk of flare. Patients with predictors of relapse are more likely to experience a flare and thus be in the cohort with disease reoccurrence, compared with an individual without these risk factors. The published literature provides HRs, RRs, and odds ratios relating to the impact of these factors, which can be used to guide the discussion regarding the impact on future relapse and allow individualized augmentation of these general flare risks for the patient.

Monitoring After De-escalation

CD and UC are progressive relapsing conditions requiring diligent follow-up once medical therapy is stopped.^{57,58} With up to half of subjects flaring within the first few years after de-escalation, and approximately 80% of subjects requiring reinitiation of biologic therapy within 7 years of medication withdrawal, patients must understand that stopping some or all medical therapy requires close monitoring and engagement. In patients in whom this is being considered, compliance with proactive monitoring is a necessity (Figure 2).⁴⁰ Noninvasive markers of disease activity provide an important means



to assess recurrence of inflammation. The STORI trial found that the median CRP and fecal calprotectin values per patient were higher in relapsers compared with nonrelapsers and that CRP >5 mg/L and fecal calprotectin >250 μ g/g were associated with relapse (HRs of relapse were 4.2 and 6.5, respectively).⁵⁹ A prospective study followed 49 subjects with CD and UC in clinical and endoscopic remission for 12 months after stopping anti-TNF therapy. Significant increases in median fecal calprotectin levels were found 2 ($P = .0014$), 4 ($P = .0056$), and 6 ($P = .0029$) months before endoscopic evidence of disease.⁶⁰ Both studies demonstrate the association between elevated fecal calprotectin and subsequent disease activity, with the later finding elevations occur as early as 6 months before objective disease reoccurrence and predicting relapse.

Little guidance is available for an evidence-based monitoring strategy after de-escalation. As relapse is highest in the first year after medication withdrawal, monitoring should be most intense during this period.⁸ Based on our experience, after drug withdrawal serial monitoring of fecal calprotectin should be performed every 3 months for 12 months, with direct comparison to the calprotectin levels obtained at the time of disease assessment before de-escalation. Close attention should be paid to any elevation or relative change in its values. Regularly scheduled office visits are important to elicit any subtle changes in clinical state that might represent early disease reoccurrence. Depending on the type of de-escalation strategy employed, and the patient's risk factors for reoccurrence, office visits should be planned every 3–4 months for the first 12 months. During such visits CRP, hemoglobin, and WBC count should be

assessed to evaluate markers associated with flare.²⁴ Repeat colonoscopy or imaging should be performed if a significant change in symptoms occurs or abnormal biomarkers are detected. While not based on available literature, we consider empiric endoscopic or imaging-based assessment 6–12 months after withdrawal, factoring in patient risk factors, clinical course, and the de-escalation strategy employed. After the first 12 months, monitoring can be liberalized, though should still be structured and proactive, pending the patient's course over the prior year. Trough drug levels, when IMs are withdrawn from combination with anti-TNF agents, should be obtained 1–3 months after withdrawal, depending upon the agent used, allowing for early drug optimization.

Your Patient Flared: Now What?

Reinitiation of the withdrawn therapy is frequently successful at controlling active disease. Kennedy et al¹⁴ demonstrated that after thiopurine withdrawal, 74% of subjects with CD and 92% of subjects with UC who flare and restart therapy are able to successfully recapture response. Similar results were found in another retrospective study in CD demonstrating that 22 of 23 subjects with disease reoccurrence were successfully retreated with azathioprine.¹³ A recent meta-analysis demonstrated similar success rates for reinitiating the same anti-TNF therapy, capturing response in 82% and 85% of patients with CD and UC, respectively.⁵⁶ It should be noted that the duration of follow-up is a limiting factor in many of the reinitiation studies.

The severity of the patient's disease flare and a risk benefit discussion of available treatment options should dictate which therapy is initiated. Despite the high success rate of medication reinitiation, patients may opt for alternative treatments. For example, patients previously treated with a thiopurine might opt for an alternative medication without the associated risk of lymphoma or skin cancer, such as vedolizumab.⁶¹ Reinduction of a previously utilized biologic agent requires close drug-level monitoring with early optimization, given the risk of antidrug antibodies with episodic drug exposure, particularly with anti-TNF agents.⁶² Based on data from infliximab, in which trough levels $>2 \mu\text{g/mL}$ and concomitant use of IM have been shown to be predictive of response to reinduction, we combined reinduced anti-TNF agents with IMs and assess drug levels and antidrug antibodies early in the treatment course.⁶³ Depending on the anti-TNF agent chosen, trough levels should be checked within 1–3 months of starting the medication and optimized to assure adequate dosing.

There is concern for possible infusion reactions with reinitiation of infliximab. Premedication is often considered, though it has not consistently been shown to reduce infusion reactions.⁶⁴ Most infusion reactions occur with the second or third infliximab infusion. Despite a lack of consensus regarding the appropriate reinduction infusion interval, we recommend a 0-, 4-, and 8-week infusion schedule, with antidrug antibody levels checked at week 2.⁶³ The presence of antidrug antibodies at week 2 precludes continued drug administration and an alternative agent should be started. There are limited data available for reinduction of non-anti-TNF agents. The Phase 3, Randomized, Placebo Controlled, Blinded, Multicenter Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab in Patients with Moderate to Severe Crohn's Disease study (GEMINI 2) study randomized some subjects to placebo after induction, followed by reinitiation of vedolizumab during the long-term extension portion of the trial. The response and remission rates were 56% and 48%, respectively, for these subjects.⁶⁵

Alternative Strategies

Dose reduction and medication interval lengthening provide alternative de-escalation strategies aimed at reducing drug levels. While in IBD there are no data linking high drug levels with increased complications, this remains a viable management strategy. Roblin et al⁵³ demonstrated that thiopurine dose reduction, when used in combination with infliximab, did not impact infliximab trough levels, with 6-thioguanine levels $>105 \text{ pmol}/8 \times 10^8$ red blood cells associated with improved infliximab pharmacokinetics. The Trough Concentration Adapted Infliximab Treatment (TAXIT) randomized controlled trial evaluated whether dosing based on drug monitoring impacted remission rates in CD and UC. The authors showed that infliximab dose reduction, to achieve a

trough level between 3 and 7 $\mu\text{g/mL}$, did not lead to flares or elevation in inflammatory markers.⁶⁶ This highlights that individuals with supratherapeutic levels may do just as well after monitored dose reduction.

Two retrospective studies evaluated dose de-escalation of adalimumab. Pouillon et al⁶⁷ demonstrated that almost 63% of the 56 patients with IBD were able to successfully reduce their adalimumab injections to every 3 weeks. Inactive disease on MR imaging and at endoscopy was associated with reduced risk of failure. A similar rate was found by Baert et al⁶³ in a large cohort of adalimumab treated Crohn's patients, with de-escalation attempted in 54% of subjects and successful in 63% of patients.

Future Directions

Much of the evidence regarding de-escalation is limited to retrospective studies. Furthermore, many of the studies evaluating risk factors for disease flare are small and have limited durations of follow-up. Results from ongoing and planned prospective studies should provide additional data to inform this approach and may have a significant impact on our treatment algorithms. The SPARE study, (A prospective randomized controlled trial comparing infliximab-antimetabolites combination therapy to anti-metabolites monotherapy and infliximab monotherapy in Crohn's disease patients in sustained steroid free remission on combination therapy), part of the BIOCYCLE project (BIOlogical therapy CYCLEs towards tailored, needs-driven, safer and cost-effective management of Crohn's disease) will prospectively follow subjects with CD in remission on combination biologic and IM therapy, IM therapy alone, or a biologic therapy alone (PHC-13-2014). The CURE study (Changing the coUrse of cRohn's Disease With an Early Use of Adalimumab) will evaluate patients with early CD in deep remission and withdraw adalimumab to assess rates of sustained remission at 1 year ([NCT03306446](#)). Additional information will be provided in UC by the BIOSTOP trial (Anti-tumor Necrosis Factor in Patients With Ulcerative Colitis in Clinical Remission: to Continue or Not?), which assesses outcomes with discontinuing or continuing anti-TNF treatment in those in sustained clinical remission ([NCT03011268](#)). There is a significant need for research into the de-escalation of non-anti-TNF biologic agents, with no data currently available for ustekinumab and vedolizumab. Furthermore, the lack of immunogenicity with small molecule agents makes their intermittent use an attractive therapeutic strategy. However, no data are available regarding the risks or benefits to this approach.

Conclusions

De-escalation of IM and biologic therapy is frequently discussed with patients with CD and UC in clinical practice. Patient interest in reducing drug therapy often

drives these discussions, with physicians providing guidance regarding the risk of stopping medications as well as performing an evidence-based assessment of the feasibility and likely success of medication withdrawal. Clinical application of the available evidence can be challenging; however, an individualized approach is paramount, accounting for specific patient risk factors of flare balanced against the risks of medication continuation. We provide a stepwise algorithmic approach to de-escalation, which can provide a framework for providers to approach this therapeutic strategy in the real world, assure close proactive monitoring to assess for relapse, and prompt management of any reoccurrence.

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Reprint requests

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Conflicts of interest

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