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ECCO Topical Review

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European Crohn's and Colitis Organisation Topical Review on Treatment Withdrawal ['Exit Strategies'] in Inflammatory Bowel Disease

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Abstract

Clinically effective therapies now exist for remission maintenance in both ulcerative colitis [UC] and Crohn's Disease [CD]. For each major class of IBD medications [5-aminosalicyclates, immunomodulators, and biologic agents], used alone or in combination, there is a risk of relapse following reduction or cessation of treatment. A consensus expert panel convened by the European Crohn's and Colitis Organisation [ECCO] reviewed the published literature and agreed a series of consensus practice points. The objective of the expert consensus is to provide evidence-based guidance for clinical practice so that physicians can make informed decisions in partnership with their patients. The likelihood of relapse with stopping each class of IBD medication is reviewed. Factors associated with an altered risk of relapse with withdrawal are evaluated, and strategies to monitor and allow early identification of relapse are considered. In general, patients in clinical, biochemical, and endoscopic remission are more likely to remain well when treatments are stopped. Reintroduction of the same treatment is usually, but not always, successful. The decision to stop a treatment needs to be individualized, and shared decision making with the patient should take place.

Key Words: Crohn's disease; ulcerative colitis; inflammatory bowel disease; discontinuation; therapy

1. Introduction

Whereas there is an emerging consensus on the optimal approach to initiation of a range of therapies in inflammatory bowel disease [IBD], there remains greater uncertainty about the risks, benefits, and timing of stopping treatment when patients are in stable remission on therapy. It is therefore timely to review the current evidence about the risks of disease relapse [balanced against the risks and costs of continued treatment] associated with withdrawal of the agents commonly used for remission maintenance in both ulcerative colitis [UC] and Crohn's disease [CD]. The risk/benefit ratio of stopping differs depending on whether patients are receiving either 5-aminosalicylates [5ASA], immunomodulators [IM] or biologic therapies such as tumour necrosis factor inhibitors [TNFi] either alone or in combination. Patients often wish to stop or reduce treatment if there are not undue risks. The challenge involved in getting an individual patient back into remission and the likelihood of successful re-treatment with the same or other drugs are key considerations. Treatment costs associated with indefinite maintenance therapy are also considerable, and some toxicity of treatment may be related to the cumulative duration of exposure to treatment. This is particularly important given that sustained treatment with certain drugs such as thiopurines has been associated with a convincing increase in the risk of cancers such as lymphoma, non-melanoma skin cancer, myeloproliferative disorders, and urothelial cancers.[1–4] The objective of the expert consensus is therefore to provide evidence-based guidance for clinical practice so that physicians can make informed decisions, in partnership with their patients, about the optimal exit strategy from treatment.

2. Methods

The European Crohn's and Colitis Organisation [ECCO] set up a topical review consensus group on the issue of treatment withdrawal ['exit strategies']. ECCO topical reviews result from expert opinion consensus and are endorsed by ECCO. As controlled data are lacking, a topical review is distinct from the ECCO consensus guidelines and is intended to provide guidance in clinical areas where scientific evidence is lacking. An open call was announced to all ECCO members, following which 15 individuals were selected based on their expertise in the topic, and three subgroups were formed.

Working Group 1 focused on withdrawal of 5-aminosalicyclates [5ASA; mesalazine, olsalazine, balsalazide, and sulphasalazine] with their major focus therefore on UC. Topics examined included: optimal duration of 5ASA treatment; timing/strategy for dose reduction; risks, benefits and timing of stopping treatment; success of re-treatment; factors associated with high risk of relapse on stopping; and optimal monitoring following withdrawal. Risks of 5ASA withdrawal in CD were also discussed.

Working Group 2 focused on withdrawal of immunomodulators [IM; azathioprine, mercaptopurine, and methotrexate] including: risks, benefits, and timing of stopping IM monotherapy in UC and CD; risks, benefits, and timing of stopping IM when used in combination with biologic therapies in UC and CD; the evidence for a role for IM dose reduction; factors determining risk of relapse on stopping therapy; optimal monitoring following withdrawal; and success of re-treatment.

Working Group 3 examined withdrawal of biologic therapy [primarily the approved TNF inhibitors; infliximab, adalimumab, golimumab] including: risks, benefits, and timing of stopping TNFi monotherapy in UC and CD; risks, benefits, and timing of stopping anti-TNF used in combination with IM in UC and CD; evidence for anti-TNF dose reduction or increasing dose intervals in patients in remission on treatment; factors determining risk of relapse on stopping therapy; optimal monitoring following withdrawal, and success of re-treatment. Data on outcomes after stopping other recently approved biologics, eg vedolizumab and ustekinumab, were also sought.

The working groups performed a systematic literature search of their topic with appropriate key words, using Medline/Pubmed and the Cochrane database, as well as their own files. Discussions and exchange of the published evidence among the working party members and a preliminary voting round took place, followed by a revision of the statements. The working parties met in Barcelona on 15 February 2017 to agree on the statements. Statements were accepted when 80% or more participants were in agreement, and were henceforth termed an agreed *Current Practice Position*. The group leaders and their respective working party wrote the final section for each subgroup. It is intended that the statements be read in context, with qualifying comments and not in isolation. The final text was edited for consistency of style by the steering committee and two members of the Guidelines Committee of ECCO who were not involved in the consensus. In several areas, the level of evidence is low, which reflects the paucity of randomised controlled trials. Consequently, where appropriate, expert opinion is included.

Section 1—General Considerations

Current Practice Position 1.1

Before withdrawal or reduction of any maintenance IBD therapy is considered, an appropriate re-evaluation of disease activity using a combination of clinical, biochemical, endoscopic/histological, and/or radiological techniques should be performed to inform the evaluation of risks and benefits of stopping. Disease history, severity, and extent are important factors to be taken into account

Current Practice Position 1.2

Decisions on treatment withdrawal should be informed by patient preference

Current Practice Position 1.3

Optimal monitoring following withdrawal of maintenance treatment has not been defined; however, monitoring of symptoms, inflammatory markers such as C-reactive protein/faecal calprotectin, and/or endoscopy/imaging for reassessment seem reasonable

There is good evidence that patients with subclinical disease activity are at much higher risk of relapse when any treatment is reduced or withdrawn. The specific evidence is reviewed relative to each class of medication, but it is agreed that re-evaluation of disease activity using techniques appropriate to the patient should be undertaken to ensure that counselling can be informed by a realistic estimation of the risks of relapse. A given risk of relapse over time may be acceptable to one patient but not to another; therefore the preference of the specific patient is important in formulating an exit strategy from treatment.

After withdrawal of any therapy, patients require regular follow-up because recurrence of disease is common. Optimum surveillance in

terms of timing of clinical, biochemical, and endoscopic follow-up has not been defined in prospective studies. It is acknowledged that disease may recur in the absence of clinical symptoms, so symptom-based monitoring alone is considered insufficient. A significant proportion of patients consider mild symptoms of relapse to be normal and even health care professionals often underestimate symptoms indicating a relapse.[5] Even mild symptoms are associated with a reduced quality of life in IBD;[6,7] and, as these symptoms may sometimes be associated with severe intestinal lesions putting the patient at risk of complications, a close follow-up of disease activity after withdrawing or reducing treatment is key to identifying disease flares at any early stage when they may be more likely to respond to therapeutic intervention.

Complete mucosal[8–13] and, mainly in ulcerative colitis, histological healing[14,15] are presently the best prognostic markers for risk of relapse in subsequent years. However, repeated colonoscopy with biopsies is not acceptable to patients and carries procedure-related risks and substantial costs. Biomarkers can therefore assist in identifying patients at risk of symptomatic relapse; these include C-reactive protein [CRP] and faecal biomarkers.[16–18] Studies have confirmed a significant association between CRP levels and the risk of relapse in patients with CD or UC.[19–25] More data are available on the prognostic significance of faecal biomarkers such as calprotectin, lactoferrin, or faecal haemoglobin to predict relapse.[26–31] Faecal calprotectin [FCP] concentration has been repeatedly validated as an indicator of endoscopic evidence of mucosal inflammation in UC and CD.[32–34] Increased FCP is consistently able to predict the risk of a future flare, especially within the following 2–3 months.[35,36] Although there is no clear consensus on how often FCP should be determined, intervals of 3 months after withdrawal seem reasonable in clinical practice.[37] However, it is still a matter of debate if a rise in FCP levels during follow-up by itself provides sufficient reason for intensifying therapy or introducing new treatment. In this context, Lasson *et al.* evaluated whether pharmacological intervention guided by FCP prolongs remission in patients with UC.[38] Although this approach did not result in an overall reduction of relapse, patients who were subject to the active intervention had fewer disease relapses as compared with patients in the control group, despite comparable FCP levels. These results offer some evidence that measuring FCP levels alone may be used to guide 5-ASA dosing and withdrawal.

Section 2—Withdrawal of 5-ASA

Benefits of long-term 5-ASA treatment

Current Practice Position 2.1

5-ASA maintenance therapy is generally safe and reduces the probability of relapse and the risk of colorectal cancer

The efficacy of 5-aminosalicylic acid [5-ASA] in maintenance of UC remission is well established. A recent Cochrane meta-analysis confirmed that 5-ASA is superior to placebo for maintenance therapy in ulcerative colitis.[39] The updated ECCO guidelines on UC treatment state that mesalazine compounds are the first-line maintenance treatment in patients responding to mesalazine or steroids [oral or rectal].[40]

The Toronto consensus guidelines recommend, in patients with oral 5-ASA induced complete remission of mild to moderate active UC of any extent, continuing oral therapy of at least 2 g/day to maintain complete remission.[41] Recent meta-analyses show that both oral and topical 5-ASA drugs are not associated with any greater number of adverse events than placebo. Adverse effects were commonly mild, including flatulence, abdominal pain, nausea, diarrhoea, and headache.[42,43] Rare serious adverse effects of 5-ASA, such as nephrotoxicity, are described.[44]

Case-control studies have shown that regular, long-term use of 5-ASA significantly reduces the risk of colorectal cancer by up to 75% in UC patients.[45,46] A 10-year cohort study demonstrated that 31% of UC patients who stopped or did not comply with 5-ASA therapy, developed colorectal cancer compared with only 3% who continued long-term treatment.[47] Furthermore, several systematic reviews and meta-analyses of observational studies confirm the protective role of 5-ASA use against development of colorectal cancer and dysplasia.[48–50]

Given the excellent safety profile of 5-ASA, the risks of stopping treatment therefore generally exceed the benefits in most UC patients.

Optimal duration of treatment

Current Practice Position 2.2

In general, 5-ASA treatment should not be discontinued in patients with UC even during remission

The optimal duration of 5-ASA therapy is unclear. In most trials of maintenance therapy with 5-ASA, the endpoint is the absence of relapse or failure to maintain clinical remission after 6 to 12 months. Only a small number of retrospective studies have assessed the benefit of maintenance with sulphasalazine [SSZ] or 5-ASA in the longer term. In 1973, a study reported that maintenance treatment with SSZ 2 g/day continued to have a major effect at reducing relapse, even in patients treated for more than 3 years.[51] However, another study reported no benefit of maintaining SSZ for patients symptom-free on treatment for more than a year.[52] In a double-blind randomised controlled trial [RCT], 112 UC patients in remission for > 1year on 5-ASA or SSZ were randomised to oral mesalazine 1.2 g/day or placebo [treatment withdrawal] for 12 months.[53] In patients with disease remission for 1-2 years, mesalazine appeared significantly more effective than placebo for preventing relapse at 12 months [mesalazine 23% and placebo 49%, $p = 0.035$]. For patients in remission for more than 2 years [51 patients], there was no difference in relapse rates [18% vs 26%, respectively].

Considering the benefits in terms of disease control and the prevention of colonic cancer, the general recommendation is therefore to continue 5-ASA treatments in the long term, even in patients in clinical and endoscopic remission. However, the recent update to the UC guidelines recognizes that intermittent therapy is acceptable in some patients with proctitis.[40] The panel also considered that a discussion about stopping treatment might also be considered in some selected UC patients with: 1] limited disease extent [eg proctosigmoiditis]; 2] remission for several years; 3] history of a first or single disease flare only; and 4] not having required systemic corticosteroid therapy [recognizing that a primary goal of maintenance therapy is to avoid corticosteroid use].

Timing/strategy for dose reduction

Current Practice Position 2.3

In UC patients with high adherence to the drug, mild clinical course of the disease, low faecal calprotectin levels, and/or complete mucosal healing, 5-ASA maintenance dose reduction can be considered

The ideal dosing of oral 5-ASA maintenance therapy has not been clearly defined. The ECCO UC guidelines suggest that the effective dose of oral 5-ASA to maintain remission is 2 g/day, and that for rectal treatment 3 g/week in divided doses may be adequate.[40] Higher doses [greater than 2–2.4 g/daily] are probably required for patients with low drug adherence, extensive colitis, and/or frequently relapsing disease.[42,54] Although safe, higher doses can lead to poor adherence and certainly increase medical costs.[42,55]

Data obtained from the Veterans Health system from 2001–2011, regarding 4452 UC patients with a median follow-up of 6 years, showed no difference in the long-term flare risk between low [2.4–2.8 g/day] vs high [4.4–4.8 g/day] doses of mesalazine, provided moderate to high levels of treatment adherence. However, among patients with low adherence, there was a significant reduction in the risk of flares with high dose maintenance (hazard ratio [HR] = 0.28, $p = 0.003$).[56] In an Italian study, although no difference was found in relapse rates at 1 year on mesalazine 1.2 g compared with 2.4 g/day, patients with extensive UC in the 2.4 g group remained in remission for a longer time than those in the 1.2 g group [143 vs 47 days, $p < 0.005$]. When the results for patients in remission at 12 months were analysed after stratifying for frequently relapsing disease [> 3 relapses/year] vs less frequent relapses, 2.4 g/day also performed significantly better than 1.2 g/day [75% vs 33%, respectively].[57] A recent RCT of 112 UC patients in remission showed that in patients younger than 40 years and/or with extensive disease, mesalazine 4.8 g resulted in an increased rate/duration of remission at 1 year compared with 2.4 g.[58]

One further recent study, including 203 UC patients in remission, showed that 5-ASA dose reduction is more successful if a Mayo endoscopic subscore [MES] of 0 is achieved.[59] The remission maintenance rate was higher with an MES of 0 compared with 1 [$p = 0.007$].[59] Two recent RCTs, regarding 119 and 91 patients with quiescent UC, showed that FCP of > 200 and > 300 µg/g, respectively, can identify patients with a higher risk for a flare.[38,60] Persistent histological activity also appears to predict risk of relapse in UC patients in clinical remission on treatment.[61] Reduction to a maintenance oral 5-ASA dose of 2–2.4 g/daily or below, in the presence of a raised FCP or persistent endoscopic and/or histological inflammation, was therefore considered by the panel to be best avoided.

Factors associated with high risk of UC relapse on stopping 5-ASA

Current Practice Position 2.4

There is heterogeneity in the risk of relapse after the discontinuation of 5-ASA maintenance in patients with UC. The risk of relapse with stopping 5-ASA maintenance is increased in patients with extensive colitis and history of frequent disease relapses

It is critical to establish predictors of the relapse risk after discontinuation of 5-ASA for individual patients. As already outlined, few studies specifically examine 5-ASA withdrawal. Relapse rates are higher in patients with left-sided or extensive colitis at diagnosis (hazard ratio = 1.46; 95% confidence interval [CI] = 1.01–2.10; $p = 0.04$) and initial haemoglobin level < 10.5 g/dL [hazard ratio = 0.43; 95% CI = 0.22–0.81; $p = 0.01$].[62] The effect of disease extent was not seen as clearly in other studies, though again patients with distal colitis had a slightly better course.[63] As patients with extensive ulcerative colitis or with frequent relapses may benefit from a higher dose of maintenance therapy,[64] withdrawal of 5-ASA when used as monotherapy should be avoided in this subgroup. A proportion of these patients will, however, require treatment escalation of maintenance treatment to either immunomodulator and/or anti-TNF therapy, and it is unclear whether continued 5-ASA in such patients adds much incremental therapeutic benefit. However, there may be additive benefits especially in terms of chemoprevention.

Success of re-treatment with 5-ASA

Current Practice Position 2.5

In patients having stopped 5-ASA during a first successful course of oral corticosteroids for an acute flare, resuming 5-ASA after the control of the flare may be effective

Most UC patients receive 5-ASAs in order to induce and maintain remission.[65] There are no published data on the efficacy of resuming 5-ASA for a flare after stopping the drug while in remission. However, a large proportion of patients will experience a flare despite 5-ASA requiring treatment with oral glucocorticocoids [GCS], thus warranting a decision about how to proceed in terms of maintenance treatment once remission has been achieved. In an observational study of 143 mild-to-moderate UC patients naïve to immunosuppressive therapy, treated for the first time with oral corticosteroids, 52 [36%] patients achieved clinical remission after weaning from the GCS. Of these, 35 were restarted on 5-ASA [minimum dose 2.4 g/day] as maintenance therapy[66] ;22 patients [63% of those who recommenced 5-ASA] remained in remission on 5-ASA after 1 year but only 7 [20%] at 10 years' follow-up These data suggest that in this setting, 5-ASA is insufficient for long-term maintenance in most patients. Only male gender and short duration of disease could be identified as predictive factors of the time-to-relapse in this group of patients. Similar findings were reported in a letter describing 13 patients with moderate to severe UC, who were restarted on 5-ASA 4.8 g/day once GCS had been tapered to 20 mg and they were in clinical remission. Nine [69%] patients remained in remission for a median of 20 weeks after steroids were discontinued.[67]

Risks of 5-ASA withdrawal in Crohn's disease

The scientific evidence regarding the efficacy of 5-ASA in CD patients is in sharp contrast to clinical practice. Several systematic reviews have concluded that the role of 5-ASA in CD, to either induce remission or prevent relapses, is no better than placebo or, at best, remains uncertain.[68–70] Accordingly, international guidelines do not recommend the use of 5-ASA in CD.[71] However, in population-based cohorts more than 50% of CD patients at some point in their disease course receive 5-ASA for long periods. The consequence of withdrawal of 5-ASA in CD patients remains unclear and, in two cohorts, some kind of 5ASA-dependence was described.[72,73]

Section 3–Withdrawal of Immunomodulators [Azathioprine, Mercaptopurine or Methotrexate]

Withdrawal of IM when used as monotherapy

Current Practice Position 3.1

There is a cumulative risk of relapse with time after withdrawal of IM monotherapy in both CD and UC, and it is estimated that approximately 30% of patients relapse by 2 years and 50–75% relapse by 5 years

Current Practice Position 3.2

It is reasonable to re-consider, in conjunction with the patient, the risks and benefits of continued IM monotherapy for IBD patients treated for 3–4 years if there is no evidence of continuing disease activity

Current Practice Position 3.3

Factors predictive of relapse following withdrawal of IM monotherapy include elevated markers of subclinical disease activity [in both CD and UC] and disease extent/localization [peri-anal disease in CD, extensive disease in UC]

ECCO guidelines support the use of thiopurine immunomodulators (azathioprine [AZA] and mercaptopurine [MP]) as effective maintenance therapy for both CD and UC.[40,71] In addition, the guidelines recognize that methotrexate [MTX], used as an immunomodulator, is effective for remission maintenance in CD.[71] The CESAME cohort study has, however, highlighted the risks associated with long-term use of thiopurine IM in IBD patients, including elevated risk of lymphoproliferative disorders, non-melanoma skin cancers, myeloid disorders, and urinary tract cancers.[1–4] Therefore periodic re-evaluation of the risk/benefit ratio of continued treatment with these agents seems important. Whereas some studies have shown a reduction in the risk of colorectal neoplasia in UC patients treated with thiopurines,[74] no convincing reduction in colorectal cancer with thiopurine IM use was oberved in a recent meta-analysis.[75] Therefore the only trade-off for the long-term risks of treatment may be a sustained reduction in the risk of disease relapse.

Early studies suggested a low risk of relapse following azathioprine withdrawal in CD, and therefore a traditional practice has evolved of considering stopping if a patient remains in remission for 3–4 years.[76] Subsequent studies have not provided strong evidence for this 3–4 year 'cut-off'. Based on extrapolation from transplant data, it seems likely that the risks of neoplasia with thiopurine treatment are related to duration of exposure and only begin to accumulate significantly after several years of therapy.

In CD, an initial multicentre double-blind study of AZA-treated patients, in clinical remission for at least 3.5 years, observed that 3/40 patients who continued treatment relapsed by 18 months compared with 9/43 patients who stopped [based on the non-inferiority design, the authors failed to reject the hypothesis that placebo was inferior to AZA continuation].[77] At 1,3, and 5 years after withdrawal, cumulative risk of relapse was 14%, 53%, and 63%, respectively. Three subsequent RCTs also show higher relapse rates in the drug withdrawal arm, from 8% to 25% at 6 months, 17% to 53% at 12 months, 21% to 31% at 18 months, and 31% at 24 months.[78–80] In a subsequent meta-analysis of studies in CD, thiopurine IM continuation decreased the risk of relapse at 6, 12, and 18 months with pooled odds ratios of 0.22, 0.25, and 0.35, respectively, and a pooled odds ratio of 0.53 at 5 years [based on data from two studies].[81] No prospective studies of MTX withdrawal in CD have been reported,but retrospective studies report a high risk of relapse [approximately 80% at 12 months] in patients stopping therapy.[82] There is significant heterogeneity between studies regarding the duration and definition of remission preceding IM withdrawal. It is therefore likely that if only patients with sustained true biological remission [i.e symptomatic, biochemical, and endoscopic/radiological remission] were studied, the risk of relapse would be lower.

There are fewer studies of stopping IM monotherapy in UC. Only one multicentre double-blind RCT of withdrawal of AZA in UC patients has been reported. For UC patients in short-term remission with AZA, 1-year relapse rates of 59% were observed with AZA withdrawal and 36% with continued therapy [p = 0.039].[83] In a multicentre retrospective study, after AZA withdrawal one-third of UC patients relapsed within 12 months, half within 2 years, and two-thirds within 5 years.[84] Cohort studies reported discrepant relapse rates after IM withdrawal: from 11% to 77% at 12 months, 21% to 100% at 24 months, 43% to 65% at 5 years, and up to 87% with longer follow-up periods.[85,86]

A recent systematic review has summarised the predictive factors for relapse in both CD and UC after thiopurine IM withdrawal.[87] These are summarised in Table 1. Age may be a key consideration in assessing the risk/benefit trade-off when considering stopping IM therapy. The recently published BERENICE study modelled mortality risk in CD patients according to IM use, age, and disease extent.[88] The model favoured sustained IM treatment in CD patients with extensive colitis, irrespective of age [estimated life-years gained 0.19; 95% CI = 0.06-0.24]. However, in patients without extensive colitis, the mortality model favoured stopping IM treatment in men > 40 years and women > 45 years. It is notable that the vast majority of deaths in CD patients [> 96%] are unrelated to disease or treatment.

Table 1. Factors associated with higher relapse rates in CD [left column] and UC [right column] following withdrawal of thiopurine IM monotherapy. Based on Torres *et al.* 2015.[87]

Factors associated with higher CD relapse risk	Factors associated with higher UC relapse risk
Elevated C-reactive protein level[23,77,89]	**Increased leukocyte count**[23,91]
Increased leukocyte or neutrophil count[23,89]	
Low haemoglobin level[77,89]	
High-risk disease [peri-anal involvement]	Extensive disease [pancolonic/extensive][84]
Younger age[76]	Younger age[83]
Male gender[76]	Male gender[84]
Short duration of remission[76]	**Number of relapses on azathioprine**[84,91]
Shorter time since latest steroids[77]	**Shorter duration of azathioprine**[84,91]
Higher dose of azathioprine[79]	Longer time from diagnosis to azathioprine[91]
Thiopurine tapering before de-escalation[23]	
Smoking cessation[90]	

Bold type identifies factors observed consistently.

Stopping IM when used as a part of combination therapy

Current Practice Position 3.4

The rate of relapse [in the subsequent 2 years] following IM withdrawal in CD patients treated with combination therapy for > 6 months is probably not greater than with continued combination therapy. Relapse rates may be higher in UC, but data are limited

Current Practice Position 3.5

Higher infliximab trough levels at withdrawal are associated with lower rates of relapse following IM discontinuation

Current Practice Position 3.6

IM withdrawal in patients treated in combination with anti-TNF therapy may be inappropriate in patients with high-risk/refractory disease or in patients 'at risk' of biologic failure

RCT have shown that combination therapy with infliximab [IFX] and concomitant azathioprine [AZA] results in significantly higher rates of clinical remission and mucosal healing as compared with monotherapy in both CD and UC.[92,93] However, as already outlined, an increased infection and malignancy risk has been demonstrated in IBD patients receiving immunomodulators [IM]. The risk of neoplasia related to anti-TNF therapy remains more uncertain, and is being addressed by large prospective observational studies such as I-CARE. Therefore, there is interest in de-escalation of combination therapy once remission is achieved and, given the relative efficacy and safety of the two agents, stopping IM treatment is often the favoured approach.

In two randomised trials, the proportion of CD patients in clinical remission who experienced a relapse was similar in those stopping IM compared with those continuing combination therapy with anti-TNF.[94,95] Retrospective cohort studies in CD have shown similar findings.[96,97] Only one study has reported outcomes in UC. This retrospective analysis on IM withdrawal from combination therapy with IFX found a significantly higher rate of UC relapse in the discontinuation cohort [12% vs 3% trimesters with clinical flare, $p = 0.049$]. The mean time to relapse after IM withdrawal was 7 months [compared with 17 months in patient who continued combination therapy].[98]

Considering that the average duration of combination therapy in these studies was 1–2 years, it therefore appears that in CD patients receiving combination therapy with IFX, continuation of IM beyond this time frame probably offers no additional benefit over scheduled IFX monotherapy. However in some trials, continued combined therapy was associated with higher median IFX trough and decreased CRP levels. Thus it is reasonable to combine IM and biologics for at least 1 year, until sustained clinical and endoscopic remission is reached, with the decision on IM discontinuation also guided by the trough level of biologic at this time. In high-risk patients with extensive/complicated disease, where a disease relapse could have important clinical consequences [eg risk of extensive resection, permanent ostomy, or short small bowel syndrome], it is reasonable to decide to continue combination therapy indefinitely, balancing the risk for disease progression and the potential side effects of long-term combination therapy on an individual basis.

IM dose reduction vs withdrawal

A single small randomised study on azathioprine dose reduction [compared with continuation at full dose or withdrawal in IBD patients in remission on combination treatment for 1 year] has reported that the positive impact of IM on infliximab drug levels can be sustained with a 50% dose reduction. No increase in the risk of relapse with dose reduction was observed, but the study may have been underpowered to detect a difference in clinical outcomes.[99] The potential risks and benefits of IM dose reduction in place of stopping require further evaluation.

Factors predictive of relapse following IM withdrawal

Factors predictive of relapse should be considered before stopping IM, and these are similar to those outlined in Table 1. Shorter duration of combination therapy before withdrawal and lower trough biologic levels at the time of withdrawal may be additional specific factors to consider in this particular context. Certain patients tend to make neutralising antibodies to therapeutic monoclonal antibodies, and patients who are known to have anti-drug antibodies consistently to their current or previous anti-TNF agents may be at increased risk of treatment failure following IM withdrawal. Depending on the context, continued combination therapy may be a better option for this group of patients.

Success of re-treatment, concept of drug holidays

Current Practice Position 3.7

Studies on re-treatment with IM following relapse generally report good rates of clinical response and remission. However, only short-term follow-up is reported, and potential long term consequences require evaluation in further studies

In one study of withdrawal of IM monotherapy in CD patients, only 1/23 patients who relapsed and were re-treated by AZA did not achieve remission. A median duration of remission of 28 months with the second course of IM was reported.[89] In a larger multicentre retrospective study, re-introduction of thiopurine was successful in 31/42 [74%] of CD patients with moderate to severe relapse,[23] a number requiring either anti-TNF therapy or surgical resection. Interestingly, both the risk of relapse and success of re-treatment were greater in UC than CD in the same study; 22/24 [92%] of UC patients re-entered remission on retreatment with IM but 50% required corticosteroids to achieve clinical remission.[23]

The concept of drug holiday has emerged in the treatment of other immune-mediated disorders where stopping therapy for a defined period is suggested to reduce the risk of infectious or other complications [eg 6-month drug holiday from natalizumab following 12–24 months of treatment in relapsing and remitting multiple sclerosis]. Spontaneous regression of IM-related neoplasia such melanoma and lymphoma following withdrawal of immunosuppressants is well described.[100] It is possible that allowing periodic immune reconstitution by stopping or reducing the intensity of immune suppression may moderate some of the risks of long-term IM therapy. However, there is no evidence currently to support the

concept of drug holidays from IM therapy in IBD. The risks and benefits should be evaluated in prospective studies.

Section 4–Withdrawal of Anti-TNF Agents

Risks, benefits, and timing of stopping anti-TNF used as monotherapy or in combination with IM in UC and CD

Current practice position 4.1

The risk of relapse after anti-TNF withdrawal is between 30–40% at 1 year, and greater than 50% beyond 2 years

Current practice position 4.2

The clinical benefits of anti-TNF withdrawal [lower infection or cancer risk] are at present theoretical, as no controlled study has been performed

The use of anti-TNF therapy is associated with several clinical benefits in IBD, such as higher mucosal healing, fewer hospitalisations and surgical procedures, and improved quality of life.[8,101–103] However, TNFi agents are expensive and cause severe side effects, such as infection[104] and possibly malignancy.[105] Although some decision analysis models have established that TNFi agents are cost-effective,[106] it is not so certain that they remain so in the long run. However, the concerns related to discontinuation of TNFi in IBD patients include the risk of relapse, the possible loss of efficacy when the drug has to be restarted, the risk of infusion reactions or other adverse events at re-treatment, and, finally, the worries over losing future—and limited—medical treatment options.[107]

The aim of a recent study was to systematically review and perform a meta-analysis of the risk of relapse after discontinuation of TNFi in IBD patients.[108] In total, 27 studies [21 infliximab, 6 infliximab/adalimumab] were included.[108] The overall risk of relapse after discontinuation of anti-TNF therapy was 44% for CD [95% CI = 36–51%; I^2 = 79%; 912 patients] and 38% for UC [23–52%; I^2 = 82%; 266 patients]. In CD, the relapse rate was 38% at 6 months after discontinuation [short term], 40% at 12 months [medium term], and 49% at > 25 months [long term]. In UC, 28% of patients relapsed at 12 months [and 36% at medium term, eg 12–24 months after the discontinuation of anti-TNF therapy].

Although the overall relapse rate after discontinuation was somewhat higher in CD than UC patients [44% vs 38%], some of the UC studies included had shorter follow-up.[108] Some studies, which included both CD and UC patients, found a non-significant trend for longer persistence of remission after IFX discontinuation in patients with UC.[107] However, consequences of the relapse may be more serious in UC: the colectomy rate after stopping anti-TNF in remission was around 10% within 1 year after TNFi withdrawal.[109] Obviously, these differences should be confirmed in adequately controlled studies.

Experience with a longer follow-up period [> 1 year] is very limited. The risk of relapse ≥ 25 months after discontinuing anti-TNF agents in the present meta-analysis was approximately 50%. Some studies followed up the patients for up to 10 years.[107,110–112] The relapse rate beyond 5 years reached 70%.[111,112] Therefore, if followed for long enough, most patients in whom anti-TNF therapy has been stopped will eventually relapse. On the other hand, a minority of patients may achieve 'indefinite' remission without treatment.

In summary, there remains a lack of high quality studies in this area. We need more studies, ideally randomised controlled trials, to compare the TNFi discontinuation strategy with a control group where the TNFi is maintained, and where the natural disease course with standard TNFi treatment [including the well-known loss of response to these drugs] is ascertained.

Factors determining risk of relapse on stopping therapy

Current practice position 4.3

Patients in deep [clinical, biological, and endoscopic] remission probably have a lower risk of relapse after anti-TNF discontinuation. Therefore, anti-TNF withdrawal should probably be considered only in patients in long-standing stable clinical, biological, and endoscopic remission

Current practice position 4.4

Patients with previous need for anti-TNF dose escalation seem to be at high risk of relapse after discontinuation

Current practice position 4.5

Maintenance of immunomodulator treatment after anti-TNF discontinuation seems to reduce the risk of relapse

A recent review systematically evaluated the factors associated with the risk of relapse after TNFi discontinuation in IBD patients, in order to help the clinician to decide whether and when these drugs can be stopped.[113] These are summarised in Table 2.

Mucosal healing is often perceived as a key element and deserves specific comments. Several authors have demonstrated that mucosal healing in CD is associated with lower rates of abdominal surgery and hospitalisation[102] and with longer relapse-free survival during ongoing TNFi therapy.[8,101] Accordingly, several of the studies[109–111,116,127] included in a previous meta-analysis showed that, when anti-TNF treatment was stopped based exclusively on achievement of clinical remission [without taking into account endoscopic remission], 42% of CD patients relapsed during the following year.[108] However, if patients discontinued TNFi agents after achieving not only clinical but also endoscopic remission, the relapse rate at 1 year decreased to 26%. Similar differences were observed for UC patients: relapse rates were 50% and 33% after discontinuation of therapy based exclusively on clinical remission and on endoscopic remission, respectively. It should be noted, however, that not all studies demonstrate a correlation between mucosal healing at discontinuation and the frequency of or time to clinical relapse, in either CD or UC patients.[128–131,133]

When considered in isolation, none of the risk factors outlined in Table 2 is able to accurately predict the probability of relapse after discontinuation of TNFi therapy. Patients with a high [or low] risk of relapse could perhaps be best identified using a combination of clinical, biological, and endoscopic markers. The multivariable analysis in the STORI trial revealed several risk factors for relapse: male sex, absence of surgical resection, high leukocyte count, low haemoglobin level, high CRP, elevated FCP, high IFX trough levels, and no mucosal healing.[116] Two different relapse-predicting models have been developed with the STORI trial data: those models could identify a subgroup of patients with a low [15%] risk of relapse within 1 year. The results suggest that simple parameters may be used to identify a subgroup of patients with a low risk of relapse, in whom withdrawal of TNFi treatment can be considered. These

Table 2. Factors associated with altered risk of CD relapse following anti-TNF withdrawal

Demographics	Age [at diagnosis]	Conflicting reports[114,115]
	Gender	Conflicting reports, possible increase in males[116]
	Smoking	Increased risk of relapse in active smokers[117]
Clinical factors	Disease duration	Uncertain
	Disease location	Higher risk for ileocolonic than isolated ileal disease[118] Higher risk if associated fistulising peri-anal disease[117]
	Previous surgery	Conflicting reports[116,119]
	Complicated disease	Possible increased risk if previous stricture/fistula[114]
	Previous dose escalation	Increased risk if required previous dose optimisation[120]
	Concomitant IM	Absence of IM—increased relapse risk[117,121]
	Mucosal healing	Reduced risk of relapse in most studies[115,116]
Laboratory markers	Haemoglobin	Hb < 14.5 g/dL may increase the risk[116]
	Leukocyte counts	White cell count > 6 x 10^9/L may increase the risk[116]
	C-reactive protein	Raised CRP on withdrawal—increased relapse risk[116]
	Faecal calprotectin	Elevated FCP—increased relapse risk[114,116]
	Infliximab levels	Adequate IFX trough associated with increased risk[116,122]
Immune factors	Mucosal cytokines	Elevated TNF/IL17-A—increased relapse risk in CD[123]
Microbial factor	Firmicutes	Decreased counts may confer increased risk[124]
	F. Prausnitzii	Decreased counts may confer increased risk[124]
Genetic markers	NOD2/CARD 15	Not predictive[125]
	FCGR3A/CD16a	Increased risk for V/V homozygotes[126]

parameters and models still need to be validated, and their useability in a 'real-world' setting remains to be established.[133]

Lack of concomitant IM medication [eg thiopurines and methotrexate] after stopping TNFi was associated with a higher rate of relapse in some studies.[108] Although previous failure of IM was associated with a lower beneficial effect,[117] the protective effect of IM drugs has been confirmed, even if they were previously ineffective for controlling IBD. A recent and very large study, including more than 1000 patients,[121] showed that the lack of IM maintenance treatment after TNFi was stopped was a predictive factor for relapse after discontinuation of anti-TNF therapy. However, other studies could not confirm this beneficial effect of co-treatment with immunosuppressive drugs for the prevention of relapse after discontinuation of TNFi.[134]

Evidence for anti-TNF dose reduction or increasing dose intervals in patients in remission

Current practice position 4.6

Anti-TNF dose de-escalation seems to have little impact on disease remission provided the trough level of the drug remains within an appropriate target window

Current practice position 4.7

A state of deep remission [clinical, biological, and endoscopic remission] probably decreases the risk of relapse after dose de-escalation

Current practice position 4.8

In patients having needed a previous dose escalation due to loss of response, subsequent dose de-escalation is associated with a high rate of relapse

Optimal dosing of biologics is especially important because of the risk of treatment immunogenicity, adverse effects, and low cost-effectiveness due to high cost. There are a few studies investigating the impact of TNFi reduction [by dose reduction or increasing dose intervals] on maintenance of disease remission.

In the landmark TAXIT trial, patients in clinical remission with IFX trough levels [TLs] > 7 µg /mL had dose de-escalation to a target trough concentration [TC] of 3–7 µg/mL. De-escalation was by reducing dose to 5 mg/kg [if previously on 10 mg/kg] or increasing the interval between IFX infusions by 2 weeks [to a maximum interval of 12 weeks]. Of 72 patients with TLs > 7 µg/ml, 93% achieved the target range after dose reduction. This resulted in a 28% reduction in drug cost [$p < 0.001$] without change in the proportion of patients in remission or in CRP concentration.[135] Another pilot trial indicates that CD patients in deep remission may increase the dose interval of IFX to 10 weeks without risking loss of response, provided that levels of FCP are maintained in the normal range.[136]

In another prospective study of 20 adult IBD patients who achieved deep remission after treatment with IFX at 10 mg/kg every 8 weeks for secondary loss of response, IFX dose was decreased by 1 mg/kg at each infusion to a dose of 5 mg/kg, or to get a target trough concentration of 3–7 µg/mL. No significant change was observed in the mean Crohn's Disease Activity Index [CDAI] scores and FCP levels for CD, or the Mayo score for UC, before and during follow-up after the therapeutic de-escalation.[137] However, de-escalation in patients having previously required dose escalation may be more hazardous: a relatively high proportion of patients seem to relapse after such treatment de-escalation in the short term,[138–140] and only one-third of patients who relapse after de-escalation regain remission with 're-escalation'.[140] Likewise, eight of 24 patients had lost response after a median follow-up of only 7 months after 'de-intensification' of the TNFi therapy in a Spanish study.[141]

Stopping biologics in peri-anal disease and other particular situations

Current practice position 4.9

Patients with peri-anal fistulas with response to anti-TNF therapy have a higher risk of relapse on withdrawal compared with luminal CD, and anti-TNF discontinuation is not generally recommended in this population

Current practice position 4.10

In the setting of postoperative prophylaxis, anti-TNF withdrawal may be associated with higher risk of recurrence

Current practice position 4.11

Discontinuation of anti-TNF in an IBD patient in remission, during the second trimester of pregnancy, appears safe for the mother and the newborn

Current practice position 4.12

The role of anti-TNF treatment in pouchitis and the impact of its withdrawal are not yet defined

Fistulising peri-anal disease

Few studies specifically assessed the risk of relapse of fistulising peri-anal CD after discontinuation.[108] Domenech *et al*. showed that in peri-anal disease, early relapse was the rule after stopping IFX treatment, with only one-third of patients maintaining remission at 1 year.[142] A major drawback of this study was that the response to IFX was only measured in terms of the physical examination because of its retrospective design, and imaging techniques were not systematically performed.[143] It is well-known that peri-anal disease is often active despite external closure of fistulas[144]; in fact, patients with complex fistulas often need long-term treatment, and it has been suggested that response to TNFi treatment in peri-anal disease should be evaluated by imaging techniques rather than by physical examination alone.[143,145] In a similar study, 58% of patients with luminal CD remained in corticosteroid-free complete remission after discontinuation of IFX, whereas the fistulas remained closed in only 35% of patients.[146]

Postoperative prophylaxis

CD commonly recurs after intestinal resection.[147] It was recently demonstrated that administration of TNFi after intestinal resection in patients with CD effectively reduces postoperative recurrence.[148] Consequently, a clinically relevant question is whether stopping TNFi treatment after some time [eg 1 year after surgery in patients in remission] leads to recurrence. Regueiro *et al*. randomly assigned 24 patients with CD who had undergone ileocolonic resection to receive IFX or placebo for 1 year,[149] and demonstrated that IFX prevented endoscopic recurrence. At the end of the trial, 11 patients were offered open-label continuation of IFX; eight of the 11 patients elected to stop the drug and all eight patients had endoscopic recurrence at 1 year. In another study, 12 patients who started IFX immediately after surgery were still free of clinical and endoscopic recurrence of CD 3 years later.[150] However, discontinuation of IFX led to endoscopic recurrence after 4 months in 10 of 12 patients [83%]. Fortunately, remission was achieved after re-treating all 10 patients with IFX. Finally, in a recent postoperative study, nearly three-quarters of the IFX patients stopped treatment at 1 year after resection while in complete endoscopic remission.[151] All of these patients subsequently experienced endoscopic recurrence and most required additional surgery.

Pregnancy

The use of TNFi agents after the second trimester leads to fetal intra-uterine exposure.[152] To limit this exposure, it is generally recommended to discontinue the treatment around gestational Week 30 or even earlier.[153] This strategy has proven safe for the newborn.[154] However, it is unclear whether it is also safe for the mother [that is, whether it is associated with an increased risk of relapse of IBD].

The course of IBD in pregnant women who stopped taking TNFi agents was recently assessed.[155] Treatment was discontinued in patients with quiescent disease before gestational Week 30. In those taking IFX, 12 [71%] discontinued treatment, and all patients remained in remission. Since all the patients taking adalimumab were in remission, they all discontinued treatment before gestational Week 30; relapse was recorded in two patients, both of whom were receiving an escalated dose of TNFi. All patients who resumed treatment remained in remission during follow-up. In a further recent study, the same authors evaluated the maternal safety of discontinuing TNFi in the second trimester by comparing relapse between women who stopped and who continued TNFi.[156] Patients in remission around gestational Week 20 stopped TNFi therapy before Week 25 [study group, 32 patients]. Those not in remission around Week 20 continued TNFi until at least Week 30 [control group, 22 patients]. In the study group, two patients relapsed at Weeks 30 and 36, respectively, after stopping TNFi therapy in Week 22, whereas in the control group one patient relapsed. The differences were not statistically significant. There were no differences in birthweight, gestation period, congenital abnormalities, or APGAR score between the study group and the control group. Therefore, discontinuation of anti-TNF treatment in the second trimester of pregnancy in IBD women in sustained remission seems safe for the mother in terms of disease control and risks related to resumption of treatment.

Pouchitis

In recent years, TNFi therapy administered for the medical management of chronic refractory pouchitis has yielded encouraging results.[157] However, data regarding optimal duration of administration are lacking.[158] The only study to report on the long-term outcome of patients with chronic refractory pouchitis after discontinuation of successful TNFi therapy indicates that IFX could be discontinued in those who maintain complete clinical response after 1 year of therapy.[159] These results need to be confirmed in future studies.

Optimal monitoring following withdrawal of biologic therapy

Current practice position 4.13

Due to high risk of relapse, patients stopping anti-TNFs should have closer follow-up clinically and with biomarkers

Current practice position 4.14

Most relapses occur within 6–12 months after withdrawal, and a more intensive follow-up should therefore be applied during the first year

Current practice position 4.15

After anti-TNF withdrawal, an elevation of FCP [and to a lesser extent CRP] usually occurs a few months before clinical relapse

Current practice position 4.16

Strict clinical evaluation with frequent CRP and FCP measurements should be performed after anti-TNF discontinuation. Larger prospective studies are needed to determine the optimal interval for measuring FCP levels to predict relapse

Current practice position 4.17

Elevation of FCP or CRP values after anti-TNF discontinuation should trigger prompt re-testing, and if elevated tests are confirmed, the patient should be carefully re-assessed, preferably with endoscopy and/or imaging

Many of the patients in whom TNFi therapy is interrupted will, over time, experience endoscopic relapse, which in turn leads to clinical relapse.[159] A larger proportion of relapses occur within 6–12 months after withdrawal and a decreasing proportion is observed thereafter. Therefore, more intensive follow-up is probably recommended during the first year of follow-up after TNFi withdrawal.

In a STORI sub-study, the usefulness of close monitoring of CRP levels to predict relapse of CD after discontinuation of IFX was evaluated[160]: patients were monitored every 2 months until 18 months of follow-up or clinical relapse. CRP and FCP levels were found to be highly variable, regardless of the occurrence of relapse. However, a consistent rise in CRP was observed in the 4 months before relapse, and CRP values > 5 mg/L were associated with relapse in the short-term [hazard ratio = 4]. Similarly, FCP increased in the 4 months before a relapse, and FCP > 250 µg/g was associated with relapse in the short term [hazard ratio > 6].

In a more recent study, prospectively enrolled IBD patients in clinical, endoscopic, and FCP-based [< 100 µg/g] remission after more than 1 year of TNFi therapy were followed for 12 months after discontinuation.[161] During follow-up, 31% of patients relapsed; they had shown constantly elevated FCP for a median of 94 days before relapse. A significant increase in median FCP was seen 2, 4, and 6 months before endoscopic relapse. In contrast, stable, normal FCP during follow-up was highly predictive of clinical and endoscopic remission.

Larger prospective studies are needed to determine the optimal interval for measuring the markers in prediction of relapse, as well as to determine the benefit of re-starting the treatment based solely on elevated/rising FCP during follow-up.[161]

Efficacy and safety of re-treatment with the same anti-TNF after relapse

Current practice position 4.18

Resuming the same anti-TNF in patients who relapse following anti-TNF withdrawal for sustained remission is usually safe and effective

Current practice position 4.19

Immunomodulator co-treatment decreases the risk of treatment failure and infusion reactions after re-treatment with the same anti-TNF. Therefore, co-treatment with immunomodulators is recommended if tolerated

A recent meta-analysis assessed the response to retreatment with the same TNFi, following relapse after discontinuing treatment.[108] Re-treatment with the same TNFi drug induced remission in 80% of IBD patients [95% CI = 68–91%; I^2 = 86%; 290 patients].[107,109,116,128,130132,162,163] The results were similar in CD and UC. The tolerance to retreatment was also good in the STORI trial.[116] These results contrast with the notion that drug 'holidays' have historically been associated with a higher risk of immunisation resulting in hypersensitivity reactions to the drug and loss of effect.[164] A possible explanation for this finding could be the fact that in most studies, TNFi agents were initially given on a scheduled maintenance basis rather than on demand, a practice that was customary in the past.[159] Obviously, the high efficacy of re-initiation of anti-TNF drugs may reflect the fact that these patients are a selected group, previously identified as anti-TNF responders. Such a favourable outcome following re-treatment of relapsing patients, after transient discontinuation of maintenance therapy with TNFi drugs, has been suggested in studies on rheumatoid arthritis[165,166] and ankylosing spondylitis.[167] Longer-term follow-up in CD indicates that up to 6 years after resuming infliximab, only 30% of the patients experienced a secondary failure.

A key aspect could also be the concomitant IM during drug holidays, which has been associated with higher efficacy and less acute infusion reactions.[158,168] A recent study evaluated a group of patients who required re-treatment with IFX because of a clinical relapse after at least 6 months of discontinuation of the first treatment.[162] Infusion reactions were recorded in 24% of patients, of whom 17% discontinued treatment owing to severe reactions. Patients who maintained IM during the holiday between the two IFX treatments had significantly fewer re-infusion reactions. Before resuming the same TNFi treatment, anti-drug antibodies levels are usually low or undetectable, and cannot predict efficacy or safety of re-treatment. On the contrary, low trough levels and occurrence of anti-drug antibodies early after resuming the treatment are associated with a high risk of no response, loss of response, and infusion reaction.[169]

Section 5–Conclusions

The likelihood of relapse with stopping treatment varies between the different classes of IBD medication. Although indefinite treatment with 5-ASA is safe and generally recommended [in UC], there is a strong rationale for addressing the potential to stop or reduce therapy with IM and TNFi drugs, especially when used in combination. In general, patients in clinical, biochemical, and endoscopic remission are more likely to remain well when treatments are stopped, and this is probably a condition before considering an exit strategy. Factors associated with an altered risk of relapse on withdrawal are useful in selecting patients likely to relapse early when off treatment. Strategies to monitor and allow early identification of relapse are a key consideration. In general, re-introduction of the same treatment is usually, but not always, successful. However, some patients with 'high-risk' disease should be counselled against discontinuation. Ultimately, the decision to stop a treatment needs to be tailored to the individual patient and the decision to stop or reduce taken in a shared way. Based on their review of the current published literature, the contributors identify several research questions that should be the subject of future investigation, and these are summarised in Table 3. Further randomised controlled studies to compare withdrawal of treatment with standard maintenance are required. In this respect, the SPARE study [CD], the STOP IT study [CD], the BIOSTOP study [UC], and the EXIT study [UC and CD] will add greatly to the evidence.

Table 3. High priority research questions about treatment withdrawal for future study

General	What is the role of noninvasive markers such as FCP or imaging eg small bowel ultrasound in identification of 'pre-clinical' disease relapse in the asymptomatic patient
	What is the optimal monitoring strategy following withdrawal of therapy
5ASA	Is there an increased risk of relapse with stopping 5ASA in patients who have required escalation to IM and/or TNFi therapy
	Prospective study of 5-ASA discontinuation in CD which incorporates biochemical markers, e.g FCP, to identify factors which predict CD relapse
IMM	Is there a role for IM dose reduction rather than withdrawal in stable patients in remission on IM monotherapy or in combination with a biologic
	Prospective data on outcomes of MTX withdrawal in CD following remission are needed
	The risks and benefits of planned IM drug holidays to allow immune reconstitution should be explored
Biologics	Data on outcomes following vedolizumab and ustekinumab withdrawal and success of re-treatment are required
	The global benefit/risk profile of cycles of biologic treatment vs continuous treatment should be prospectively assessed
	Further controlled studies on TNFi withdrawal and/or dose de-escalation are needed

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