Challenge of treatment de-escalation in inflammatory bowel diseases

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Inflammatory bowel diseases (IBDs) encompass chronic conditions predominantly affecting young individuals and necessitate long-term, advanced treatments to manage disease burden and mitigate progressive tissue damage.[1] Within this context, the matter of treatment discontinuation in patients who have achieved sustained remission, including those undergoing combination therapy, holds significant importance for both clinicians and patients. The primary considerations for potential treatment de-escalation or cessation include safety concerns, the financial implications of prolonged therapy and patients' willingness or preference.

In *Gut*, Gisbert *et al*[2] address this important question and report the results of the EXIT trial, a randomised placebo-controlled trial on 140 patients in clinical remission under anti-tumour necrosis factor (TNF) antibody and immunomodulators who were randomly assigned to either withdraw or maintain the anti-TNF antibody.

Four prospective clinical trials have investigated the question of anti-TNF de-escalation in IBD[3–6] but two specifically address treatment de-escalation in patients achieving clinical remission while on combination therapy with infliximab (IFX) and an immunomodulator.[3 4] The STORI (infliximab diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressors) trial was the first prospective, single-arm study evaluating clinical relapse after IFX withdrawal in patients in corticosteroid-free remission for at least 6 months on combination therapy with an immunomodulator.[3] After a median follow-up of 24 months, 45% experienced relapse. Key findings included a proposed multivariable model incorporating faecal calprotectin (FC), C reactive protein and endoscopic scores to identify suitable candidates for treatment de-escalation. Additionally, a 93% remission rate was observed after a single IFX dose in patients who experienced relapse, with 98% achieving a clinical response.

The open-label SPARE (withdrawal of infliximab or concomitant immunosuppressant therapy in patients with Crohn's disease (CD) on combination therapy) trial proposed an improved design by including three arms (IFX withdrawal, immunomodulator withdrawal and maintenance of both therapies), the comparison of the time spent in remission between the three strategies and a longer follow-up of 2 years.[4] This trial confirmed an increased risk of relapse over 2 years in patients discontinuing IFX (35%) compared with those continuing IFX, either as monotherapy (9%) or in combination (12%) with an immunosuppressant. Interestingly, time spent in remission was numerically very close in all groups thanks to an effective retreatment with IFX in patients who experienced a relapse.

These two trials underscore the potential for cyclic treatment strategies in a subset of well-selected patients.

The EXIT trial employed an innovative quadruple-blind design to minimise the nocebo effect and ambitiously aimed to recruit both CD and ulcerative colitis (UC) patients undergoing treatment with either IFX or adalimumab (ADA). Contrary to previous studies, the proportion of patients experiencing clinical relapse at 1 year was similar between the group maintaining combination therapy and the group discontinuing anti-TNF treatment. However, FC levels >250 µg/g were significantly more frequent in the withdrawal group (33%) than in the maintenance group (13%).

While differences in clinical relapse rates were not statistically significant, the proportion of relapses was numerically double in the withdrawal group (13%) compared with the maintenance group (6%). There was a numerical increase in significant endoscopic lesions (deep ulcers, Simple Endoscopic Score for CD (SES-CD)>4 or superficial ulcers affecting >10% of the surface) and radiological lesions (oedema on T2-weighted imaging or ulcers in ≥2 intestinal segments) in the IFX withdrawal group. Endoscopic activity was noted in 19% of the withdrawal group vs 8.5% in the maintenance group, while radiological lesions were observed in 35% vs 20%, respectively. The lack of statistical power and the shorter follow-up (1 year) compared with other trials may explain the absence of significant differences. Recruitment was lower than expected (70 vs 100 per arm), and endoscopies were performed on only 59 patients per group, likely due to the challenges posed by the COVID-19 pandemic. Given that FC and endoscopy are validated predictors of relapse in de-escalation studies,[3 4] the EXIT trial findings suggest that patients discontinuing anti-TNF therapy may be at higher risk of future clinical relapse due to increased markers of endoscopic, radiological and biochemical inflammation, despite no statistically significant differences in clinical relapse rates over 1 year.

Although UC and CD share common pathophysiological features, they are distinct entities, with UC potentially exhibiting more aggressive clinical flare-ups and an urgent need for colectomy. This suggests that the de-escalation strategy may need to be approached differently for each disease.[7] This study is the first to assess de-escalation in both UC and CD patients. Unfortunately, recruitment numbers did not permit a direct comparison between the two conditions.

While data on de-escalation with ADA are available from retrospective trials, this study is the first prospective trial to include both IFX and ADA in de-escalation strategies. Unfortunately, due to the small sample size, comparisons between these two groups were not assessable.

To conclude, this study contributes to the literature on a challenging topic with few randomised controlled trials available. Treatment de-escalation in patients receiving combination therapy with anti-TNF agents seems to be safe at 1 year in patients in sustained steroid-free remission, although endoscopic and biological biomarkers should be closely monitored to identify patients at risk of medium-term relapse. Interestingly, with careful follow-up after de-escalation, early retreatment proves effective in more than 90% of patients, suggesting that this strategy does not lead to a poor disease course or missed opportunities for the patient .[8] Studies focusing on de-escalation in highly selected patients, particularly those in endoscopic and biological remission, are needed to better identify individuals most suitable for this approach. Additionally, in the context of cycling treatments, aside from biological therapies,

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small molecules such as JAK inhibitors may be better candidates due to their rapid onset of action and lack of immunogenicity. This specific strategy also requires further validation.

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REFERENCES

1 Pariente B, Cosnes J, Danese S, *et al*. Development of the Crohn's disease digestive damage score, the Lémann score. *Inflamm Bowel Dis* 2011;17:1415–22.
2 Gisbert JP, Donday MG, Riestra S, *et al*. Withdrawal of antitumour necrosis factor in inflammatory bowel disease patients in remission: a randomised placebo-controlled clinical trial of GETECCU. *Gut* 2025;74:387–96.
3 Louis E, Mary J-Y, Vernier-Massouille G, *et al*. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 2012;142:63–70.
4 Louis E, Resche-Rigon M, Laharie D, *et al*. Withdrawal of infliximab or concomitant immunosuppressant therapy in patients with Crohn's disease on combination therapy (SPARE): a multicentre, open-label, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2023;8:215–27.
5 Kobayashi T, Motoya S, Nakamura S, *et al*. Discontinuation of infliximab in patients with ulcerative colitis in remission (HAYABUSA): a multicentre, open-label, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2021;6:429–37.
6 Buhl S, Steenholdt C, Brynskov J, *et al*. Discontinuation of Infliximab Therapy in Patients with Crohn's Disease. *NEJM Evid* 2022;1:EVIDoa2200061.
7 Torres J, Boyapati RK, Kennedy NA, *et al*. Systematic Review of Effects of Withdrawal of Immunomodulators or Biologic Agents From Patients With Inflammatory Bowel Disease. *Gastroenterology* 2015;149:1716–30.
8 Reenaers C, Mary J-Y, Nachury M, *et al*. Outcomes 7 Years After Infliximab Withdrawal for Patients With Crohn's Disease in Sustained Remission. *Clin Gastroenterol Hepatol* 2018;16:234–43.