Treatment De-Escalation in Patients With Inflammatory Bowel Disease

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Abstract: Inflammatory bowel disease follows a relapsing and remitting course that can be augmented with the use of various pharmacologic therapies. Treatments used to induce or maintain remission may not be required indefinitely. The associated side-effect profile, adverse events, and costs are additional motivators for providers to treat patients with the lowest dose of effective medications. De-escalation of therapy, whether dose reduction or drug discontinuation, must be carefully considered on an individual patient basis. The steps for de-escalation include confirmation of deep remission, development of a maintenance strategy, discussion of the rescue threshold and treatment options in the event of relapse, and appropriate discussion with the patient of this plan.

Keywords
De-escalation, treat to target, inflammatory bowel disease

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC), which are chronic inflammatory conditions that require careful attention for individualized patient-directed management. The natural history of IBD follows a progressive course or a relapsing and remitting pattern. Without treatment, the disease may progress to more extensive inflammation and a greater likelihood of complications such as bowel obstruction, surgery, hospitalization, or disability.[1] The goal of medical management is to control inflammation and to prevent clinical symptoms and complications.[2,3] Historically, induction therapy dictated the maintenance approach—patients worked their way "up" to certain therapies ("earned" them). For some therapies, the drug is initially loaded with higher or more frequent doses, and then subsequently decreased to a long-term stable maintenance regimen. The decision of when to transition to maintenance dosing is guided either by time, in the setting of anti–tumor necrosis factor (TNF)-α therapy, or by measures of clinical or objective (biomarkers or endoscopic) response. One might assume that after the initial inflammatory burden is controlled, some of these medications could be decreased further or even discontinued entirely, but when and how to do this is much less intuitive.

Although the benefits of medications in achieving disease remission outweigh the risks that they may carry, a gastroenterologist's

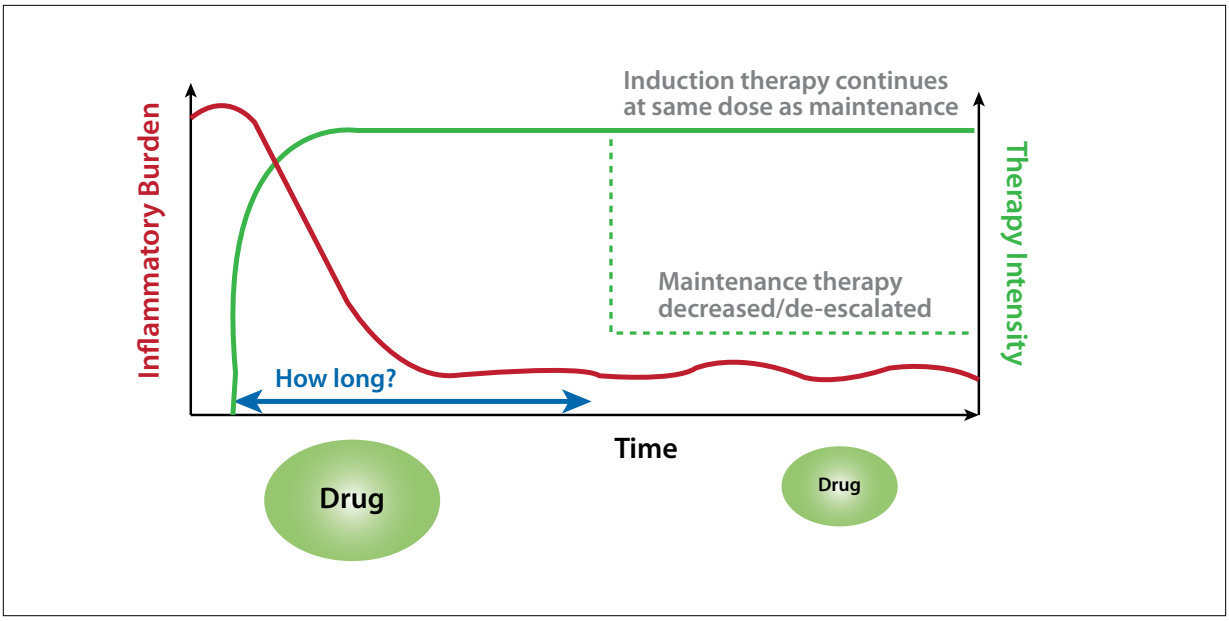

Figure 1. The principle of matching therapeutic intensity with inflammatory burden over time. The size of the drug sphere represents the intensity of therapy at different times of the management period.

goal continues to be to use the lowest effective dose of an effective therapy. 5-aminosalicylic acid (5-ASA) agents have been associated with general gastrointestinal symptoms, headaches, infertility, and pancreatitis.[4,5] Anti–TNF-α inhibitors carry a risk of serious infection and malignancy.[6,7] In addition, cost to both the patient and the health care system must be factored in. Therefore, it is imperative that de-escalation be considered when appropriate.

De-escalation of therapy in IBD can be defined as either decreasing the dose of a drug or discontinuing a therapy entirely. This article outlines the evidence surrounding de-escalation and how this method can be implemented in practice. An overall approach to planning de-escalation, strategies to monitor for and predict relapse, and steps for re-initiation of therapy when necessary are described.

Goals in the Management of Inflammatory Bowel Disease

Glasziou and colleagues have described the 5 phases of chronic disease management.[8] These include pretreatment assessment, initial medication titration (induction of remission), maintenance of disease control (remission), monitoring for loss of response and re-establishment of disease control, and cessation of therapy. Each phase varies in its monitoring objectives and optimal duration. Ongoing patient care should cycle through these stages over time. Management of IBD is typically focused around phases 1 to 4, and, more recently, the care of patients with IBD has explored further the de-escalation of therapeutic intensity. Matching disease activity to the timing and intensity of medical therapy is fundamental to this process (Figure 1).

Recently, the concept of tight control has emerged in IBD. This involves a treat-to-target approach to management with individual targets of disease control identified (Figure 2).[9] After a diagnosis of IBD has been made and a baseline assessment of disease activity has been performed, the initial choice of therapy is matched to the unique phenotype and needs of the individual patient. Approximately 3 to 6 months later, the patient should be reassessed clinically, biochemically, and endoscopically to evaluate for the target. At this point, if the target of therapy is not reached, further adjustments are made to escalate or change the therapy. Once the target is reached, the patient enters the disease monitoring portion of the treat-to-target cycle. However, if the targets are met, then after a period of stability, de-escalation with ongoing close monitoring becomes a possible option.

Support for De-Escalation

The concept of de-escalation of therapy has been discussed for many years, and its efficacy has been evaluated

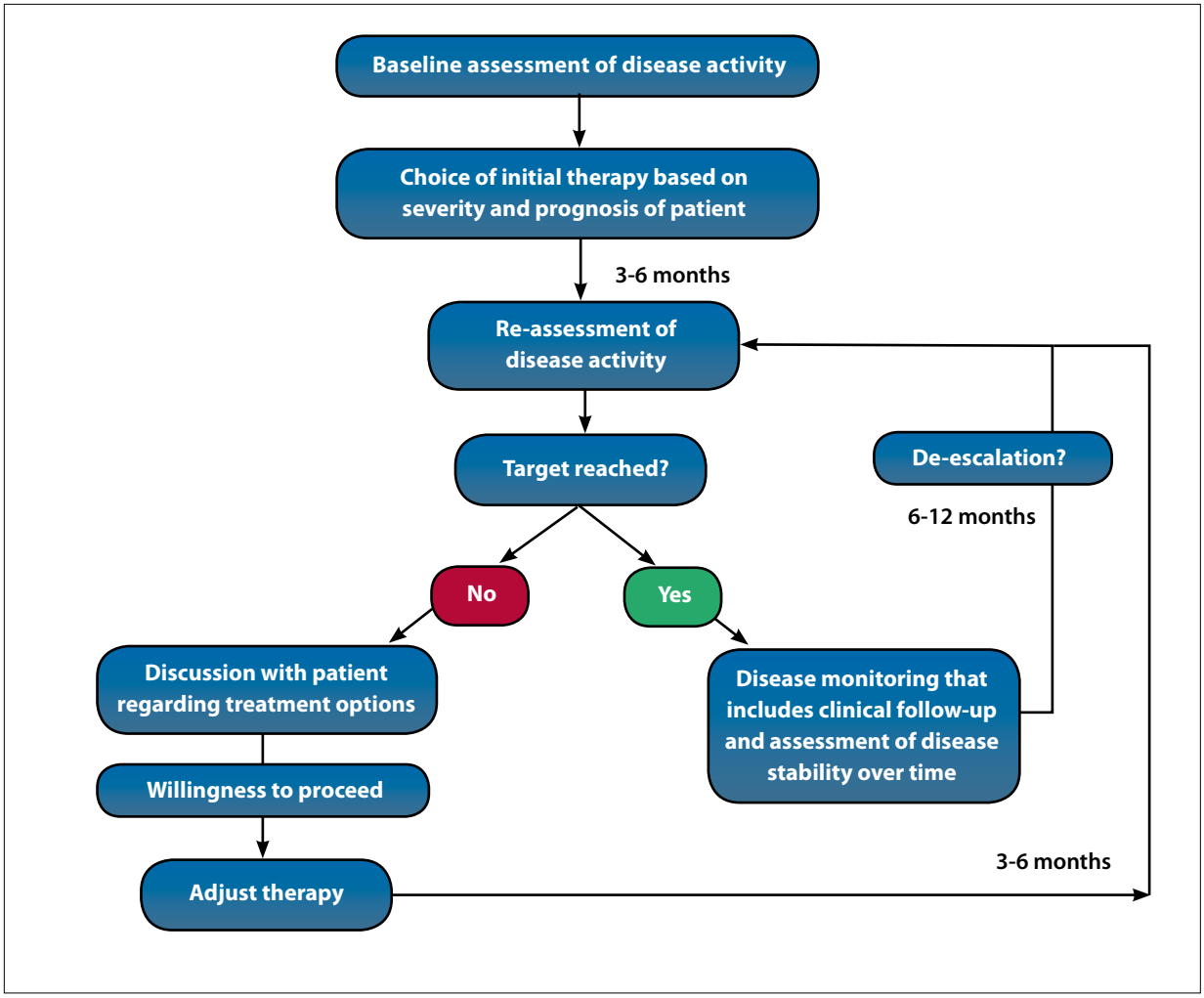

Figure 2. A treat-to-target algorithm. Modified from Christensen B, Rubin DT.[9]

for several of the therapeutic agents that are currently available.

Khan and colleagues evaluated maintenance dosing of 5-ASA agents comparing low (2.4-2.8 g/day) to high (4.4-4.8 g/day) dosing, and found no difference in long-term flare risk between these groups so long as adherence was at least moderate.[10] There has been only one prospective, open-label study of scheduled dose reduction of 5-ASA agents in patients with UC.[11] In this trial, after induction with 4.8 g/day of multimatrix mesalamine, patients who achieved complete or partial remission by week 8 entered a 12-month maintenance phase, in which the multimatrix mesalamine dose was decreased to 2.4 g/day. A notable predictor of preservation of remission on maintenance dosing was complete remission status (defined as a modified UC–Disease Activity Index score ≤1, with a score of 0 for both rectal bleeding and stool frequency, and a ≥1-point reduction in endoscopy score from baseline) after induction. Patients who had achieved complete remission compared with partial remission prior to dose reduction were twice as likely to remain in remission at 12 months. This is in line with the notion that prior to consideration of de-escalation, remission must be confirmed.

Another example of therapy de-escalation is post-induction of remission with corticosteroids. Despite being effective for induction of remission in IBD, corticosteroids are not effective nor are they tolerable as maintenance therapy, and are, therefore, not recommended for the maintenance of remission.[12]

The evidence does not suggest that de-escalation is without risk. A multicenter study described a group of IBD patients who had achieved sustained remission on thiopurine monotherapy that was then discontinued,

and found that within 1 year after discontinuation, 23% of CD patients and 12% of UC patients experienced a moderate-severe relapse.[13] Elevated C-reactive protein (CRP) levels and white blood cell (WBC) counts were predictive of relapse in both CD and UC patients. It is of interest, however, that there was a significant proportion of patients who remained in remission off therapy. Being able to identify who these patients may be is important to this approach.

In combination therapy, which is the utilization of an immunomodulator in addition to an anti–TNF-α inhibitor, the support for de-escalation is strong. The ongoing debate around the need for combination therapy has, for some time, been an area of contention. For patients who do get treated with dual agents, the next issue is when is it safe to step down to monotherapy. The best data currently available suggest that the benefit of combination therapy is short term. Van Assche and colleagues noted that stopping the immunomodulator after 6 months did not appear to affect 1- to 2-year remission rates.[14] In this study, higher CRP levels as well as lower anti–TNF-α inhibitor levels were again associated with disease activity, requiring rescue infliximab (Remicade, Janssen).[14]

There has also been investigation into discontinuing infliximab in patients receiving combination therapy. The open-label STORI (Infliximab Discontinuation in Crohn's Disease Patients in Stable Remission on Combined Therapy With Immunosuppressors) study evaluated patients with CD in stable remission on infliximab and an antimetabolite agent.[15] In this study, approximately 50% of the patients experienced relapse within 1 year after infliximab discontinuation. Long-term outcomes of this group were assessed after a median follow-up of 7 years.[16] Of the 102 patients included, no biologic agent was restarted in 21% of patients. Severe complications, including the necessitation of surgery or the development of perianal disease, occurred in 8% of patients. In patients who were started on a biologic therapy, infliximab was reselected in the majority, and 65% of these patients achieved successful remission. It is important to note, however, the limitations of this study, including the lack of a control arm as well as that most of the biologic starts were a restart of the prior infliximab therapy. Providers now know that restarting the same biologic therapy carries a risk of immunogenicity and have techniques to circumvent this.

Currently, the ongoing BIOCYCLE (Biological Therapy Cycles) project aims to determine the efficacy, safety, and feasibility of de-escalating anti–TNF-α or antimetabolite therapy in patients with CD. The core of this project is the SPARE (A Prospective Randomized Controlled Trial Comparing Infliximab-Antimetabolites Combination Therapy to Antimetabolites Monotherapy and Infliximab Monotherapy in Crohn's Disease Patients in Sustained Steroid-Free Remission on Combination Therapy) clinical trial, a multicenter trial of 300 patients with luminal CD. Patients must be on combination therapy with anti–TNF-α and antimetabolites for at least 1 year and in corticosteroid-free remission for at least 6 months prior to enrollment. Patients are then randomized into 3 arms: 1 arm continues the combination therapy, another arm discontinues infliximab, and the final arm discontinues the antimetabolite. The SPARE trial aims to assess the duration of remission, the rate of relapse, and the ability of biomarkers such as CRP and fecal calprotectin (FCal) to predict this relapse, with a follow-up of 104 weeks.[17]

Tools to Monitor and Predict Relapse

It is vital to predetermine which patients can safely de-escalate therapy. In patients who discontinued anti–TNF-α therapy, relapse rates at 2 years of follow-up were relatively heterogeneous and ranged between 47% and 64% in CD patients and 25% and 47% in UC patients.[18] In the STORI trial, the median time to relapse was 16.4 months.[19] Once a patient de-escalates therapy, however, it is essential to monitor for and predict relapse. Besides accounting for risk factors associated with a poor disease course, certain patient characteristics have been identified as being associated with a higher likelihood of relapse after treatment de-escalation. The STORI trial assessed the risk of relapse in CD patients who were treated with infliximab and an immunomodulator for 1 year and were in corticosteroid-free remission for over 6 months. Male sex (hazard ratio [HR], 3.7), the absence of surgical resection (HR, 4), and hemoglobin levels of no more than 145 g/L (HR, 6) were identified as risk factors that predict relapse within 1 to 2 years of treatment cessation. Elevated WBC counts over 6×10^9/L (HR, 2.4), CRP levels of at least 5 mg/L (HR, 3.2), and FCal levels of at least 300 mcg/g (HR, 2.5) were also predictive of relapse.[15] A subanalysis of the STORI trial confirmed these findings, in which a sudden increase in CRP and FCal levels were predictive of a relapse within the next 4 months. A CRP level of 6.1 mg/L and FCal level of 305 mcg/g were best in predicting relapse.[19] In another prospective study, FCal levels were shown to increase and remain elevated as early as 6 months prior to relapse.[20] Recent data in 160 patients with IBD showed that FCal levels of at least 100 mcg/g were the best predictor of relapse after de-escalation (area under the curve, 0.84; sensitivity, 0.76; specificity, 0.86; positive predictive value, 0.77; negative predictive value, 0.85). Patients concurrently on corticosteroids were at an even

higher risk (HR, 1.67; *P*<.001).[21] These results suggest that follow-up with serial FCal and/or CRP levels may serve as a useful monitoring strategy in order to predict relapse before patients become symptomatic and, thus, to allow for early intervention.

Studies of predictors of relapse upon de-escalation of an immunomodulator have been limited. In CD patients on combination therapy, stopping an immunomodulator had its own set of relapse-predictive factors. These included a younger age at diagnosis, a short duration of combination therapy at time of withdrawal, methotrexate as the immunomodulatory agent, and a history of infliximab discontinuation due to loss of response.[22]

Mucosal healing was also shown to predict sustained clinical remission after infliximab de-escalation in multiple studies.[15,23,24] A Crohn's Disease Endoscopic Index of Severity score of more than 0 was associated with relapse in CD patients de-escalated from infliximab (HR, 2.3).[15] In UC patients, a study from our institution reported that histologic normalization (normal mucosa with no features of chronicity) was associated with a decreased risk of relapse when compared with quiescent disease (HR, 4.3; *P*=.007) and active disease (HR, 6.69; *P*=.001). In this study, 91%, 68%, and 53% of patients had relapse-free survival at 1, 3, and 5 years, respectively.[23]

Research has also shown that patients with lower infliximab levels at the time of de-escalation have a lower risk of relapse. Louis and colleagues reported a higher relapse rate in patients with an infliximab trough level of more than 2 mg/L (HR, 2.5; 95% CI, 1.1-5.4).[15] This finding highlights the importance of utilizing therapeutic drug monitoring in a clinical setting as yet another objective marker to help identify the ideal patient for de-escalation. A combination of these patient factors may allow for the identification of the right candidate for therapy withdrawal.

Restarting Therapy After a Drug Holiday

In the case of relapse after a drug holiday, re-treating with the same biologic agent can be safe and effective.[15] Response rates upon retreatment ranged from 78% to 100% in CD patients and 54% to 100% in UC patients.[18] Retreatment with an immunomodulator also yields good response rates in patients with relapse. In a study conducted by Treton and colleagues, among the patients who had relapsed after azathioprine withdrawal and were re-treated with the same therapy, 22 of 23 patients (96%) achieved remission.[25] In a multicenter study conducted by Kennedy and colleagues in IBD patients initially treated with azathioprine for a minimum of 3 years, retreatment with azathioprine achieved a clinical response in 22 of 24 UC patients (92%) and 31 of 42 CD patients (74%).[13] However, 50% of UC patients and 68% of CD patients also required corticosteroids to induce remission.[13]

Interestingly, when restarting anti–TNF-α agents after a drug holiday, only a small proportion of patients are reported to experience infusion reactions. The STORI trial found a remission rate of 88% (38/43 patients) within 12 months of restarting infliximab, and reported no reactions.[15] Other studies have also confirmed a high rate of clinical remission in response to restarting the same anti–TNF-α agent. In UC patients, remission rates ranged from 70% to 90% at 12 months of follow-up.[20,26-28] In CD patients, remission rates ranged from 70% to 100%.[15,20,26,28,29] Some of the studies, however, reported a premedication requirement. Infusion reactions upon restarting anti–TNF-α agents have been reported as well but at variable rates, with one study reporting up to a 12% rate of acute infusion reactions and an 8% rate of delayed infusion reactions.[26] Predicting the success of restarting an anti–TNF-α agent is also possible. Baert and colleagues demonstrated that the absence of antibodies to infliximab and the use of an immunomodulator concomitantly upon restarting infliximab were associated with a short-term response (*P*=.19) in both UC and CD patients.[26] The predictors of long-term response (at 15 months of follow-up) included originally de-escalating therapy due to pregnancy or clinical remission (*P*=.033) and higher infliximab trough levels (*P*=.21). Furthermore, it was reported to be safer to restart therapy if no drug antibodies were detectable (*P*=.004).[26] The presence of antibodies against infliximab at week 6 of restarting treatment reduced infliximab serum concentrations, which were found to be significantly different between patients who achieved a response and nonresponders.[29]

A modified clinical algorithm for restarting infliximab was developed at our institution based on this evidence. A patient who had discontinued infliximab for at least 6 months (intentional or nonintentional discontinuation or due to loss of response) would receive the first dose of infliximab with premedication. Premedication consists of prednisone 40 mg one day prior to infusion, followed by a second dose of 40 mg combined with 650 mg of acetaminophen and 25 mg of diphenhydramine on the day of the infusion. The infliximab level and presence of antibodies to infliximab are obtained 7 to 10 days postinfusion. Patients with a detectable drug level and negative antibodies continue with a standard loading dosing regimen at week 2 (or, practically speaking, week 3) and week 4. On the other hand, if positive antibodies to infliximab are detected, then an alternative therapeutic option should be sought.[30]

Table. Approach to De-Escalation

1. Discuss with the patient the risks and benefits of this approach, as well as the backup plan if de-escalation fails.
2. Confirm deep remission with endoscopic evidence of mucosal healing. This should be present for >1 year on the current regimen at the current dosage.
3. Confirm optimization of therapy. It is crucial to make sure that this regimen is achieving its goal and that the patient's drug levels or metabolites are adequate.
4. De-escalate the chosen therapy in dose, or stop altogether.
5. Monitor for subclinical relapse. Serial monitoring for early signs of activity is necessary to prevent significant relapse. This should consist of serial clinical assessments and may involve scoping, C-reactive protein, and/or fecal calprotectin.
6. Know the rescue plan. If the patient does require re-escalation of therapy, the prior therapy may or may not be the best agent for him or her at that time. Medication decisions must be made based on the current presentation.

Approach to Planning De-Escalation

The consideration of, and approach to, de-escalation should be determined on an individual patient basis. Our suggested stepwise approach to management involving the periods both prior to and after de-escalation is outlined in the Table.

Providers should proceed with caution when considering de-escalating the highest-risk patients. This includes patients with either historical risk factors (eg, young age at diagnosis, smoking, positive family history) or phenotypic risk factors (eg, upper gastrointestinal CD, penetrating disease, perianal disease). In one study evaluating relapse-free survival after discontinuing infliximab monotherapy, patients with luminal CD had a cumulative probability of being free of relapse of 69% at 12 months, whereas only 34% of patients with perianal CD sustained remission off therapy.[31]

Conclusion

The advent of effective disease monitoring and increase in medical options have led to rising interest and evidence for de-escalation of therapy in IBD. Drug side effects and associated costs suggest that patients should be on less-intensive therapy, and this is supported by emerging evidence that de-escalation can be implemented effectively. A careful approach to de-escalation involves identifying which patients have been sufficiently optimized, balancing the risk of adverse effects from therapy with the risk of relapse after withdrawal. Prospective trials are needed and are ongoing to further identify predictors of which IBD patients will remain in remission after de-escalation.

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