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Review Article

De-escalation of Therapy in Patients with Quiescent Inflammatory Bowel Disease

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Inflammatory bowel disease is a chronic disease of unknown origin that requires long-term treatment. The optical duration of maintenance treatment once remission has been achieved remains unclear. When discussing a de-escalation strategy, not only the likelihood of relapse but also, the outcome of retreatment for relapse after de-escalation should be considered. Previous evidence has demonstrated controversial results for risk factors for relapse after de-escalation due to the various definitions of remission and relapse. In fact, endoscopic or histologic remission has been suggested as a treatment target; however, it might not always be indicative of a successful drug withdrawal. For better risk stratification of relapse after de-escalation, it may be necessary to evaluate both the current and previous treatments. Following de-escalation, biomarkers should be closely monitored. In addition to the risk of relapse, a comprehensive understanding of the overall outcome, such as the long-term safety, patient quality of life, and impact on healthcare costs, is necessary. Therefore, a shared decision-making with patients on a case-by-case basis is imperative. **(Gut Liver 2023;17:181-189)**

Key Words: Inflammatory bowel diseases; De-escalation; Withdrawal; Biological therapy; Immunosuppressive agents

INTRODUCTION

Inflammatory bowel disease (IBD) consists of ulcerative colitis (UC) and Crohn's disease (CD), and it is a chronic inflammation of the digestive tract with unknown etiology that often requires lifelong treatment.[1,2] In addition to 5-aminosalicylic acids (5-ASA) and immunomodulators, biologics and small molecules have become available as maintenance therapy for IBD. Owing to their remarkably improved efficacy which allows long-term use, clinicians may often encounter the patient's question about whether the therapy could be discontinued from various situations, such as pill burden, long-term safety, medical expenses, life events, and socio-economic issues.

However, a gap remains between each piece of evidence regarding the de-escalation of maintenance treatment.[3-10] This may be attributed to the heterogeneity of the criteria, especially due to the retrospective design and lack of randomized controlled trials (RCTs) that could address this limitation. Therefore, it is essential to combine these evidence and incorporate them into an individualized decision-making for patients. The overall outcome of the de-escalation of treatment in terms of disease control should be discussed considering the aspects listed in Fig. 1.

RELAPSE DUE TO DE-ESCALATION

It is important to note that the disease relapse may occur even when the treatment is continued. Notably, the difference between the continued and discontinued groups is relapse solely attributed to drug discontinuation. In addition, for better interpretation of a piece of evidence regarding treatment de-escalation, we need to understand that the definition of remission and relapse varies across trials. Specifically, they were defined by clinical symptoms, biomarkers, endoscopic findings, need of reinduction of the therapy or switching therapy, or physician's global assessment.

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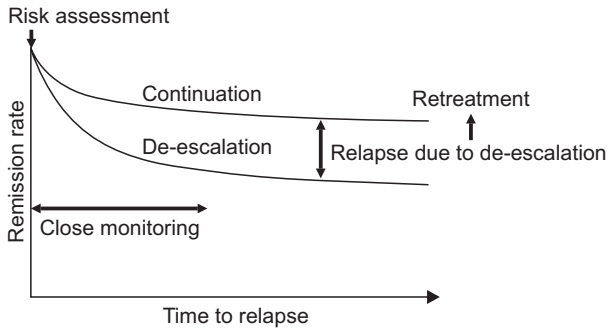

Fig. 1. Concept of a de-escalation strategy. Four factors should be considered during de-escalation: relapse due to de-escalation, outcome of retreatment, risk factors for relapse after de-escalation, and monitoring strategy after withdrawal.

1. 5-ASA

1) 5-ASA monotherapy

A recent systematic review evaluated five RCTs on UC to assess the discontinuation of 5-ASA, including sulfasalazine, olsalazine, and mesalazine. Relapse rates in the 5-ASA group were 12% to 41% at 6 months and 18% to 23% at 12 months, whereas in the placebo group, they were 29% to 60% at 6 months and 26% to 49% at 12 months, suggesting that discontinuation of 5-ASA increases the risk of relapse.[11-16] However, there is no clear evidence to address the effect of discontinuation of 5-ASA in quiescent CD.

In the Cochrane review of 5-ASA maintenance therapy in UC, RCTs that examined various dosing regimens during remission maintenance showed that low-dose 5-ASA is as effective as high-dose in clinical and endoscopic remission. These findings suggest that dose reduction of 5-ASA is reasonable once patients achieve remission.[17]

Although 5-ASA is frequently used in CD, its efficacy remains controversial. A Cochrane systematic review and meta-analysis showed no difference in the relapse rate at 1 year between 5-ASA and placebo in CD, justifying its discontinuation.[18] In patients with surgically-induced remission, however, 5-ASA was superior to placebo in preventing relapse.[19]

2) 5-ASA with immunomodulator

The American Gastroenterological Association guidelines suggest against the continuation of 5-ASA in patients with moderate to severe UC who required their therapy to be escalated to immunomodulators from 5-ASA monotherapy.[20] In steroid-dependent UC, there was no significant increase of relapse after discontinuation of olsalazine from the combination therapy with azathioprine.[21] However, it is important to consider that de-escalation or changing 5-ASA may affect thiopurine metabolism because of their pharmacological interaction, which may diminish the efficacy of thiopurines.[22,23]

3) 5-ASA with biologics

In a *post hoc* pooled analysis using patient data from clinical trials of infliximab and golimumab for UC, there was no significant difference in clinical remission or response, as well as histological healing, between those treated with and without 5-ASA.[24] However, this study did not evaluate the impact of concomitant 5-ASA beyond 52 weeks because of the short observation period of the included clinical trials.

In a retrospective observational cohort study examining the effect of concomitant use of 5-ASA in UC patients following the use of vedolizumab, there was no significant difference in steroid-free remission or endoscopic remission at 6 and 12 months between groups with and without 5-ASA.[25] Although this study was limited by a small sample size, there was a numerical difference in endoscopic remission between patients with and without 5-ASA at 6 months (28.6% vs 39.5%, p=0.36) and 12 months (42.5% vs 53.1%, p=0.32), suggesting the need for further evaluation in a larger cohort.

Two national database cohort studies conducted in the United States and Denmark found that 5-ASA discontinuation after starting tumor necrosis factor inhibitors (TNFi) for CD was not associated with an increased composite outcome as defined by new corticosteroid use, CD-related hospitalization, or surgery.[26]

2. Immunomodulators: 6-mercaptoprine, azathioprine, and methotrexate

1) Immunomodulator monotherapy

A single RCT that evaluated relapse following discontinuation of immunomodulator monotherapy in patients with UC showed that the relapse rate at 1 year was higher in the placebo group than in the azathioprine continuation group (36% vs 59%).[27] Furthermore, a multicenter observational retrospective study in patients with UC demonstrated a high probability of relapse; with two-thirds in 5 years after discontinuation of azathioprine.[28]

A recent systematic review and meta-analysis revealed that discontinuation of immunomodulator monotherapy in patients with CD was associated with an increased risk of relapse within 24 months.[9] In addition, an observational study showed that in the long-term follow-up of patients with CD who discontinued immunomodulators after more than 3 years, the cumulative probabilities of relapse were 14.0%, 52.8%, and 62.7% at 1, 3, and 5 years, respectively.[29]

2) Immunomodulator combination therapy

There is a single RCT comparing azathioprine continu-

ation (2–2.5 mg/kg), dose reduction (1–1.25 mg/kg), and discontinuation from the combination therapy with infliximab in IBD patients. The clinical relapse rate was not significantly different, but it was numerically higher with a significant decrease in the infliximab trough level at week 56 in the discontinuation group.[30] Therefore, dose reduction of immunomodulators, not discontinuation, might be a reasonable strategy in patients receiving combination therapy.

A multicenter retrospective observational study revealed that patients with UC who received a combination therapy of infliximab and immunomodulators for at least 9 months had a lower rate of relapse than those who discontinued immunomodulator therapy within 9 months after induction therapy with infliximab.[31]

In contrast to infliximab, the benefit of combining azathioprine with adalimumab is unclear based on the findings from the RCT in CD.[32] In addition, an RCT examining the outcome of immunomodulator discontinuation from combination therapy with adalimumab in CD showed no significant difference in corticosteroid-free clinical remission, endoscopic remission, trough concentration, and anti-drug antibody development after 52 weeks.[33] However, the sample size of the RCT was smaller than that predetermined for the trial.

Based on such evidence, a recent systematic review and meta-analysis reported no significant increase in relapse due to immunomodulator discontinuation from the combination treatment with TNFi in patients with IBD.[9]

Evidence is lacking on the outcomes of immunomodulator withdrawal from combination therapy with other biologics. However, the development of anti-drug antibodies is very rare in RCTs for ustekinumab or vedolizumab, suggesting that their combination with immunomodulators might be less beneficial.[34-37]

3. Anti-TNF-α

1) Discontinuation of TNFi

A systematic review and meta-analysis showed that 28% of UC and 36% of CD patients relapsed at 12 months following TNFi discontinuation;[4] however, it only included observational studies.

The HAYABUSA study was the first RCT to evaluate infliximab discontinuation in quiescent UC. The trial revealed that 80% of the infliximab-continued group and 54% of the infliximab-discontinued group were in remission 48 weeks after randomization. There was a significant difference between the two groups even after adjusting for the use of immunomodulators and Mayo endoscopic subscore.[38]

In contrast, a recent RCT analyzing infliximab discontinuation in CD showed a considerably higher risk of clinical relapse in the placebo group after 48 weeks, regardless of deeper remission at baseline (relapse-free survival: 51% vs 100%).[39]

In addition, a recent large-scale retrospective observational study of 1,000 IBD patients who discontinued infliximab or adalimumab demonstrated that 12% of patients relapsed annually, and the cumulative relapse rate at 5 years was 48% after discontinuation.[40]

2) Dose reduction of TNFi

A recent systematic review reported that the rate of clinical relapse after dose reduction and prolongation of interval of biologics are similar to that after discontinuation.[10] However, most of the eligible studies were uncontrolled observational studies.

Dose reduction was examined in part in the TAXIT trial to test the usefulness of dose adjustment based on therapeutic drug monitoring. Patients with trough levels >7 μg/mL at the time of randomization, who were adjusted for dose reduction to a target trough level of 3–7 μg/mL had no difference in the rate of clinical remission, suggesting the presence of a group of patients who can reduce the dose of biologics based on the drug concentration.[41]

In the subgroup analysis of the CALM study, 36 out of 46 patients who were de-escalated from adalimumab every week to every other week remained de-escalated at week 48. Twenty-one out of 36 (58%) achieved mucosal healing at week 48. This is interesting because this may suggest that treatment could be still de-escalated even after once escalated.[42]

In one of the studies included in the previous systematic review,[10] dose de-escalation of infliximab in IBD was conducted based on clinical and biological remission with or without trough levels of infliximab. This revealed that dose de-escalation based on trough level was associated with a decreased risk of relapse.[43]

4. Janus kinase inhibitor

1) Discontinuation of tofacitinib

The outcome of tofacitinib discontinuation was evaluated in the OCTAVE clinical trial program. Patients with moderate-to-severe UC who achieved clinical response with tofacitinib 10 mg or 15 mg twice a day (BID) following the 8-week induction trial were randomly assigned to the placebo group. About one-third of patients remained in remission after 52 weeks.[44] This data included patients with a shorter duration of clinical response and remission before discontinuation, but it may suggest the effect of tofacitinib discontinuation.

2) Dose reduction of tofacitinib

Patients enrolled in the OCTAVE open study who had been on tofacitinib 10 mg BID for at least 2 years were randomly assigned to either the 10 mg BID continuation group or the 5 mg BID dose reduction group. The primary endpoint of remission ratio at the 6th month was 77.1% and 90.0% in patients treated with 5 mg and 10 mg BID, respectively, and adverse events were similar in both groups.[45]

OUTCOMES OF RETREATMENT FOR RELAPSE AFTER DE-ESCALATION

When considering a de-escalation strategy, the outcome of retreatment should be considered. Here, we describe the evidence of retreatment with different medications.

1. 5-ASA

A single-center prospective study that included UC patients who relapsed during maintenance therapy with mesalazine 1.5–2.25 g/day showed that 44% and 66% achieved clinical remission and improvement, respectively, at 8 weeks after dose increase at 4.0 g/day.[46]

2. Immunomodulator

A previous trial analyzed 66 patients with CD in sustained remission (>42 months) who discontinued azathioprine. Among the 32 patients who relapsed after azathioprine discontinuation, 22 of the 23 who were retreated with azathioprine alone at the time of relapse were in remission. The remaining nine patients did not restart azathioprine because they either underwent surgery (n=4), achieved remission with infliximab (n=1), infliximab plus azathioprine (n=1), or methotrexate (n=3). However, this study did not include patients with perianal disease and postoperation.[29]

Another multicenter retrospective cohort study in the United Kingdom that followed UC and CD after discontinuation of immunomodulators revealed that the majority of patients who restarted immunomodulators upon relapse regained and maintained remission after induction therapy with systemic steroids. However, we should consider that a small proportion of patients experienced relapse requiring surgery, especially in CD.[47]

3. TNFi

In a previous meta-analysis that analyzed the efficacy of retreatment with the same TNFi in patients who relapsed after its discontinuation, 85% of UC and 82% of CD regained response.[4]

A recent RCT for discontinuation of infliximab in UC demonstrated that 12 of 21 patients in the discontinuation group were retreated with infliximab, which resulted in remission of eight cases (66.7%) at the 8th week following retreatment with no development of infusion reactions.[38] A large-scale observational study also showed that 60% of patients who relapsed after discontinuation were treated with the same TNFi, in which 73% of patients achieved remission.[40] However, decisions on whether the same TNFi should be used were made by physicians or patients in clinical practice; therefore, the outcome might have been biased.

4. Tofacitinib

Patients who were randomized into the placebo group discontinued tofacitinib at the 8th week in OCTAVE Sustain.[48] Retreatment with 10 mg BID of tofacitinib was administered if the patient had relapsed. Of these, 74.0% regained a clinical response at the 2nd month.[44]

ASSESSMENT OF RISK FACTORS FOR RELAPSE

1. Understanding the disease status

The risk factors for relapse associated with drug withdrawal reported in the literature are summarized in Table 1.

Deep remission is defined as the histological mucosal healing in UC and transmural healing in CD as well as clinical and biochemical remission. Although this has been suggested as an ideal treatment target, there is limited evidence on whether they could guarantee a successful de-escalation. In a recent RCT that assessed the effectiveness of infliximab discontinuation in UC and CD with mucosal healing or transmural healing, there were significant differences between the placebo and continued groups regarding the rate of relapse. These findings suggest that achieving a more stringent target alone may not prevent future relapse following de-escalation;[38,39] therefore, it is necessary to assess whether disease control depends on the current medication.

2. Understanding the individual treatment history and contribution of medication

To better understand the medication's contribution to current disease control, it is necessary to assess the current medications and complete treatment history. For example, a patient who has been escalated to combination therapy with infliximab despite previous immunomodulator monotherapy and a patient on combination therapy to whom immunomodulator has been added after developing

Table 1. Risk of Relapse Associated with De-escalation

Medication	Risk factor for relapse of UC	Risk factor for relapse of CD
5-ASA monotherapy	Younger age[49] Extensive disease[49] Shorter duration of remission[12] History of multiple flares[50] Non-mucosal healing (MES>0)[51]	NA
Immunomodulator monotherapy	Younger age[27] Male sex[28] Extensive disease[28,52] Number of relapses on azathioprine[28,52] Shorter duration of remission with azathioprine[28,52] Longer time from diagnosis to azathioprine[52] Without concomitant 5-ASA[28] Withdrawal due to AE[28] Increased WBC[47,52] Increased platelet[52] Elevated CRP and ESR[52]	Younger age[53] Male sex[53] Extensive colitis[54] Shorter duration of remission[53] Shorter interval since last steroid therapy[55] Higher dose of azathioprine at de-escalation[56,57] Tapering of thiopurine before withdrawal[47] Elevated CRP level[29,47,55] Increased WBC/neutrophil[29] Low hemoglobin level[29,55]
Immunomodulator combination therapy	Shorter duration of combination therapy[31]	Undetectable infliximab trough level at discontinuation[58] Elevated CRP level[58]
TNFi	Younger age at diagnosis[40] Without concomitant immunomodulator[40] De-escalation without endoscopic evaluation[4] Appropriate infliximab trough level before de-escalation[41] Elevated CRP[38] Histologically active (Nancy<2)[38] Elective decision[40] Withdrawal due to AE[40]	Younger age at diagnosis[40,59] Male sex[60] Ileocolonic disease[61] Without concomitant immunomodulator[40] De-escalation without endoscopic evaluation[4] Without history of operation[60] Appropriate infliximab trough level before de-escalation[41] Previous TNFi dose escalation[61] Previous TNFi treatment[61] Low hemoglobin level[60] Increased WBC[59,60] Elevated CRP/FC level[58-61] Elective decision[40] Withdrawal due to AE[40]
Janus kinase inhibitor	Prior TNFi failure[45] MES 0<1[45]	NA

UC, ulcerative colitis; CD, Crohn's disease; 5-ASA, 5-aminosalicylic acid; MES, Mayo endoscopic score; NA, not available; AE, adverse event; WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TNFi, tumor necrosis factor inhibitor.

loss of response to infliximab might be different in terms of the risk of relapse after discontinuation of immunomodulators.

Therapeutic drug monitoring may help us understand the contribution of each treatment to current disease control. Drobne *et al.*[58] reported that patients with therapeutic trough levels of infliximab at the time of immunomodulator discontinuation were associated with a lower rate of relapse than those with undetectable. Similarly, the STORI trial revealed that the risk of relapse was higher in patients with a trough level of 2 μg/mL or higher at the time of infliximab discontinuation.[60] In addition, Ben-Horin *et al.*[62] reported that a higher proportion of IBD patients with measurable drug levels before TNFi discontinuation relapsed during 12 months median follow-up compared to patients with undetectable drug levels.

Furthermore, the HAYABUSA study demonstrated that the presence of an acute inflammatory reaction, as reflected by neutrophil infiltration, may indicate that disease activity still exists, but the current treatment contributes to disease control, preventing relapse with a high risk of relapse upon withdrawal.[38]

MONITORING STRATEGY AFTER WITHDRAWAL

The European Crohn's and Colitis Organisation exit strategy recommends that careful follow-up during the first year after withdrawal is required since most patients relapse during the early phase following withdrawal, especially with TNFi.[7] Results from the HAYABUSA study demonstrated that the between-group difference in the remission rate became significant as early as the 16th week.[38]

This suggests that the risk of relapse might be higher early during the course after discontinuation. However, only a few reports have explored the monitoring strategy after de-escalation.

A prospective cohort study revealed that patients who relapsed after withdrawal showed elevated fecal calprotectin (FC) levels at a median of 3 months before relapse.[63] Another observational study of a prospectively registered database demonstrated that an FC >200 μg/g during monitoring after de-escalation was highly predictive of future clinical relapses.[64]

In fact, the CALM trial suggests that a tight control strategy using biomarkers after treatment de-escalation is useful. Although more patients in the tight control group de-escalated treatment with adalimumab at 36 weeks, the tight control group still achieved significantly better disease control. These results suggest that tight monitoring with FC/C-reactive protein is a useful strategy after treatment de-escalation.[42]

Based on these pieces of evidence, monitoring the FC and C-reactive protein every 3 months especially after withdrawal may be desirable. However, a larger prospective study is needed to determine the optimal monitoring strategy.

FUTURE DIRECTION

It is important to consider not only the treatment efficacy in maintaining remission, but also the long-term safety (e.g., infection, cancer risk), chemoprevention, quality of life, and impact on healthcare costs when discussing treatment de-escalation.[65]

The European initiative BIOCYCLE project aimed to investigate the long-term efficacy, safety, and cost of treatment withdrawal in patients with quiescent CD. In one trial of the project, the SPARE clinical trial (NCT02177071) was conducted in three arms; a group with both infliximab and immunomodulator continuation, infliximab discontinuation, and immunomodulator discontinuation. In addition to assessing the relapse rate and time remaining in remission, it evaluates the cost-effectiveness, quality of life, and biomarkers to predict the risk of relapse and disease progression. This discernment may help establish a new treatment strategy and allow utilization of a decision-making tool.

Recent studies suggest that the gut microbiome may play an important role in IBD. A lower proportion of Firmicutes was shown to be associated with a higher rate of relapse after infliximab discontinuation in CD, suggesting microbiome analysis could predict the future relapse following de-escalation.[66]

The difference in natural history between UC and CD should also be taken into account. CD is considered more progressive in which fistula and stenosis could develop before the clinical relapse after the treatment withdrawal. Therefore, the short-term risk of relapse may not be sufficient to justify de-escalation, especially in CD.

CONCLUSION

Understanding the accumulated evidence and evaluating the contribution of each treatment per patient is crucial for stratifying the future risk of relapse after de-escalation. Finally, a shared decision-making that balances the advantages and disadvantages of de-escalation with patients on a case-to-case basis is indispensable.

CONFLICTS OF INTEREST

Y.M. has served as a speaker of AbbVie; received research funding from Japan Foundation for Applied Enzymology; and as an endowed chair of AbbVie, JIMRO, Zeria Pharmaceutical, Kyorin Pharmaceutical, Mochida Pharmaceutical, Otsuka Holdings, and EA Pharma. T.K. has served as a speaker, a consultant, and an advisory board member of AbbVie, Ajinomoto Pharma, Asahi Kasei Medical, Astellas, Alfresa Pharma, Celltrion, Covidien, EA Pharma, Eisai, Eli Lilly, Ferring Pharmaceuticals, Gilead Sciences, Janssen Pharmaceutical, JIMRO, Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Nippon Kayaku, Pfizer, Takeda Pharmaceutical, Thermo Scientific, and Zeria Pharmaceutical; and received research funding from AbbVie, Alfresa Pharma, Asahi Kasei Medical, Activaid, Bristol Myers Squibb, JMDC Inc., EA Pharma, Kyorin Pharmaceutical, Mochida Pharmaceutical, Nippon Kayaku, Otsuka Holdings, Sekisui Medical, Thermo Fisher Scientific, and Zeria Pharmaceutical. Except for that, no potential conflict of interest relevant to this article was reported.

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