Biological therapy for inflammatory bowel disease: cyclical rather than lifelong treatment?

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ABSTRACT

Inflammatory bowel disease (IBD) treatment was revolutionised with the arrival of biological therapy two decades ago. There are now multiple biologics and increasingly novel small molecules licensed for the treatment of IBD. Treatment guidelines highlight the need for effective control of inflammation and early escalation to advanced therapies to avoid long-term complications. Consequently, a large proportion of patients with IBD receive advanced therapies for a long time. Despite their beneficial risk–benefit profile, these treatments are not without risk of side effects, are costly to healthcare providers and pose a burden to the patient. It is, therefore, paramount to examine in which circumstances a temporary cessation of therapy can be attempted without undue clinical risk. Some patients may benefit from cyclical rather than continuous treatment. This review examines the risk of relapse after discontinuation of advanced therapies, how to identify patients at the lowest risk of relapse and the chance of recapturing response when flaring after discontinuation.

INTRODUCTION

Inflammatory bowel disease (IBD) predominantly comprises ulcerative colitis (UC) and Crohn’s disease (CD). It affects people of all ages but mainly presents in adolescence and early adulthood. Symptoms may include diarrhoea, rectal bleeding, abdominal pain, fatigue, lethargy, weight loss and inflammation in extraintestinal organs such as the skin, eyes and joints. Traditional treatment aims focused on symptom relief, but with better therapies and an understanding that full control of inflammation is associated with better long-term outcomes, the focus has shifted to aiming for mucosal healing.

Since there are no curative medical therapies, IBD is a non-communicable, chronic disease that needs lifelong treatment in the vast majority of cases. Traditional step-up approaches starting with mesalazine (for UC only), followed by immunomodulators and then biologics have been complimented by top-down approaches for select cases with poor prognosis. In the UK, approximately 30% of CD and 15% of UC patients are currently being treated with advanced therapies. The choice of therapeutic agents for moderate to severe IBD has increased and comprises anti-tumour necrosis factor (TNF) biologics (infliximab, adalimumab, golimumab (UC only) and certolizumab (CD only)), anti-integrin biologics (vedolizumab), anti-IL12/23 biologics (ustekinumab), anti-IL23 biologics (risankizumab (CD only), mirikizumab (UC only), oral Janus-Kinase (JAK) inhibitors (tofacitinib (UC only), filgotinib (UC only) and upadacitinib) as well as S1P-inhibitors (ozanimod (UC only)).

Advanced therapies are being used when conventional approaches with immunomodulators are ineffective or not tolerated, when a severe phenotype requires top-down treatment, when faster disease control than achievable with an immunomodulator is needed and when acute severe flares lead to hospital admission. When infliximab was first used for IBD episodic treatment was often applied with short treatment cycles of a few weeks only. This approach proved insufficient to achieve good disease control and maintenance therapy has been advocated since.

Achieving good control of inflammation rather than just symptom control is associated with a reduced flare rate, and a reduced
need for hospitalisation or surgery. Currently available advanced therapies are not without risk or side effects, however. As all advanced therapies suppress the immune system there is an increased risk of infections, which is higher in those on combination therapy with anti-TNF and immunomodulators. While the relative risk is static with age, the absolute risk of severe infections becomes greater and more problematic, therefore, with increasing age. However, even younger patients often report frequent minor infections that nevertheless impact on quality of life.

There is also an increased risk of malignancy with immunosuppressive therapies (skin cancer and lymphoma mainly associated with TNFs and thiopurines). Tofacitinib was associated with an increased malignancy risk in a non-IBD study. Regulatory authorities have nevertheless assumed that this may be a class effect for all JAK inhibitors, although in the absence of firm evidence in the field of IBD. While there are so far no data suggesting increased risk of malignancy for vedolizumab and ustekinumab, we should be mindful that meaningful observational data often take a decade or more to show such associations. In addition, there are concerns for JAK inhibitor associations with major cardiovascular events and, remarkably, venous thromboembolism, especially those inhibiting both JAK1 and JAK3.

We should, therefore, consider how long advanced therapies for IBD should be continued for. The European Crohn’s and Colitis Organisation (ECCO) has recently published a topical review on this topic. In this review article, we will outline the cases for and against cyclical treatment plans with advanced therapies for IBD using the ECCO work as a scaffold. Cyclical treatment plans rely on treatment periods of at least 12 months and should not be confused with historical episodic treatment for 6–8 weeks only. Additionally, we will not discuss here the so-called ‘exit strategies’, that is, not the scope of this review. We will outline the evidence to consider and provide practical advice (figure 1).

**POTENTIAL BENEFITS OF STOPPING ADVANCED THERAPIES**

Most randomised controlled trials for IBD cover 1 year of blinded therapy followed by open-label extension treatment. We, therefore, rely on unblinded, uncontrolled data and observational studies to examine the longer-term risk versus benefit ratio for advanced therapies. While such studies show maintained benefit for therapy greater than a year the data become weaker and sparse for treatment beyond a cycle of 3–5 years. As such there is less certainty that the benefits outweigh the risks in longer-term compared with shorter treatment durations.

The risk of side effects is the main potential benefit of stopping advanced IBD therapies and a reduced risk of infections, malignancy, cardiovascular or thromboembolic events is an important clinical consideration. In addition, patients may wish for a break from immunosuppressive therapy and experience ‘drug holiday’. This may reduce the number of minor infections or may allow for travel to areas where infection risk (such as high risk of tuberculosis) and vaccination considerations (e.g., yellow fever or other live vaccines) may otherwise be prohibitive. The ability to undergo live vaccinations during a biologics break can be of importance to children and those adults planning to travel to high-risk areas for tuberculosis or yellow fever, for example. We should also consider that patients in their early 20s have a life expectancy of another 60 years. It is hard to conceive that such a patient would be treated with the same advanced therapy agent uninterrupted for 60 years.

The final benefit of stopping advanced therapies is cost. Depending on the healthcare system this may benefit the patient directly (self-pay or large copayment) or indirectly (universal healthcare systems) by allowing for more funds to be available for healthcare of the population.

While the advent of biosimilars has reduced cost considerably in some jurisdictions like the UK, the overall cost for advanced therapies remains high.

**RISKS OF STOPPING ADVANCED THERAPY**

The main risk of stopping therapy includes a flare of the disease with a potential risk of hospitalisation or surgery. The majority of available data concern anti-TNF especially infliximab. These studies include randomised controlled trials of stopping therapies, and prospective and retrospective observational studies. The data on non-TNF biologics and JAK inhibitors are very scarce.

Four randomised controlled trials examine anti-TNF withdrawal both in UC and CD. The HAYABUSA trial reported that in patients with UC (in clinical remission for at least 14 weeks) 46% experienced a relapse at week 48 in the group stopping infliximab compared with 20% of those who continued it. SPARE was a large multicentre European trial of 211 patients with CD on combination therapy with infliximab and an immunomodulator in sustained steroid-free remission for at least 6 months. Patients were randomised to either continuation of comotherapy, discontinuation of infliximab or discontinuation of the immunomodulator. Relapse rates at 2 years were 12%, 35% and 9%, respectively. STOP-IT included 115 patients with CD in full clinical, biochemical and endoscopic or radiological remission for at least 12 months. Patients were randomised to continue infliximab or to receive a similar placebo (only study with full blinding) with relapse rates of 0% and 49% after 1 year. In contrast, the Spanish EXIT study found no increased risk of relapse in a placebo controlled randomised controlled trial of anti-TNF withdrawal in 140 patients with IBD in clinical and endoscopic remission who were all on immunomodulators. At 12 months, sustained clinical remission occurred in 76% of the withdrawal and 84% of the maintenance arm (p=NS). Small numerical difference in relapse (13% vs 6%) and endoscopic lesions (19% vs 8%) were not significant. There was, however, a significant difference in the proportion of patients with...
a faecal calprotectin >250 µg/g (33% vs 14%). As this study stands in contrast to the other RCT results, we should acknowledge that the numerical differences at 12 months may have led to significant differences at a later time point especially as the faecal calprotectin rose more often in the withdrawal group.

Observational data on the risk of anti-TNF discontinuation in patients with CD have been examined by several meta-analyses. An individual patient’s data meta-analysis (usually more robust than summary data meta-analyses) reported on 1317 patients with luminal CD from 8 retrospective and 6 prospective studies (median treatment duration 23 months), who were in clinical or endoscopic remission for at least 6 months. The combined primary outcome included requiring at least one of biological retreatment for a flare, requirement for steroids, requirements for new immunosuppressants (71% remained on immunosuppressants at time of anti-TNF discontinuation) or surgery. The cumulative relapses rates were 38% at 12 months and 52% at 24 months. Similar rates have been reported in subsequent studies. Longer-term follow-up of patients withdrawn from anti-TNF treatment suggests that relapse rates remain at 50% after 2 years and likely remain stable after 3–5 years.

There is a single study on elective vedolizumab withdrawal. Relapse rates were 64% after a median of 11 months. In contrast to the anti-TNF studies treatment withdrawal occurred, however, for many different reasons (pregnancy, patient choice, reimbursement limitations). This makes the study hard to interpret. No studies on elective ustekinumab withdrawal have so far been published.

In summary, relapse rates after anti-TNF withdrawal are around 40% at 1 year and 50% at 2 years. Many patients

Figure 1  Proposed flow chart for consideration of de-escalation of anti-tumour necrosis factor (TNF) therapy.
require retreatment, but rates seem to be stable after 3–5 years. High-quality data on biologics other than anti-TNF are currently lacking.

**PREDICTORS OF OUTCOMES OF STOPPING**

Predictors of outcome of stopping of anti-TNF therapy can be divided into disease phenotype, treatment history and laboratory markers. These also overlap largely with markers of more severe trajectories of disease. Table 1 summarises factors associated with either continued remission or relapse. Data on endoscopic and imaging factors are conflicting, and hence not included in the table.

**CHANCE OF RECAPTURE OF RESPONSE IN CASE OF FLARES**

Data on recapture of response in case of flare postdiscontinuation are limited to infliximab. The majority of published studies report that 70%–90% of patients recommencing Infliximab regain clinical remission. It is, therefore, sensible to attempt retreatment with same agent that was electively discontinued. Patients should be counselled when discussing treatment discontinuation that not everyone recaptures response and remission on retreatment. Furthermore, the risk of an infusion reaction on retreatment, although generally low around 9%, should be acknowledged. Therapeutic drug monitoring may be useful prior to discontinuation as the absence of antidrug antibodies is associated with a better response on retreatment. Equally cotreatment with an immunomodulator appears protective against non-recapture or remission. Whether a patient on a specific biosimilar infliximab should have the same biosimilar readministered is controversial. Italian guidance advises against multiple switches but two recent cohort studies have shown multiple biosimilar infliximab switches to be safe and effective. There are unfortunately very few data on recapture of response for molecules other than infliximab.

**THOUGHTS ON SMALL MOLECULES**

In contrast to biological agents, small molecules used in IBD (tofacitinib, filgotinib, upadacitinib and ozanimod) are smaller structures not associated with antidrug antibody formation. Cyclical treatment with biologics

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**Table 1  Factors associated with outcomes of biologics discontinuation**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Favours remission</th>
<th>Favours flare</th>
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<tbody>
<tr>
<td>Disease phenotype</td>
<td></td>
<td></td>
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<tr>
<td>Age at diagnosis &lt;16–25 years</td>
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<tr>
<td>Perianal CD present</td>
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<tr>
<td>Location CD ileocolonic disease</td>
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<tr>
<td>Location CD isolated upper GI disease</td>
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<td>Behaviour CD stricturing or penetrating</td>
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<tr>
<td>Extension UC Pancolitis</td>
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<td>Patient characteristics</td>
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<tr>
<td>Gender Male</td>
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<tr>
<td>Smoking Active smoking</td>
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<tr>
<td>Treatment history</td>
<td></td>
<td></td>
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<tr>
<td>Anti-TNF treatment Longer duration</td>
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<tr>
<td>Dosing Escalated anti-TNF dosing</td>
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<tr>
<td>Surgery Previous resection</td>
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<tr>
<td>Anti-TNF Adalimumab&gt;Infliximab</td>
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<tr>
<td>Adverse event As reason for stopping</td>
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<tr>
<td>Disease status Ongoing symptoms</td>
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<tr>
<td>Combo therapy Continuation of immunomodulator</td>
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<tr>
<td>Laboratory markers</td>
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<tr>
<td>Haemoglobin &lt;145 g/L</td>
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<tr>
<td>White cell count &gt;5–25×10⁹/L</td>
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<tr>
<td>CRP ≥5 mg/L</td>
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<tr>
<td>Faecal calprotectin &gt;50 or &gt;250 µg/g</td>
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<tr>
<td>Infliximab trough levels Undetectable Higher levels</td>
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CD, Crohn’s disease; CRP, C reactive protein; GI, gastrointestinal; TNF, Tumour Necrosis Factor; UC, ulcerative colitis.
risks the formation of antidrug antibodies (chimeric>humanised>fully human), which in turn increases the risk of anaphylactic reactions and reduced efficacy in subsequent treatment cycles. Small molecules may therefore—at least in theory—be better suited for cyclical or episodic treatment as a lack of efficacy due antidrug antibody formation is avoided. Recapturing response is, however, complex and other factors may still affect disease control in cases of flares following treatment cessation. There are currently few data examining these scenarios and any considerations are, therefore, based on theoretical reasoning rather than evidence.

PROPOSED ALGORITHM FOR ANTI-TNF BIOLOGICS

Given the current lack of evidence for treatments other than anti-TNF biologics, the proposed algorithm is limited to these agents. It is conceivable that in future the evidence will suffice for inclusion of other agents. This algorithm reflects the views and clinical experience of the authors and may guide other clinicians in their decision-making.

Patients on anti-TNF biologics in stable clinical remission with faecal calprotectin in remission range may be considered for treatment de-escalation (figure 1). Deep remission should be confirmed by endoscopy for those with colonic and/or isolated terminal ileal disease and those with small bowel disease should undergo small bowel imaging by ultrasound, MRI scans or CT scans. Patients without deep remission should not be offered de-escalation. Any decisions should be shared between clinician and patient, based on full counselling about the potential benefits and risks of the plan for discontinuation of anti-TNF biologics. Especially, the individual circumstances in life (big life events ahead: exams, commencing new jobs, relocation, wedding, pregnancy planned) and in phenotype (perianal disease, extraintestinal manifestations) as well as previous treatments (first-line biologic, combination therapy with immunomodulator) should be taken into account. When patients and clinicians agree, a monitoring plan postdiscontinuation should be agreed. This should, in an ideal world, include faecal calprotectin and C reactive protein measurements at key time points, for example, 3–6 months, but we acknowledge that this is not popular with patients35 and that there needs to be sufficient capacity within the IBD clinic to actively monitor results and act on them. Indeed, a timely clinical and endoscopic reassessment should be made when IBD symptoms occur.

FUTURE DIRECTIONS

With further studies emerging, we will gain a better understanding on the possible risks and benefits of episodic treatment with non-anti-TNF biologics and small molecules. The advent of further biosimilars will likely reduce costs pressures and decision-making will increasingly be based on risk versus benefit considerations for individual patients. Given the lifelong nature of IBD and the lack of curative treatments, we need to be better equipped in identifying patients who may discontinue therapy and understand the frequency of monitoring better to allow for timely recapture of response in times of flare.

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