



ECCO Topical Review on Biological Treatment Cycles in Crohn's Disease

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Abstract

There are now a growing number of licensed biological therapies for patients with Crohn's disease. However, there can be significant costs associated with long-term maintenance treatment, as well as some concerns about potential side-effects. As a result, there has been increasing interest in elective biological treatment discontinuation in selected patients, after a sustained period of remission. Following discontinuation, in cases of relapse, evidence to date has suggested that remission may often be regained by re-treatment with the same biological agent. Therefore, a concept has emerged in which cycles of biological therapy might be used. If this treatment strategy were to be applied in a subgroup of patients at low risk of relapse, cycling might allow a substantial number of patients to have a lower, overall therapeutic burden—ensuring decreased exposure to biological therapy but still enabling appropriate disease control.

Currently, there remains uncertainty about the benefit–risk balance for using cycles of biological treatment for patients with Crohn's disease. Accordingly, an expert panel was convened by the European Crohn's and Colitis Organisation [ECCO] to review the published literature and agree a series of consensus practice points. The panel aimed to provide evidence-based guidance on multiple aspects of biological treatment discontinuation and cycling, including the risk of relapse after elective treatment discontinuation, predictors of probable relapse or remission, safety, patient preferences, and pharmacoeconomic aspects. Crucially, discussions about biological treatment discontinuation and cycling should be individualized, to enable shared decision-making by patients with their clinicians.

Key Words: Crohn's disease; biological treatment; discontinuation; re-initiation; biocycle; cycling; treatment cycles; cost; effectiveness; safety; patient preferences

1. Introduction

The introduction of biological agents has revolutionized the management of Crohn's disease [CD], with significant clinical benefits for patients, including better inflammatory disease control leading to decreased complications, fewer hospitalizations and improved quality of life.¹ However, biological agents are not curative for CD, and notably disease worsening can take place upon cessation of biological therapy.^{2–11} For this reason, continuous maintenance treatment has typically been advised for most patients with CD in order to avoid relapse and subsequent disease progression.

Concerns such as the risk of side-effects and incremental costs of long-term biological therapy have led to a growing interest from both patients and clinicians on the topic of treatment discontinuation,¹² and whether this could be considered after achieving remission in a subgroup of patients. In some countries, the continuation of a biological agent for long periods of time is subject to highly restrictive reimbursement rules, sometimes requiring mandatory treatment discontinuation. Conversely, there has been apprehension around discontinuation of biological agents in patients with previously well-controlled CD, due to the possibility for more disease flares, complications, immunogenicity and possible loss of efficacy when a biological treatment has to be restarted.

A recent European Crohn's and Colitis Organisation [ECCO] Topical Review focusing on treatment discontinuation [withdrawal] discussed that the risks, benefits and timing of stopping biological treatment are uncertain, and suggested that this treatment strategy should not be routinely considered for all patients.¹³ However, in a subset of patients who achieve a prolonged period of clinical and endoscopic remission, elective biological treatment discontinuation could become a relevant point to consider.^{13,14} It was widely recognized that a greater understanding of factors determining benefits and risks from discontinuation were required—and that a critical factor behind the decision to discontinue biological treatment for any individual patient would be to understand the likelihood of successful re-treatment, in case of disease relapse.^{13,15}

There are potential benefits from even transient or intermittent biological treatment discontinuation, with reduced total lifetime treatment burden for patients, a period of time without drug administration worries, and potentially reduced adverse events and costs.¹⁶ This concept builds on the original idea of elective treatment discontinuation, and considers whether using 'cycles' of biological treatments might be considered for patients living with CD.³ If applied in a subgroup of patients at low risk of relapse, this strategy might allow a reduction in therapeutic burden.¹³

It is important to note that biological treatment cycling would be entirely different to the historical on-demand use of anti-tumour necrosis factor [anti-TNF] agents, where treatment was given in a pulsed manner to treat active disease.¹⁷ The major difference is that patients had not achieved a period of sustained remission when on-demand therapy was being used, whereas the concept of cycling would only apply to patients having achieved sustained periods of remission on maintenance biological treatment.

A key clinical question is whether a cycling strategy with repeated and rapid recapture of remission after resuming treatment would offer similar long-term disease control as seen with current maintenance therapy approaches.^{14,18} It is expected that the interval between cycles may vary from patient

to patient. Whether this temporary discontinuation of treatment is beneficial for patients and is actually cost-saving may therefore depend on the length of the interval, the occurrence of complications, the ability to recognize these complications at an early stage by proactive monitoring, and re-treatment before a relapse has become clinically evident.^{19,20}

With the advent and use of more effective monitoring tools to detect subclinical disease activity, coupled with the greater availability of advanced therapies, there may be increasing comfort with biological treatment cycling in the future.¹⁴ In particular, the low risk of immunogenicity to newer therapies may also increase the willingness to attempt biological treatment cycling.³

The aim of this ECCO Topical Review is to provide evidence-based guidance for clinical practice and support shared decision-making by patients and clinicians regarding the strategy of biological therapy cycling in CD. This will include a critical appraisal on the concept of biological treatment cycling, clarification on the appropriateness of certain patient cohorts to undergo selection for this strategy, and strategies to monitor and restart treatment if needed [Figure 1].

2. Methods

ECCO commissioned a topical review consensus group on the subject of biological treatment cycles ['biocycling']. ECCO topical reviews result from expert opinion consensus and are endorsed by ECCO. Due to limited availability of controlled data, the ECCO topical reviews are distinct from ECCO consensus guidelines, and topical reviews are intended to provide guidance in clinical areas where scientific evidence is lacking or limited. Following an open-call across all ECCO members, 15 participants were selected based on their expertise in the topic, and three subgroups were formed.

Working group 1 focused on frequency of relapse following biological treatment discontinuation. Working group 2 focused on predictors of outcome following treatment discontinuation and patient selection for biological cycling. Working group 3 focused on safety, patient preferences and pharmacoeconomic aspects of biological cycling.

The working groups performed a comprehensive literature search of the topic with appropriate key words, using Medline/PubMed, the Cochrane Database and Scopus on January 28, 2022. Additional references were identified through reviewed articles. Discussion of the published evidence took place, with generation of draft statements. A preliminary voting round then took place, followed by revision of the statements. The working parties subsequently met on September 14, 2022 to further discuss, refine and agree on the statements. These statements were accepted when 80% or more of the participants were in agreement, and were then designated as a *Current Practice Position* [CPP]. Each working group wrote the final section on their respective section, followed by integration into a single manuscript by N.N., P.S. and K.P. It is intended that CPPs be read in context, with supporting text comments and not in isolation. The final text was edited by N.N., P.S. and K.P. for consistency of style, and by members of the Guidelines and Education Committees of ECCO, as well as the ECCO Governing Board, who were not involved in development of the consensus. In several areas covered in the present paper, it is recognized that the quality of evidence is low, which reflects the paucity of research including a lack

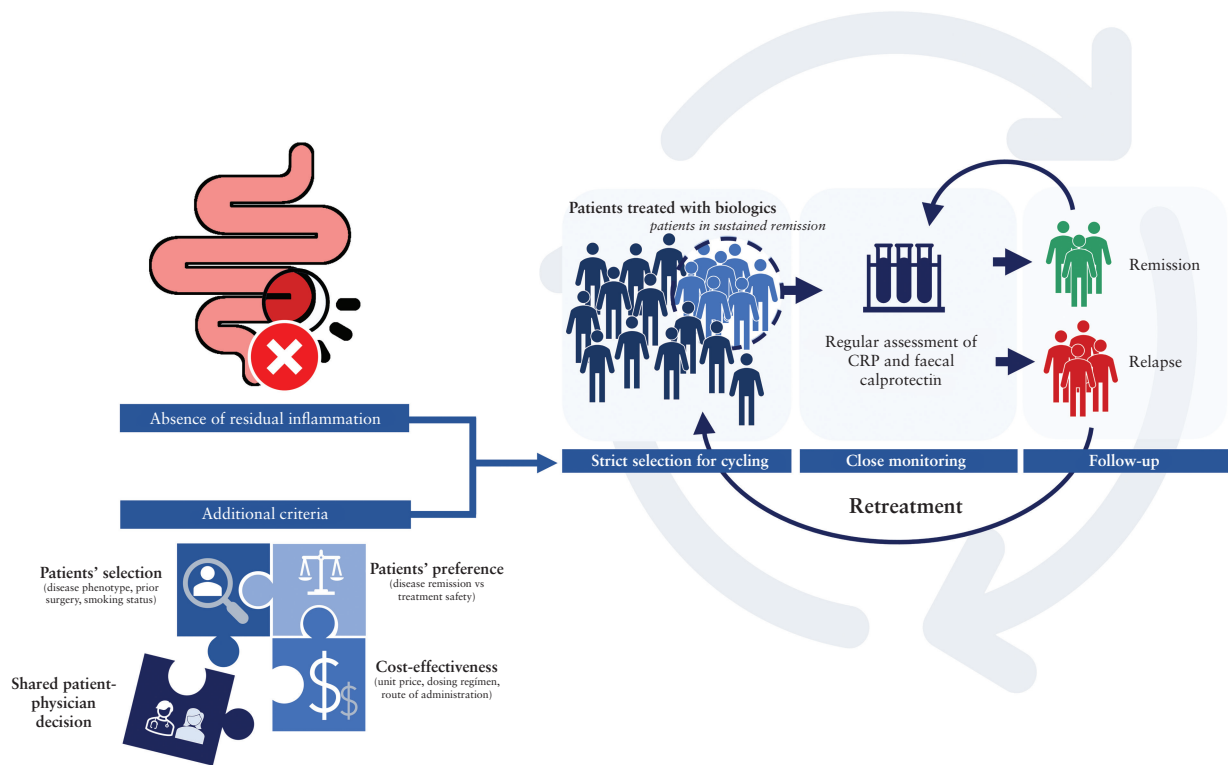


Figure 1. Biological treatment cycles in Crohn's disease. Biological treatment discontinuation and cycling for patients, involving re-treatment with the same biologic agent to achieve remission. Demonstration of the need to carefully consider patient selection, patient preferences and pharmacoeconomic costs.

of randomized controlled trials [RCTs] for biological treatment cycles. Accordingly, where appropriate, expert opinion is included.

Frequency of short-term relapse after anti-TNF discontinuation

ECCO Current Practice Position 1:

The risk of relapse after anti-TNF discontinuation for patients with Crohn's disease in sustained remission (>6 months), and usually maintained on an immunosuppressant, is approximately 40% at 1 year, and 50% at 2 years

Anti-TNF therapies have been shown to be effective for inducing and maintaining remission in CD, promoting mucosal healing and improving longer-term outcomes.^{13,21} Due to safety and cost concerns that come with prolonged use, it has been suggested that anti-TNF maintenance therapy could be discontinued in some patients.¹³

The STORI study assessed infliximab discontinuation in 115 patients with CD in stable remission. This was the first study to prospectively assess the risk of relapse after stopping infliximab, in patients who had been on combined maintenance therapy with immunosuppressants for at least 1 year, demonstrating a 1-year relapse rate of 44%.²²

Several meta-analyses have also evaluated the risk of relapse after anti-TNF discontinuation, for patients with CD in remission [Supplementary Table 1].^{6,9,23} All these meta-analyses have included both retrospective and prospective observational cohort data, with the most recent being an individual patient data meta-analysis of 1317 patients with CD

from 14 studies [eight retrospective and six prospective cohort studies].⁹ The primary outcome was relapse that necessitated re-initiation of biological treatment, corticosteroids, immunosuppressants or need for surgery. In this meta-analysis, patients were on infliximab or adalimumab therapy for a median of 23 months [range 14–40 months] before anti-TNF discontinuation, and had been in clinical or endoscopic remission for at least 6 months prior to withdrawal. The majority of patients [71%] had received concomitant immunosuppressants at anti-TNF withdrawal. Of note, patients with perianal CD as an indication for anti-TNF therapy were excluded. The overall cumulative rate of relapse was 38% at 1 year, and 52% at 2 years of follow-up,⁹ with a similar frequency of relapse reported in other recent meta-analyses.^{6,23}

More recently, there has also been RCT-level evidence reported to evaluate the risk of relapse from anti-TNF discontinuation. Initially, the HAYABUSA trial in patients with ulcerative colitis demonstrated relapse of 46% at week 48 after infliximab discontinuation, compared to a 20% risk of relapse in the 46 patients who continued infliximab.²⁴ Moreover, two further RCTs have evaluated the risk of relapse after anti-TNF withdrawal in patients with CD.^{25,26}

The SPARE trial aimed to assess the relapse rate over 2 years in 211 adults with CD treated with infliximab on combination with an immunosuppressant [thiopurine or methotrexate] for at least 8 months, who were in sustained steroid-free remission >6 months.²⁶ Participants were randomized into three groups, continuing combination therapy, withdrawing infliximab or withdrawing the immunosuppressant. Randomization was stratified according to disease duration before start of first anti-TNF, failure of immunosuppressant prior to start of infliximab and presence of ulcers at

baseline endoscopy. At baseline, all patients had a Crohn's disease activity index [CDAI] <150. In total, 39 patients had disease relapse by the end of 2 years, with the majority being in the infliximab discontinuation group [$n = 26$]. The rate of relapse was 36% in the 71 patients who discontinued infliximab, and 14% in the 67 patients who continued on combination therapy.

The STOP-IT trial included 115 adults with luminal CD in complete remission [clinical, biochemical and endoscopic/radiological remission], and who had been treated with infliximab therapy for at least 1 year.²⁵ Half of the participants were on combination therapy with immunosuppressants. This was the first placebo-controlled discontinuation RCT reported in the inflammatory bowel disease [IBD] literature, with patients randomized either to continue infliximab or receive placebo. After 1 year, the relapse rate was 49% in the patients who discontinued infliximab and receive placebo, and 0% in those patients who continued infliximab.

Further data on the discontinuation of anti-TNF therapy in different settings and populations is anticipated from follow-up that will take place from several ongoing RCTs including: BIOSTOP [EudraCT number 2016-001409-18], In-TARGET [NCT02425865], CURE [NCT03306446], PROFILE [ISRCTN11808228]²⁷ and EXIT [EudraCT number 2015-001410-10].²⁸ Overall, the findings from RCTs of anti-TNF discontinuation have been remarkably consistent with previous findings from observational data and corresponding meta-analyses,^{6,9} supporting the conclusion that in a relevant subgroup of patients with CD, anti-TNF biological treatment discontinuation may occur with ongoing maintenance of remission in ~50% of patients, at 2 years follow-up.

Frequency of longer-term relapse after anti-TNF discontinuation

ECCO Current Practice Position 2:

The long-term (>2 years) risk of relapse after anti-TNF discontinuation in patients with Crohn's disease in sustained remission (>6 months) is $\geq 50\%$

Data from longer follow-up periods after anti-TNF discontinuation are limited. A meta-analysis found that 50% of patients with CD remained in remission after >2 years of anti-TNF withdrawal.⁶ In line with these results, a further study analysed the risk of relapse in 1055 patients with IBD who discontinued anti-TNF treatment after achieving clinical remission. After a median follow-up of 34 months, the cumulative incidence of relapse was 50%.²⁹ Moreover, the risk of relapse seemed to reach a plateau after 5 years, such that after 5–7 years of follow-up, ~50% of the patients still were in clinical remission.²⁹ Similar results were reported in another study in which 52% of the patients who discontinued infliximab remained in remission after 10 years of follow-up.³⁰ However, the follow-up cohort from STORI demonstrated lower numbers, with only 22 [21%] of the patients who had stopped infliximab still being in clinical remission without any further need for biological treatment, after 7 years of follow-up.³¹ These results suggest that some patients might sustain clinical remission for >2 years after anti-TNF discontinuation, although many will require

re-treatment with biological therapy after a period of time, and that long-term data on other more objective measures of outcome are currently lacking.

Effectiveness of re-treatment after relapse following anti-TNF withdrawal

ECCO Current Practice Position 3:

Following anti-TNF discontinuation in patients with Crohn's disease in sustained remission, re-treatment with the same drug after relapse is generally safe and effective

There have been concerns that some patients when re-treated with the same biological agent might not respond, lose response over time, or develop immunogenicity and infusion reactions requiring an alternative therapeutic approach.^{13,32} However, data on re-treatment with the same medication after relapse following elective anti-TNF discontinuation in patients with CD in remission show that this is generally safe and effective.

The rate of recapturing remission ranges from 70 to 90%, although there is notable heterogeneity in follow-up time among studies to have reported on this, ranging from 6 weeks to 6 years.^{6,13,18,22,24,26,29,31,33,34} An extension of the EVODIS [Evolution after anti-TNF discontinuation in patients with IBD] retrospective, multicentre study showed that 74% of patients with CD who relapsed after discontinuing anti-TNF therapy and were re-treated with the same drug then regained remission.²⁹ However, a recent systematic review and meta-analysis showed that the pooled clinical remission rate of infliximab re-treatment in patients with IBD was 85% for induction therapy [at least 3 months].¹⁸ Moreover, the pooled clinical remission rate for maintenance therapy [at least 1 year] was 73%. These results are in line with two previous systemic reviews and meta-analyses demonstrating a remission recapture rate after re-treatment with the same anti-TNF of 76 and 82% in patients with CD.^{6,33}

The STORI prospective study demonstrated that re-treatment with infliximab was effective and well tolerated in 88% of patients who experienced a relapse after infliximab discontinuation.²² However, in longer-term follow-up, the cumulative incidence of re-treatment failure was 30% at 6 years.³¹ This was mostly due to loss of response or a major complication including surgery.³¹ Reassuringly, RCT-level data from SPARE have also shown that re-treatment was well tolerated and successful in almost all patients, at least in the short term. In total, 22/23 who had a disease relapse after stopping infliximab then achieved remission after re-treatment with infliximab.²⁶

Historically when there was on-demand use of infliximab, it was possible to examine the efficacy of re-treatment with infliximab, in patients who had previously responded to infliximab induction and then relapsed on maintenance therapy with an immunomodulator. One study from France assessed infliximab re-treatment in 61 patients with CD, demonstrating 80% clinical response after re-treatment.³⁵ In this cohort, infliximab re-treatment was effective and well tolerated if performed within the first 50 weeks. By contrast, re-treating with infliximab later than 50 weeks after stopping was associated with a higher risk of hypersensitivity reactions leading to subsequent infliximab discontinuation in

30% of cases.³⁵ It was speculated that the development of anti-infliximab antibodies against the restarted infliximab might have been the cause of treatment failure, although anti-infliximab antibody levels were not assessed in the study. This was also shown in a further study of infliximab re-treatment in 53 patients with CD who had previously completed infliximab induction and then received maintenance therapy with an immunomodulator. Steroid-free remission rates were lower for patients who were re-treated with infliximab, more than 12 months after infliximab discontinuation.³⁰

Re-initiating intravenous infliximab after a drug holiday has been associated with both acute [12%] and delayed [8%] infusion reactions.³² Subsequent meta-analyses have also reported similar rates, with 9% of patients experiencing infusion reactions on infliximab re-initiation, although it is important to note that most of these reactions resolved with conservative measures.¹⁸ Notably, the use of immunomodulators has been associated with a reduction in infusion reactions following biological treatment reintroduction.^{13,32} There are currently no data on re-initiating subcutaneous infliximab after a drug holiday.

Overall, to date, most data have been quite reassuring and shown that following elective discontinuation for patients in remission, re-treatment with the same biological therapy after relapse is generally safe and effective.

Frequency of relapse and re-treatment effectiveness after ustekinumab and vedolizumab discontinuation

ECCO Current Practice Position 4:

The risk of relapse and re-treatment success after ustekinumab or vedolizumab discontinuation in patients with Crohn's disease is relatively unknown

Data on re-treatment with biological agents other than anti-TNF therapies are scarce. Ustekinumab has been shown to be effective for inducing and maintaining remission in CD, promoting endoscopic healing and improving clinical outcomes.³⁶ Although short-term safety data have been quite reassuring to date, longer-term therapy might be associated with substantial cost and potential safety concerns. Therefore, ustekinumab treatment discontinuation might, at least theoretically, be considered in some cases. However, an important point to note is that biological therapies such as ustekinumab have often been used as second- or third-line agents, and in such instances clinicians and patients might be more reluctant to discontinue the treatment, even following a period of sustained remission.

Currently there are no data on elective ustekinumab discontinuation following a sustained period of remission in CD. In the 5-year long-term extension of the pivotal IM-UNITI trial, of 237 patients, 113 [48%] did discontinue ustekinumab.³⁶ However, the reasons for drug discontinuation were loss of efficacy or patient withdrawal of consent, and not due to elective biological treatment discontinuation.

Vedolizumab has also been shown to be effective for CD, for both short- and longer-term outcomes.³⁷ Much like ustekinumab, longer-term follow-ups from the pivotal clinical trials have not provided data on elective drug discontinuation following a sustained period of remission. There is, however, a

retrospective study from France, which assessed vedolizumab discontinuation in 95 patients [58 with CD and 37 with ulcerative colitis]. After a median follow-up of 11 months after vedolizumab discontinuation, 64% of patients experienced relapse.³⁸ However, in that study the vedolizumab was discontinued for a wide variety of reasons including: pregnancy [39%], safety concerns [28%], patient choice [25%] or reimbursement issues [8%]. C-reactive protein [CRP] < 5 mg/L at the time of discontinuation (hazard ratio [HR] = 0.56, 95% confidence interval [CI] [0.33–0.95]) and elective/voluntary discontinuation (HR = 0.41, 95% CI [0.21–0.80]) were factors associated with lack of relapse during follow-up. Among the 61 patients with disease relapse, vedolizumab was re-introduced in 24 [39%] resulting in a 14-week steroid-free remission rate of 71%.³⁸

With these very limited data, it seems that relapse after vedolizumab discontinuation is, at least, as common as with anti-TNF. Re-initiation of treatment with vedolizumab seems to be effective in about two-thirds of patients. However, more data are needed on larger and more diverse population cohorts. Data on relapse following elective discontinuation and re-treatment with ustekinumab are currently lacking.

Predictors of relapse after biological treatment discontinuation

ECCO Current Practice Position 5:

Data on predictors of relapse after biological treatment discontinuation in patients with Crohn's disease are many and heterogeneous

Signs of 'residual disease activity' may be the best predictor for disease relapse, and treatment discontinuation should be carefully considered in this category of patients

The data on predictors of relapse after biological therapy discontinuation in patients with CD mostly relate to anti-TNF medications, particularly infliximab. Identified predictors of relapse mainly consist of clinical variables and laboratory markers [Supplementary Table 1]. In terms of clinical predictors, there are multiple factors which have been associated with a higher risk of relapse after anti-TNF drug discontinuation including: age at diagnosis <16–25 years,^{5,9,33,39} age at anti-TNF cessation,³⁹ male gender,²² active smoking,^{5,9,39} longer disease duration at first biologic administration,^{5,39} fistulizing perianal CD,⁵ receiving escalated anti-TNF doses,⁵ receiving anti-TNF for the prevention of post-operative recurrence,⁵ previous surgical resection,⁴⁰ ileocolonic [L3] disease,⁴⁰ or isolated upper disease [L4],^{9,39} stricturing [B2]³³ or penetrating [B3] disease behaviour,⁶ treatment with adalimumab vs infliximab,^{9,39,41} elective discontinuation vs discontinuation for top-down strategy,⁴¹ discontinuation because of adverse events,^{41,42} clinical symptoms at cessation,³⁹ and previous biological therapy.^{39,42} By contrast, maintenance of immunosuppressants after anti-TNF discontinuation has been suggested to be a protective factor against relapse in some studies.^{11,41}

The laboratory markers that have been associated with relapse at the point of biological therapy discontinuation are: haemoglobin levels <145 g/L⁵, white cell count >5–25 × 10⁹/L,^{5,33} CRP ≥ 5 mg/L [both for anti-TNF,^{5,9} and vedolizumab,³⁸ discontinuation], varying thresholds of faecal calprotectin [FC] >50,³³ or >250 µg/g,⁵ as well as varying

thresholds of infliximab trough levels ≥ 2 mg/mL,⁵ or >6 mg/mL.⁴³ These data suggesting that higher infliximab trough levels at discontinuation are associated with greater risk of relapse perhaps indicate that active inflammation is being controlled and CD being kept in remission by the presence of sufficient drug concentrations.^{22,44} In contrast, undetectable anti-TNF drug levels in patients with long-term deep remission have been associated with a greater likelihood to be in remission at 12 months following discontinuation of anti-TNF therapy.⁴⁵

There are conflicting data on the predictive value of endoscopy for disease relapse following biological treatment discontinuation. Several studies have reported no correlation between endoscopic healing and the frequency or time to relapse.^{33,40,42,46} Others have shown that there does appear to be an increased risk for relapse in patients with a Crohn's disease endoscopic index of severity [CDEIS] >0 .^{22,43} A further study has suggested that magnetic resonance enterography [MRE] could be considered when evaluating anti-TNF biological discontinuation since the presence of mild activity was found to be associated with increased recurrence rates.⁴⁷ However, the utility of MRE following biological discontinuation has been disputed by others.⁴⁰ Finally, there are few data about the predictive value of genetic,⁴⁸ immune⁴⁹ and microbial⁵⁰ markers for disease relapse and there are no data currently available on the predictive role of histology and bowel ultrasound in this setting.

In conclusion, predictors of relapse are many, varied and at times conflicting, mainly due to the high heterogeneity between studies and different criteria applied to biological treatment discontinuation. However, 'residual disease activity', defined as evidence of ongoing inflammation despite the absence of clinical activity, appears to be the most useful current predictor of relapse when discontinuing biological therapy.

Predictors of remission after resuming biological treatment

ECCO Current Practice Position 6:

There are a paucity of data relating to predictive factors of response after biologic agent re-initiation in Crohn's disease, with all data limited to infliximab. Immunogenicity seems to have a negative impact on re-initiation outcomes

In patients with CD who relapse following biological treatment discontinuation, re-treatment with the same biologic agent represents an effective treatment strategy.

The selection of patients suitable for biological treatment cycling should include consideration of predictors of relapse after discontinuation, as well as predictors of response when treatment is restarted. Information on predictors of response to biologic treatment re-initiation is scarce and limited to infliximab.

Although there are conflicting results, which may be partly explained due to the heterogeneity of study populations in individual studies, the overall proportion of patients who regain remission after reinduction with infliximab treatment is 70–90% in most of the published studies [Supplementary Table 1].^{5,18}

Subsequent groups have tried to identify factors associated with the success and safety of restarting infliximab in

128 consecutive patients [105 CD and 23 ulcerative colitis], after a median discontinuation time of 15 months.³² Twenty-eight patients had withdrawn infliximab for loss of response and 100 had elective discontinuation either due to being in remission or being pregnant. Re-initiating infliximab was associated with clinical response in 85% after 14 weeks, 70% at 1 year and 61% at 4 years. Fifteen patients [12%] developed acute infusion reactions and ten had delayed infusion reactions [8%]. An absence of anti-infliximab antibodies at discontinuation, and re-initiation with concomitant immunomodulators were factors associated with short-term remission, while higher infliximab trough levels early after re-starting infliximab were associated with long-term response. Similarly, undetectable levels of antibodies to infliximab early after re-treatment was associated with fewer infusion reactions.³²

Patient selection for biological treatment cycles

ECCO Current Practice Position 7:

Before biological treatment discontinuation and cycling in patients with Crohn's disease, beside the presence of deep remission, other risk factors of disease relapse and disease progression [i.e. perianal disease or stricturing phenotype, smoking and intestinal resection] should be taken into consideration

Biological treatment discontinuation and cycling may not be appropriate for patients with potentially adverse prognostic features, a history of previously severe disease course or markers of sub-clinical disease activity. Conversely, there are certain groups in whom biological treatment discontinuation and cycling might be considered an appropriate strategy.

It is clear that safety and consideration of the benefit–risk balance for each individual plays an important consideration in patient selection. This is clearly demonstrated by the increasingly common practice to consider the discontinuation of immunomodulators in patients of older age [>60 years old] in remission on combination therapy, due to the time–exposure risk related to the risk of lymphoproliferative disorders.^{51,52}

As well as the potential predictors of relapse described above, several clinical factors will also need to be considered when contemplating biological treatment discontinuation and cycling. The presence of clinical parameters such as younger age at onset,^{5,33} perianal fistulizing disease,⁵ luminal stricturing or penetrating disease,^{5,9} may point to a higher risk for adverse outcomes. Specifically in the context of treatment discontinuation, previous surgical resection,⁴⁰ ileocolonic disease,⁴⁰ isolated upper gastrointestinal disease,⁹ stricturing disease³³ and fistulizing disease⁶ have all been associated with a greater likelihood of relapse. A particular concern in patients with CD who have more severe disease phenotypes and relapsing disease is the potential risk for complications including potentially a greater need for more operative interventions after biological treatment discontinuation. Thus, it is not only the risk of relapse but also, and even more so, the potential consequences of disease relapse that should influence selection for biological treatment discontinuation and cycling.

Patient monitoring in the context of biological treatment cycles

ECCO Current Practice Position 8:

Monitoring of Crohn's disease after biological treatment discontinuation should include regular clinical evaluation as well as objective disease assessment [i.e. C-reactive protein or faecal calprotectin], since biomarker elevation may precede clinical relapse

A tighter control of biomarkers is suggested in the first year after biological treatment discontinuation as disease relapse occurs more often in this period

After discontinuation of biological treatment, patients with CD should be closely monitored to enable detection of disease recurrence. This close monitoring or tight-control approach would typically be performed using assessment of non-invasive biomarkers such as CRP or FC. In particular, elevations in FC may indicate likelihood of clinical relapse, and help guide treatment re-initiation following elective discontinuation of biological therapy.⁵³

Most studies that have assessed the rate of relapse after biologic discontinuation are retrospective in nature and have provided only limited longitudinal data on CRP and FC. Indeed, only ten studies were identified that used a systematic approach to monitoring.^{42,53-61} Of these, three studies regularly assessed CRP,^{42,54,55} while four regularly measured FC values,^{53,56-58} and three both CRP and FC.⁵⁹⁻⁶¹ Regarding the timing of measurements, CRP values were mostly measured 2-3 months after treatment discontinuation, whereas timing of FC measurement and its cut-off value were more heterogeneous. In particular, four studies defined a normal FC level <100 µg/g,^{53,57,58,60} while one study used a cut-off level <200 µg/g,⁵⁶ and another study applied <150 µg/g.⁵⁹

In a sub-analysis of STORI, both CRP and FC were measured every 2 months for 18 months after infliximab discontinuation or until relapse.⁶¹ Despite the absolute values of CRP and FC being highly variable, it was found that elevation of the two biomarkers [CRP > 5 mg/L and FC > 250 µg/mg] was associated with disease recurrence within a median follow-up period of 10 months.⁶¹ In another prospective study of 49 patients with IBD [16 with CD] who were in clinical, biochemical and endoscopic remission after at least 1 year of treatment with anti-TNF, FC was measured monthly during the first 6 months after discontinuation, and every 2 months thereafter.⁵³ A continuous increase of FC from baseline was reported at 2, 4 and 6 months before the occurrence of clinical relapse.⁵³ Similarly, in a cohort of 160 patients undergoing de-escalation or discontinuation of immunosuppression [of whom 117 patients were being treated with biological agents], FC > 200 µg/g was associated with an increased risk for clinical relapse after a median of 3 weeks, compared to 87 weeks in patients with FC < 200 µg/g.⁵⁸

In addition, current data have shown that most relapses occur within the first year after biological treatment discontinuation.^{33,59} Therefore, it appears reasonable to closely monitor CRP and FC levels every 2-3 months in the first year after discontinuation and potentially extend the monitoring intervals in patients with sustained remission.³ However, the need for long-term monitoring should be recognized in patients who have biological treatment discontinuation,

as demonstrated by the longer-term follow-up results from STORI. Indeed, major complications, defined as surgical resection or new complex perianal lesions, could still occur relatively late after infliximab discontinuation with a median duration of 45 months.³¹

Depending on disease location, particularly in patients with isolated small-bowel CD, even in the absence of clinical disease activity and elevated biomarkers, endoscopic or cross-sectional imaging may be used to assess disease recurrence. To date, only one study has assessed endoscopic outcomes, at 4 and 12 months, after anti-TNF treatment discontinuation to assess disease relapse.⁶⁰ Therefore, currently there is insufficient evidence to define the optimal timing of endoscopic follow-up assessments after treatment discontinuation. Similarly, no prospective studies have assessed the accuracy of cross-sectional imaging or histological assessment to monitor for relapse following biological treatment discontinuation.

Future prospective research studies of larger cohorts are required to define ideal time intervals for monitoring and to help determine clinically useful cut-off levels for monitoring tools, following biological treatment discontinuation.

Pharmaco-economics of biological treatment discontinuation and cycling

ECCO Current Practice Position 9:

Cost-effectiveness of discontinuation and cycling biological therapy in patients with Crohn's disease is highly dependent on the unit price, the dosing regimen and the route of administration

Several studies have shown cost-effectiveness of anti-TNF treatment, particularly infliximab and adalimumab, for the induction of remission in patients with moderate to severe CD.⁶²⁻⁶⁵ Cost-effectiveness data are, however, much more nuanced for maintenance therapy in CD.⁶²⁻⁶⁶ Some studies have suggested a cost-effectiveness for up to 4 years of therapy with infliximab, but several other studies have questioned this cost-effectiveness, particularly for treatment durations greater than 4 years. The effectiveness assessment in the majority of these studies was based on clinical remission and clinical response using classical CDAI definitions.

In addition, higher cost-effectiveness for combination therapy of infliximab with an immunosuppressant has been demonstrated over monotherapy with infliximab.^{67,68} This cost-effectiveness has been calculated based on both increased effectiveness of treatment and decreased need for infliximab dose escalation.^{67,68} However, these results are highly sensitive to the price of infliximab, which has decreased dramatically in recent years with the advent of biosimilars.^{69,70} The results are also influenced by a patient's clinical situation, in particular the severity of their disease.

Very few studies have specifically looked at the pharmaco-economic impact of treatment cycles in CD, and more specifically at using cycles of either infliximab or immunosuppressant in patients in sustained steroid-free remission, receiving a combination of infliximab and immunosuppressant. Using Markov-type decision-tree modelling of three maintenance therapies, including two discontinuation strategies [withdrawal of infliximab or withdrawal

of the immunosuppressant], Bolin *et al.* showed that at the standard price of infliximab, the most cost-effective treatment strategy was cycles of infliximab treatment [withdrawal and re-introduction based on disease relapse] on the basis of a continuous immunosuppressant treatment.¹⁹

At a lower infliximab price, continuing the combination therapy may become cost-effective. The unit price at which this continuous strategy became cost-effective depended on the informal willingness-to-pay threshold, which was highly different across countries. For example, in 2019 it was below €100 for 100 mg in Poland with a willingness-to-pay threshold of €21 598 per quality-adjusted life-year [QALY].¹⁹ This figure was slightly below €300 for 100 mg in the UK with a willingness-to-pay threshold of €74 853 per QALY. It was around €700 in Norway with a willingness-to-pay threshold of €197 694 per QALY.¹⁹

Patient preferences on biological treatment discontinuation and cycling

ECCO Current Practice Position 10:

The priority for most patients with Crohn's disease is sustained remission. However, some patients may accept a certain risk of relapse in order to discontinue biological therapy

Several discrete choice experiment studies have assessed the most important factors for patients when making treatment decisions in CD.⁷¹⁻⁷⁴ Although there are significant differences between individuals,⁷⁵ maintaining remission has consistently been rated as the most important attribute for patients, with one study showing that patients were willing to accept a rare risk of infection or cancer for a 14% absolute increased chance of clinical remission.⁷⁴ In that study, latent class analysis also demonstrated that 45% of the cohort was risk-averse, either to adverse events and/or requiring a course of prednisolone treatment. When these preferences were used in modelling studies to compare pairs of treatments, there was a $\geq 78\%$ probability that all biological treatments were preferred over azathioprine or methotrexate, based on the balance of benefits and harms.

Very few studies have specifically addressed the question of patient preferences in the setting of biological treatment discontinuation and treatment cycles. A study performed across France and North America revealed large differences across patients, with some patients favouring sustained remission at all cost, while others were willing to accept high risks of relapse in order to discontinue therapy.¹² In line with results of the discrete choice experiments described above, the majority of patients reported preference to stop immunosuppressant medications rather than infliximab, when being in sustained steroid-free remission and receiving combination therapy. In total, 65% of patients in France and 73% in the USA reported that they would not accept a risk of relapse $>25\%$ over 2 years, while more than 50% of the patients would accept up to 5% of time spent in relapse, in order to try discontinuation of treatment.

Combining cost-effectiveness and patient preferences may be a difficult task. However, it is clear that some patients would favour a reduced number of treatments if this decreased their risk of potential side-effects. A substantial

proportion of patients would even tolerate a risk of relapse and some time spent with active disease in order to attempt discontinuation of therapy.

Safety considerations from biological treatment discontinuation and cycling: potential benefits and risks

ECCO Current Practice Position 11:

The risk-benefit balance of discontinuation and cycling of biological therapy needs to be considered for each individual patient with Crohn's disease

A decision aid considering potential benefits and risks may be helpful to enable shared decision-making about treatment

Biological treatment cycling has theoretical safety benefits from decreased drug exposure and side-effects for patients. However, there are also theoretical safety risks from cycling biological treatments including: inadequate disease control, loss of response to future cycles of therapy and greater risks of immunogenicity.

Some of the safety concerns around biological treatments in CD have been based on the premise that continued drug exposure can increase the risk of side-effects. These concerns have focused in particular on the risks associated with anti-TNF medications, including the risk of serious infections⁷⁶ and the risk of malignancies with long-term use.^{77,78} Given many of these serious anti-TNF side-effects have been linked to prolonged drug exposure, it has been suggested that cycling and reducing exposure may reduce the potential for side-effects to occur, and therefore lead to better patient outcomes in the longer term.

To date, safety data regarding use of both vedolizumab and ustekinumab have been reassuring. There have been no signals for serious infections from either vedolizumab^{37,79} or ustekinumab use.³⁶ In addition, there have been no associations with increased risk of malignancy from either vedolizumab⁸⁰ or ustekinumab use.⁸¹ Nevertheless, it is clear that longer-term safety data are required, particularly from large, well-characterized, prospective cohorts.⁸²

Despite the potential for reduced side-effects from biological treatment cycling, it is important to note that so far there has been sparse evidence to demonstrate this is actually the case.⁸³ This lack of data is partly due to historical reluctance to stop treatments for patients with CD in remission.¹⁴ Even when treatments have been stopped, almost universally the focus from studies to date has been on the risk of disease recurrence or relapse, rather than whether any safety signals or burden have been reduced.

Data from a large nationwide cohort study in France have demonstrated that the risks of lymphoma do appear to decrease after withdrawing from thiopurine medications.⁸⁴ This reduction in risk with longer time periods off-medication may also be the case for biologic medications. However crucially, this benefit has yet to be demonstrated with biological treatment cycling in CD.

A further point to consider is that focusing only on side-effects of medications ignores the potential adverse effects from inadequate disease control. As highlighted above, the STOP-IT trial demonstrated a 51% risk of relapse from

Table 1. Option grid for the choice between discontinuation and cycling of anti-TNF therapy vs continuation. Use of this tool during a clinic visit may help to facilitate the shared decision-making process

	Discontinuation and cycling of anti-TNF therapy	Continuation of anti-TNF therapy
Clinical characteristics	<p>Suitability of the patient</p> <p>Presence of all the following:</p> <ul style="list-style-type: none"> • Absence of perianal disease • Absence of fistulizing or stricturing disease • First ever anti-TNF agent [or second anti-TNF agent for reasons other than primary non-response or secondary loss of response] • Absence of extra-intestinal indications for anti-TNF agents • No use of corticosteroids [for Crohn's disease] in the past 6 months • No history of surgical resection • 18 years or older • Not currently smoking 	<p>Presence of at least one of the following:</p> <ul style="list-style-type: none"> • Perianal disease • Fistulizing or structuring disease • Second anti-TNF agent [after primary non-response or secondary loss of response on the first anti-TNF agent] • Any extra-intestinal indications for anti-TNF agents • Treatment with corticosteroids [for Crohn's disease] in the past 6 months • Previous surgical resection • Younger than 18 years • Currently smoking
Markers of disease activity	<ul style="list-style-type: none"> • Absence of symptoms of active disease • Two consecutive FC results in the target range in the previous 6 months^a • Confirmed endoscopic or radiological remission 	<ul style="list-style-type: none"> • FC out of the target range in the previous 6 months^a • Confirmed endoscopic or radiological disease activity
Benefits of discontinuation	<p>Benefit–risk balance</p> <ul style="list-style-type: none"> • One year after discontinuation, no new drug-related skin reactions • The susceptibility for infection is reduced • Reduction of direct costs of anti-TNF agents 	<ul style="list-style-type: none"> • Among those who continue anti-TNF therapy, approximately ten people out of 100 have skin reactions • Among those who continue anti-TNF therapy, the susceptibility for infection remains unchanged • Ongoing direct costs of anti-TNF agents
Risks of discontinuation	<ul style="list-style-type: none"> • One year after elective discontinuation, approximately 40 people out of 100 experience a relapse • Among the patients who experience a relapse after elective discontinuation, approximately 10–30 people out of 100 will not recapture remission with the same drug 	<ul style="list-style-type: none"> • Among those who continue anti-TNF therapy, approximately ten people out of 100 experience a clinical relapse over 1 year • Among the patients who experience a clinical relapse during continued anti-TNF therapy, dose escalation of the same drug may not recapture remission in approximately 50 people out of 100
Which is the preferred statement?	<p>Patient preferences</p> <ol style="list-style-type: none"> 1 <i>I wish to investigate what happens if I stop the medication</i> 2 <i>I wish to stop because of potential long term side-effects</i> 3 <i>I am concerned about out-of-pocket cost of the medication</i> 4 <i>I accept the risk of a flare and trust that it can be controlled when the medication is reintroduced</i> 5 <i>I accept that recapturing remission may require a course of steroid medication</i> 	<ol style="list-style-type: none"> 1 <i>I am happy to continue with my current treatment</i> 2 <i>I am more concerned about the risks of stopping than the potential side-effects</i> 3 <i>I am not concerned about out-of-pocket cost of the medication</i> 4 <i>I do not want to risk a flare of disease</i> 5 <i>I do not want to receive another course of steroid medication</i>

^aCurrently there is no single definition for the optimal cut-off point or target range for FC (faecal calprotectin) in determining remission for patients with Crohn's disease.^{104–111}

stopping infliximab in patients with CD at 1 year,²⁵ and subsequently slightly lower but similar rates were seen in the SPARE trial, with close to 40% of patients discontinuing infliximab having relapse of CD within 2 years.²⁶

In many instances, the risks of uncontrolled CD and complications arising from the disease may be comparable or higher than some of the risks associated with medications.⁸⁵ There are also concerns about potential loss of response when re-cycling back onto a treatment and potential for increased risk of immunogenicity. Data from the SPARE trial in particular have been quite reassuring, with regard both to

remission after re-initiation of infliximab and no signal being seen for early antibody formation.²⁶

For patients to make an informed, balanced and timely decision to discontinue their biological therapy, they should have the benefits and risks explained to them. For physicians to effectively communicate these outcomes, it is vital to understand that patients will perceive risks and benefits differently. To facilitate these discussions and allow exploration of patient preferences, we have designed an option grid [Table 1], which may help to support shared decision-making about treatment. The option grid covers frequently asked

questions comparing treatment discontinuation against continuation of current therapy. The option grid also focuses on the subpopulation of patients with the presumed lowest risk of relapse. Safety issues associated with long-term exposure to anti-TNF agents should be weighed against the risk of relapse after discontinuing treatment.

In summary, it is clear that there is no one-size-fits-all approach for biological treatment cycling in CD. There are multiple pharmacokinetic and pharmacodynamic factors which might influence what the right treatment is, at the right time for each specific individual, and whether discontinuation and biological treatment cycles may be appropriate. The risk-benefit balance should be considered for each individual, and discussed with patients, to enable shared decision-making. Accordingly, a decision aid may be helpful to inform this shared decision-making process.

Biological treatment discontinuation and cycling during pregnancy

Biological treatment discontinuation and/or cycling of anti-TNF therapy during pregnancy should, in general, be avoided, since the risk of relapse leads to potentially higher risk of complications for the mother and the foetus. Data on other biological treatments in this specific context are lacking. Specific statements regarding the use of biological therapies in pregnancy have been formulated and addressed in detail in the most recent ECCO Guidelines on Sexuality, Fertility, Pregnancy and Lactation.⁸⁶

Biological treatment discontinuation and cycling in patients with previous or current malignancy

ECCO Current Practice Position 12:

Discontinuation and cycling of biological therapy in patients with Crohn's disease and previous or current malignancy should be individualized and managed within a multidisciplinary team

Discontinuation of biological treatments in patients with current or previous malignancy is driven mainly by safety issues and should be discussed within a multidisciplinary team. The most recent ECCO guidelines on IBD and malignancies suggest that anti-TNF medication may be continued in active oncological disease depending on the benefit-risk balance for an individual, but that there is limited evidence in this context for other biological agents.⁸⁷ If the decision is made to stop a biological therapy in patients with active oncological disease, then the decision for re-initiation of treatment needs to be individualized and also managed within a multidisciplinary team. This should be based both on information regarding risk of tumour recurrence and disease activity of CD.

Historically, based on data from transplant recipients, the re-introduction of biological treatments or other immunomodulatory drugs was typically advised to be considered 2–5 years after the completion of oncological treatment, depending on the oncological risk of recurrence.⁸⁸ However, most of this was based on historical data on immunomodulators and small cohorts of patients on anti-TNF treatment. By contrast more recent data from patients with

IBD and previous malignancy show no increased risk of incidental or recurrent cancer when treated with vedolizumab or ustekinumab.⁸¹ Indeed, data comparing the risk of new or recurrent cancer with anti-TNF vs vedolizumab have also shown no increased risk for anti-TNF biological treatments.^{89–91}

Biological treatment discontinuation and cycling in elderly patients

ECCO Current Practice Position 13:

The indications and use of biological therapy in elderly patients with Crohn's disease do not differ from younger patients. Discontinuation and cycling should be carefully assessed individually, considering potential comorbidities, frailty and adverse events

In general, data on biological treatment discontinuation and cycling in elderly populations are limited. This is probably influenced by the underuse of biological therapies among older patients, as demonstrated by several studies including the EPIMAD cohort from France.⁹² Moreover, elderly patients are underrepresented in RCTs, and therefore data have been mainly derived from retrospective observational studies.

Some observational studies have shown that biological treatment discontinuation in elderly patients is more frequent than in younger patients.^{93–95} More recently, in a retrospective study including more than 9000 IBD patients, among whom 479 were older than 65 years, the authors observed that age >65 years was predictive of a higher likelihood for treatment discontinuation. When comparing the risk of stopping the treatment among the different biologics [including infliximab, adalimumab, golimumab, certolizumab and vedolizumab], both certolizumab and infliximab were most associated with treatment discontinuation.⁹⁶

The main reasons to stop biological treatment reported in these cohorts included lack of response and adverse events.^{93–95,97} There are indeed several studies showing a higher risk of adverse events [mainly infections] with anti-TNF therapy among elderly patients as compared to younger ones.⁷⁸ Nonetheless, it is important to consider the risks of relapsing disease activity from biological treatment discontinuation, and that the acute use of corticosteroids in elderly patients is also associated with a higher risk of adverse events. Therefore, consideration should be given to treatment strategies which minimize exposure to steroid treatment for older patients.⁹⁸

In conclusion, the decision process for discontinuation and cycling of biological therapy among elderly patients should consider several factors such as comorbidities, polypharmacy, risk of adverse events and particularly disease severity.⁹⁹

Biological treatment discontinuation and cycling in paediatric patients

ECCO Current Practice Position 14:

Discontinuation and cycling of biological therapy in patients with Crohn's disease under 18 years of age is generally not recommended due to a higher risk of relapse and age-related consequences

Patients with paediatric-onset CD have a higher risk of complications such as penetrating or stricturing behaviour, as compared to adult-onset or elderly-onset disease.¹⁰⁰ Paediatric data on anti-TNF withdrawal are limited to a few small, retrospective studies but generally suggest that discontinuation of biological treatments may be associated with higher risks than adult populations. Of 11 French paediatric patients in sustained remission on standard infliximab therapy and azathioprine, eight [73%] relapsed within 1 year after infliximab withdrawal.¹⁰¹ In another study among 21 Korean children in sustained remission on combination therapy with infliximab, 15 [71%] relapsed after infliximab withdrawal after a mean follow-up period of 28 months.¹⁰² Given these high relapse rates after discontinuation of infliximab in paediatric CD, coupled with the demonstrated therapeutic benefits of infliximab in children with luminal CD,¹⁰³ infliximab discontinuation is generally not recommended in the paediatric setting. However, given safety concerns around long-term thiopurine exposure in children, thiopurine discontinuation is typically considered for those in clinical remission who are receiving a thiopurine as part of combination therapy with an anti-TNF agent.

Conclusions

With increasing focus on patient safety, patient preferences and considerations about cost, there has been a growing interest on the topic of elective biological treatment discontinuation for patients in deep remission. However, there is widespread recognition that due to the chronic nature of CD, many patients will still require re-treatment to control disease flares following discontinuation, and data thus far have been reassuring that in the majority of patients, treatment with the same biological therapy will be able to regain disease control.

This concept of using biological treatments in cycles is a potentially attractive one, for a subgroup of patients at low risk of relapse, and this treatment strategy might allow patients to have decreased drug exposure over a prolonged period of time with a lower therapeutic burden. The criteria influencing the selection of candidates for successful treatment discontinuation relate to the risk of relapse, the consequences of a potential relapse, the potential side-effects of therapy, patients' preferences and financial costs. Consideration of biological discontinuation and cycling should be individualized, as priorities may differ from patient to patient, with some prioritizing safety and having particular concerns about side-effects, and others prioritizing disease control and accepting some degree of treatment-related risk.

Of note, most of the data on biological treatment discontinuation and cycling in CD are in the context of anti-TNF medication. Due to the lack of data, and lack of any licensed small molecules in CD at the time of writing, these advanced therapies were not considered. However, with the probable arrival of licensed small molecule treatments for CD in the near future, and their distinct properties, including rapid onset, rapid offset and lack of immunogenicity, these might be even more applicable for treatment cycling strategies. Moreover, while this article has focused on CD, the concept of discontinuation and cycling of biological therapy may be equally as appropriate in the context of ulcerative colitis.

There is a need for more data to support biological treatment discontinuation and cycling in CD, especially for non-anti-TNF medications. In particular, interventional RCTs

comparing biological treatment cycling to current maintenance therapy strategies would be highly informative. However, it is clear that with the increasing willingness to consider elective treatment discontinuation by some patients, as well as potential cost/reimbursement pressures, this topic of biological treatment discontinuation and cycling is an important area for research focus and might be considered as a future novel treatment strategy for the management of some patients with CD.

Working groups

Working group 1: Frequency of relapse following treatment discontinuation

Leader—Fernando Gomollon, Spain. Member—Peter Bossuyt, Belgium. Member—Maria Jose Casanova, Spain. Member—Javier Gisbert, Spain. Member—Konstantinos Papamichael, USA. Member—Paula Sousa, Portugal.

Working group 2: Predictors of outcome following treatment discontinuation and selection for biological cycling

Leader—Dominik Bettenworth, Germany. Member—Maria Chaparro, Spain. Member—Federica Furfaro, Italy. Member—Nik Ding, Australia. Member—Gabriele Dragoni, Italy.

Working group 3: Safety of biological cycling, patient preferences and pharmacoeconomic aspects of biological cycling

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Reviewers on behalf of ECCO

We would like to thank and acknowledge the following individuals for critical reading and helpful suggestions regarding the manuscript. Ailsa Hart, Alessandro Armuzzi, Britta Siegmund, Laurent Peyrin-Biroulet [ECCO Governing Board], Hannah Gordon, Michel Adamina [ECCO GuiCom] and Henit Yanai [ECCO EduCom].

Funding

This work was funded by the European Union's Horizon 2020 research and innovation programme, under grant agreement number 633168—BIOCYCLE [PHC-13-2014].

Conflict of Interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI statement is not only stored at the ECCO Office and the editorial office of JCC, but is also open to public scrutiny on the ECCO website [<https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html>], providing a comprehensive overview of potential conflicts of interest of authors.

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Author Contributions

This paper was a joint expert consensus activity. All authors participated intellectually and practically in this work and take public responsibility for the content of the article, including conception, design, data interpretation and writing/review of the manuscript. All authors and the ECCO Governing Board approved the final version for submission.

Data Availability

Not applicable.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

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