DE-ESCALATION OF IMMUNOMODULATOR AND BIOLOGICAL THERAPY IN INFLAMMATORY BOWEL DISEASE

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Treatment strategies for inflammatory bowel disease (IBD) focus on the induction and long-term maintenance of deep remission to avoid complications of active disease and improve long-term outcomes. Medical therapies for IBD, notably the increasingly widespread use of biological therapy, are often effective at controlling disease, but these drugs are associated with substantial adverse events, which together with other factors—including increasing treatment costs and patient preferences—leads to concerns regarding indefinite use of medical therapy. Consequently, the need to consider the safety and feasibility of drug de-escalation once IBD remission has been achieved is clear. Here, we review the current evidence surrounding de-escalation of immunomodulator and biological therapy in Crohn's disease and ulcerative colitis. We discuss strategies for de-escalation, including the selection of patients who are appropriate for treatment de-escalation and the use of proactive drug monitoring, and review the evidence on subsequent optimal follow-up. We conclude by proposing an algorithm to guide de-escalation decisions, and highlight future perspectives, including the potential effect of emerging medication and personalised medicine for these diseases.

Introduction

Therapeutic strategies for inflammatory bowel disease (IBD) have substantially changed over the past decade, with widespread acknowledgment that deep remission (defined as clinical, biochemical, and endoscopic remission) is associated with better long-term outcomes.[1] Consequently, patients are increasingly treated with biological agents, immunomodulators, or both, in early stages of disease. Two key studies support this approach: CALM[2] and REACT.[3] The CALM study showed the benefits of prompt escalation with anti-TNF therapy in patients with early Crohn's disease, with a higher proportion of those assigned to tighter disease control achieving mucosal healing and clinical remission.[2] In the REACT study, patients with Crohn's disease who received accelerated combination therapy with anti-TNF and antimetabolite drugs had a lower prevalence of major adverse outcomes, including surgery, hospital admission, and serious disease- related complications, than those receiving conventional therapy; however,

these adverse outcomes were secondary endpoints, and no difference was noted in the primary endpoint of steroid-free remission.[3]

Aggressive escalation of medical therapy early in the disease course appears to improve disease control, but once remission has been achieved both clinicians and patients face challenging questions about the timing and feasibility of treatment de-escalation. In this Review, we address the elective discontinuation of immunomodulator and biological therapy for patients who have achieved sustained clinical remission. The issues surrounding discontinuation of therapy for other reasons, including pregnancy, planned surgery, and intercurrent infection or malignancy, are addressed comprehensively elsewhere.[4-8]

Undoubtedly, the safety of immunomodulators and biological therapy is a key issue for clinicians, but the risk of drug-related adverse events must be balanced against the harmful effects of losing disease control.[9]

Particular concern has surrounded the risk of infectious complications and drug-related lymphoproliferative dis-orders. Registry data have confirmed the risks of monotherapy and have highlighted that patients on combination therapy are at greatest risk.[10,11] Withdrawal of a thiopurine drug reduces the risk of lymphoproliferative disorders, with a prospective study showing a lower incidence of such adverse events in patients with IBD who discontinued thiopurine treatment (0.20 per 1000 patient-years) and those who were never exposed to thiopurine (0.26 per 1000 patient-years) compared with those who continued thiopurine treatment (0.90 per 1000 patient-years; p=0.0054).[12] Taken together, these data suggest that de-escalation of drug therapy, in particular combination therapy, might reduce the risk of serious drug-related adverse events.

De-escalation of therapy also provides cost savings, an important consideration at a time of increasing pressure on health-care budgets worldwide. The COIN study[13] from the Netherlands showed that IBD healthcare costs are predominantly driven by the cost of medication, in particular anti-TNF therapy, which accounted for 64% of the total cost in Crohn's disease and 31% of the total cost in ulcerative colitis. Data from the TAXIT trial[14] showed that de-escalation of infliximab dosing, based on trough concentrations, led to a 28% reduction in drug costs both for patients with Crohn's disease and those with ulcerative colitis who had initially shown a full or partial response to infliximab maintenance therapy, without impairing clinical outcome. However, both studies[13,14] predate the arrival of biosimilars, which have provided significant cost savings. The cost-effectiveness of de-escalation versus non-de-escalation, based on infliximab trough concentrations, has been compared in virtual cohorts of patients with Crohn's disease in remission.[15] Over the modelled 2-year follow-up period, infliximab de-escalation, based on trough concentrations, was predicted to lead to a cost saving of 6.1%, corresponding to €25.4 million per 10 000 patients. The use of infliximab biosimilars resulted in a lower, but still substantial, absolute cost saving of €13.8 million per 10000 patients.[15]

In this Review, we discuss the best available evidence on de-escalation of immunomodulators and biological therapy for patients with IBD in remission, considering these treatments both separately and in combination. We propose an algorithm to guide de-escalation decisions and conclude by highlighting noteworthy future perspectives, including the potential effect of personalised medicine and emerging therapies.

Withdrawal of immunomodulator monotherapy

Four randomised controlled trials (RCTs) have evaluated the withdrawal of immunomodulator monotherapy in patients with Crohn's disease in clinical remission.[16-18,20] All of the studies reported higher relapse in the withdrawal groups.[30] In a multicentre, double-blind, non-inferiority withdrawal study, patients with Crohn's disease in clinical remission on azathioprine for at least 42 months were randomly assigned to either continue azathioprine or receive a placebo. The relapse rate was higher in the placebo group than in the azathioprine group (nine [21%] of 43 patients *vs* three [8%] of 40) at 18 months. The authors concluded that withdrawal of azathioprine was not equivalent to continuation with regard to maintenance of remission; as a result, azathioprine maintenance therapy should be continued beyond 3.5 years of treatment.[17] A follow-up of this study, which was limited by the small number of patients recruited (n=66), showed that the cumulative probability of relapse was 52.8% (SE 7.1) at 3 years and reached 62.7% (7.2) at 5 years. Thus, azathioprine withdrawal was associated with a high-risk of relapse even after a long period of clinical remission.[31] In a second study, 52 patients with Crohn's disease who has been treated with azathioprine for at least 48 months were randomly assigned to either continue azathioprine or switch to placebo. The proportion of patients in remission after 1 year of follow-up was lower in the placebo group (76% [SD 8]) than in the azathioprine group (96% [4]) p=0.035, but this statistically significant difference was lost after 2 years.[16] A Cochrane meta-analysis based on data from four studies with follow-up between 12 and 24 months indicated that overall, 36 (32%) of 111 patients relapsed following azathioprine withdrawal in comparison with 14 (13%) of 104 patients who relapsed after continuing azathioprine therapy (relative risk 0.42 [95% CI 0.4-0.72]; p=0.002).[32] Retrospective studies have reported higher relapse rates following the withdrawal of immunomodulators; 14-38% at 12 months, 39-71% at 24 months, 53-85% at 36 months, and 63-85% at 60 months.[30] None of these studies assessed azathioprine metabolite concentrations, which might prove to be important in predicting relapse following de-escalation of thiopurine monotherapy.

A small RCT involving patients with ulcerative colitis reported a relapse rate of 61% (17/28) for patients in long term remission when azathioprine was withdrawn versus 31% (8/26) in those continuing their azathioprine regimen (p<0.001) by the end of the first year of followup.[19] Importantly, patients who had taken azathioprine for 6 months before de-escalation were included, which might explain the high relapse rates. Longer follow-up times have been assessed in retrospective cohort studies. Relapse rates ranged from 43-65% at 5 years to 75-87% over longer periods.[30] Finally, a retrospective study of 70 patients with IBD (48 patients with Crohn's disease and 22 with ulcerative colitis) evaluated relapse rate after methotrexate withdrawal. The probability of remaining in remission was higher when methotrexate was continued (90%) than if discontinued (21%) after 12 months of follow-up, with no difference found between patients with Crohn's disease and those with ulcerative colitis.[33] We have summarised the RCTs of immunomodulator withdrawal in table 1.

In summary, withdrawal of immunomodulator monotherapy (thiopurine or methotrexate) is associated with a substantial risk of relapse both in patients with Crohn's disease and those with ulcerative colitis, even among patients who have achieved long-term remission. These data need to be weighed against the evidence for the cumulative increased risk of serious complications

with long-term therapy and the suggestion that a period off therapy will significantly reduce the risk of drug-related lymphoma.[12]

Withdrawal of the immunomodulator from combination therapy

In an open-label RCT,[28] patients with Crohn's disease receiving combination therapy with immunomodulators and infliximab for at least 6 months were randomly assigned to either continue or stop immunomodulators. No difference in the primary endpoint, the proportion of patients who required a decrease in infliximab dosing interval or cessation of infliximab due to the loss of response or clinical relapse, was found between the two groups over a 24-month period of follow-up (24 [60%] of 50 patients who continued immunomodulator *vs* 22 [55%] of 40 patients who discontinued immunomodulator), suggesting that the continuation of immunomodulators was not superior to withdrawal. Endoscopic healing, defined by the absence of mucosal ulcers, was also similar in both groups (16 [64%] of 25 in the continuation group *vs* 14 [61%] of 23 in the discontinuation group), although combination therapy was associated with lower concentrations of C-reactive protein (CRP).[29] A further open-label RCT, DIAMOND2,[34] assessed thiopurine withdrawal from the treatment regimen of patients in steroid-free clinical remission for at least 6 months following combination therapy with adalimumab. Preliminary results report no difference in the primary endpoint of steroid-free remission at 52 weeks, or in a secondary endpoint of mucosal healing, suggesting no clear benefit in continuation of immunomodulators beyond 6 months of clinical remission. However, only a small number of patients (n=50) were included, and the thiopurine dose was much lower than that commonly used in Europe.[34]

A subsequent systematic review has analysed relapse rates following immunomodulator (azathioprine) discontinuation from combination therapy in Crohn's disease. Overall, 27 (49%) of 55 patients relapsed after immunomodulator withdrawal compared with 27 (48%) of the 56 patients who continued immunomodulators (RR 1.02 [0.68-1.52]; p=0.92). However, the quality of data was considered low because of high risk of bias for study blinding and small patient numbers;[32] nevertheless, retrospective cohort studies have also suggested no difference in clinical outcome.[26,30] One observational study reported a cumulative relapse rate of 27% at a median follow-up of 14 months,[27] and a second reported 38% at 29 months.[25] The probability of relapse appears to increase substantially over time, with a third study reporting a relapse rate of 72-.% at a median follow-up of 61.6 months.[20] Finally, in a paediatric population no difference in relapse was found between those randomly assigned to either continue (33.3%) or discontinue immunomodulators (35.9%).[23]

Only a small amount of data exists regarding the relapse of patients with ulcerative colitis following immunomodulator discontinuation, but a large retrospective study reported a lower prevalence of relapse among patients who continued on combination therapy (12 [3%] of 392) than among those receiving infliximab alone (33 [12%] of 282; p=0-049).[24] Studies investigating immunomodulator withdrawal from combination therapy are summarised in table 2.

In summary, withdrawal of immunomodulators from combination therapy in Crohn's disease does not appear to increase relapse rate at up to 2 years of follow-up. However, longer prospective studies are required for both Crohn's disease and ulcerative colitis.

The effect of immunomodulators withdrawal on the immunogenicity of biological therapy

When considering the withdrawal of immunomodulators from combination therapy, the increased risk of biological immunogenicity must be acknowledged. The development of anti-drug antibodies is of greatest concern in patients given anti-TNF therapy, with the prospective PANTS study[35] reporting overall rates of antibody formation, with associated undetectable drug concentrations at week 54, to be 31.2% with infliximab and 12.3% with adalimumab.[35] Conversely, the gut selective α4β7 integrin antibody vedolizumab, and the interleukin 12/23 p40 subunit antibody ustekinumab, are associated with much lower rates of antibody formation (1-4.1% for vedolizumab and 0.4-2.9% for ustekinumab).[36] In anti-TNF therapy, the development of anti-drug antibodies is strongly associated with lower trough concentrations, loss of response, and infusion reactions.[37,38]

Several studies have suggested immunomodulator continuation is associated with improved infliximab pharmacokinetics. Initial prospective work reported higher infliximab trough concentrations in patients who continued immunomodulator therapy.[28] This association was confirmed in an RCT that found low or undetectable infliximab concentrations, with or without anti-drug antibodies, in 14.3% of those who continued azathioprine at a dose of 2-2.5 mg/kg per day, 14.8% of patients who continued with a halved azathioprine dose, and 43.3% of patients who stopped azathioprine.[20] Maintaining concentrations of the azathioprine metabolite 6-TGN at more than 105 pmol/8 x 10^8 red blood cells was suggested to prevent low infliximab trough concentrations. A separate cross-sectional study found that 6-TGN concentrations correlated with those of infliximab, and patients with lower 6-TGN concentrations (<125 pmol/8 x10^8 red blood cells) were more likely to have antibodies to infliximab (odds ratio [OR] 13, 95% CI 2.3-72.5; p<0.01).[39] A further study reported that combination therapy resulted in a longer drug antibody free survival.[40] The effect of immunomodulators on adalimumab trough concentrations is less clear, with the DIAMOND2 study[34] reporting no difference at week 52 when the immunomodulator was discontinued after at least 6 months of combination therapy. Finally, results from the PANTS study[35] have shown that concurrent immunomodulator use reduces the risk of immunogenicity for both infliximab (hazard ratio [HR] 0.39; p<0.0001) and adalimumab (HR 0.44; p<0.0001). As expected, immunogenicity was strongly associated with non-remission.[35]

The concept of optimised monotherapy, based on proactive therapeutic drug monitoring for anti-TNF drugs, has emerged as an alternative to combination therapy. In a retrospective study of 149 patients with IBD (94 patients with Crohn's disease and 55 with ulcerative colitis), the less favourable pharmacokinetic profile initially observed with infliximab monotherapy could be overcome with dose escalation based on close therapeutic drug monitoring, with no difference in infliximab discontinuation, mucosal healing, hospitalisation, or long-term steroid use over a

median follow-up of 19 months.[41] Concordant results were reported in a second retrospective study, in which early infliximab dose escalation resulted in similar clinical outcomes and infliximab trough concentrations regardless of concurrent immuno- modulator.[42]

Taken together, although these data highlight the potential negative effect of immunomodulator withdrawal on anti-TNF pharmacokinetics and immunogenicity, an increased risk of relapse has not been shown, and proactive therapeutic drug monitoring emerges as a strategy to maintain anti-TNF efficacy.

Withdrawal of anti-TNF therapy

A number of studies over the past few years have focused on anti-TNF withdrawal both in patients with Crohn's disease and those with ulcerative colitis.[43-47] Overall, most studies report a relapse rate of 40-50% over a 2-year period following discontinuation of the anti-TNF drug, but treatment with concurrent immunomodulators varies greatly between the studies.[30,48] The STORI[49] trial remains the only prospective study designed to assess prevalence of relapse after anti-TNF withdrawal, but it did not have a control group. The trial enrolled patients with Crohn's disease who had been treated for at least 1 year with infliximab and an antimetabolite, with steroid-free remission for a minimum of 6 months. The relapse rate was 43.9% (SE 5.0) at 12 months and 52.2% (SE 5.2) at 24 months.[49] Long-term outcomes, with a median follow-up of 7 years, have been published, with only 21.6% of patients remaining in remission, while 71% restarted biological therapy after a median of 13 months. Of the 64 patients who restarted biological treatment, 22 were treated unsuccessfully with infliximab, either as a result of major complications (4/22) or secondary loss of response to infliximab (18/22) after a median time of 22 months. The cumulative incidence of unsuccessful infliximab treatment was 30.1% (95% CI 18.5-42.5) 6 years after infliximab restart.[50] Importantly, major complications occurred relatively late after infliximab withdrawal (median 45 months), including 14 surgeries and four complex perianal lesions, emphasising the importance of close long-term monitoring following de-escalation.

A retrospective cohort study compared the disease course of ulcerative colitis in clinical remission for at least 12 months in patients who continued or discontinued infliximab. Patients who discontinued infliximab had a higher probability of relapse (HR 3.41 [95% CI 1.88-6.20]; p<0.001). A separate study reported the relapse rate in patients with ulcerative colitis to be 60% after 4.5 years of follow-up.[43]

A multicentre retrospective study assessed the risk of relapse both for patients with Crohn's disease and those with ulcerative colitis who discontinued anti-TNF after achieving clinical remission, with a median follow-up of 19 months.[51] The cumulative incidence of relapse was 44% per patient-year, with no significant difference between patients with Crohn's disease and those with ulcerative colitis.[51] A large retrospective cohort study from the UK reported relapse after anti-TNF withdrawal in patients with Crohn's disease, ulcerative colitis, or IBD unclassified.[46] Relapse rates were 36% at 1 year and 56% at 2 years of follow-up in patients with Crohn's disease compared with 42% at 1 year and 47% at 2 years in those with ulcerative colitis or IBD unclassified. The authors also did a meta-analysis, which supported their findings.[46] The

relapse rate at 1 year was 39% (95% CI 35-44) and 54% (49-59) at 2 years for patients with Crohn's disease, whereas the relapse rate for patients with ulcerative colitis or IBD unclassified was 35% (26-43) at 1 year and 42% (27-58) at 2 years.[46] A separate systematic review and meta-analysis produced similar results, with the overall risk of relapse after anti-TNF discontinuation being 44% in patients with Crohn's disease and 38% in those with ulcerative colitis.[57] We have summarised the largest studies evaluating de-escalation from anti-TNF (table 3).

An important and feared consequence of relapse following biological withdrawal in ulcerative colitis is colectomy. A prospective observational study reported outcomes following infliximab discontinuation in 51 patients in clinical remission: 18 (35%) patients needed to restart biological therapy, with only one patient not responding and requiring colectomy.[54] Similarly, a separate study found that only one of 48 patients required colectomy following the withdrawal of infliximab.[46] Additionally, a retrospective multinational cohort study of 193 patients found no differences in the frequency of colectomy between those who had discontinued infliximab and those who had continued on it.[58] To the best of our knowledge, no studies have evaluated the clinical outcomes after stopping other biological agents, such as vedolizumab.

Strategies for de-escalation of therapy in IBD: a review of the current evidence

Although the long-term probability of maintaining remission following de-escalation of therapy appears disappointingly low, a number of strategies have been proposed to minimise the risk of a clinically significant relapse.

STRATEGY ONE: THE SELECTION OF SUITABLE CANDIDATES FOR DE-ESCALATION

The identification of subgroups of patients who are at considerably lower risk of relapse following drug withdrawal might be possible. A number of studies have reported predictive factors for relapse, including a comprehensive systematic review that determined that the majority of predictive factors reflect known poor prognostic features, previous challenging disease course, and markers of active disease.[30] However, no predictive factors for relapse have been consistently reproduced in ulcerative colitis, making stratification difficult in this cohort.

Both demographics and clinical history must be considered when contemplating de-escalation. Young age at diagnosis and male sex are poor prognostic features for both ulcerative colitis and Crohn's disease.[30] However, of note, men younger than 35 years are at greatest risk of hepatosplenic T-cell lymphoma following more than 2 years of thiopurine therapy with or without anti-TNF, which although rare, carries a poor prognosis, underlining the challenges of decision making.[59] Conversely, the risks of both infection and malignancy increase with thiopurine and anti-TNF treatment if the patient is older than 65 years, favouring discontinuation in older patients.[10] Extensive disease is an important risk factor for Crohn's disease, which has also been proposed for ulcerative colitis; additional adverse clinical features

of Crohn's disease include smoking, perianal or colonic disease, and stricturing disease.[30,47,51,55,60] Discontinuation of biological therapy in perianal disease is associated with particularly high relapse rates, and continuation of therapy is strongly favoured in this group.[61,62] Treatment history is also important, with a previous need for surgery, unsuccessful immunomodulator therapy, or relapsing course requiring escalation of therapy associated with higher risk of relapse.[30,51]

The consequences of disease progression must also be assessed as part of the decision-making process. For example, one might decide not to de-escalate in a patient considered at low risk of relapse who has had multiple previous bowel resections, because any disease recurrence would place them at high risk of short bowel syndrome.

Important laboratory markers of active disease that predict failure of de-escalation in Crohn's disease include elevated CRP and neutrophil or white cell count, low haemoglobin, and elevated faecal calprotectin.[49,55] Subtle abnormalities might confer substantially increased risk, with a white cell count more than 6×10^9 cells per L, haemoglobin less than or equal to 14.5 g/L, and CRP greater than or equal to 5 mg/L associated with risk of relapse on withdrawal of anti-TNF in Crohn's disease.[49,50] A model from the STORI trial,[49] which incorporated these parameters, together with the additional variables of male sex, absence of surgical resection, and faecal calprotectin of 300 pg/g or greater, found that the presence of two or fewer risk factors was associated with a 15% relapse rate at 1 year.

Faecal calprotectin might be elevated in the absence of endoscopic disease activity, and can help identify patients in deep remission, with concentrations of less than 56 pg/g predictive of stable remission in both ulcerative colitis and Crohn's disease.[63] In ulcerative colitis, a white cell count of more than 9.1×10^9 cells per L predicted relapse after withdrawal of azathioprine in one retrospective study,[64] although this association has not been shown in other work. Evidence of mucosal healing at either imaging or endoscopy is associated with a reduced risk of relapse in patients with Crohn's disease, with histological grade predictive in ulcerative colitis in a single study.[60,52,65]

Importantly, up to 30% of patients with Crohn's disease considered to be in deep remission with mucosal healing and low faecal calprotectin will still relapse, highlighting the importance of additional factors, such as the microbiome.[66,67] A subanalysis of the STORI trial suggested that a low abundance of *Faecalibacterium prausnitzii* (adjusted HR 4.1 [95% CI 1.2-13.3]; p=0.014) and *Bacteroides* (3.3 [1.1-10.1]; p=0.030) predicted relapse following anti-TNF withdrawal independently of high CRP (p=0.0001).[68]

A review of recent drug concentrations might also guide de-escalation decisions. Low or undetectable infliximab trough concentrations appear helpful in predicting a reduced risk of relapse when the drug is withdrawn.[49,52] Most probably, this observation simply reflects that clinical remission has been achieved in the absence of a therapeutic dose of infliximab. The same is likely to be true for adalimumab concentration, but data are scarce. Conversely, for patients on combined infliximab and immunomodulator therapy, a higher infliximab trough concentration predicts a lower relapse rate when the immunomodulator is withdrawn.[27]

Finally, of note, most of the predictive factors arise from retrospective studies, and thus a clear need exists for a well powered prospective study in this area.

STRATEGY TWO: DOSE DE-ESCALATION

Dose reduction presents an alternative to complete drug withdrawal, providing cost savings and potentially reducing the risk of side-effects, although the reduction of side-effects has not yet been proven in patients with IBD. An increased risk of non-Hodgkin lymphoma was reported following higher doses of azathioprine in a large population of patients who had received a solid organ transplant, while higher concentrations of 6-TGN were associated with a higher risk of skin cancer in patients who had received renal transplants.[69,70] Additionally, no data are available that prove a link between higher concentrations of biological agents and side-effects in IBD; however, an association between increasing drug concentration and increased risk of infection has been reported in patients with rheumatoid arthritis.[71]

As previously outlined, one RCT has found that reduction of azathioprine, but not withdrawal, in patients receiving combination therapy, maintained similar median infliximab trough concentrations to continuation at full dose, supporting a dose de-escalation strategy.[21] The TAXIT trial[14] showed that monitoring of infliximab trough concentrations leads to more efficient dosing and allows safe dose reduction.[14] At a single tertiary health-care centre, only 115 (44%) of263 patients with Crohn's disease and ulcerative colitis who were clinically stable on infliximab maintenance therapy had optimal trough concentrations of 3-7 pg/mL and concentrations of more than 7 pg/mL were observed in 27% of the group.

Importantly, patients randomly assigned to receive a dose regimen altered on the basis of serial monitoring of trough concentrations over a 1-year period had fewer flares than did those randomly assigned to be dosed on clinical criteria alone, although no difference in remission rate was noted. Two recent studies,[72,73] further support the use of therapeutic drug monitoring to guide dose de-escalation. In a retrospective analysis of 91 patients with IBD receiving infliximab a trough concentration of more than 5-7 pg/mL before de-escalation and serial trough concentration of more than 2-4 pg/mL following de-escalation were associated with a lower risk of relapse.[72] In a further retrospective study of 96 patients with IBD, dose de-escalation of infliximab if trough concentrations were more than 7 pg/mL was associated with a decreased risk of relapse (HR 0·45; p=0·024) compared with clinical de-escalation.[73]

Lengthening of intervals between doses could also help achieve dose de-escalation. A retrospective study investigated the lengthening of dose intervals with adalimumab in patients with Crohn's disease. Adalimumab was de-escalated from every other week to every 3 weeks in patients with trough adalimumab concentrations of more than 7 pg/mL or side-effects or both. 26 (65%) of 40 patients remained in clinical remission with trough adalimumab concentrations of more than 4 pg/mL for a median follow-up of 24 months.[74] Importantly, dose de-escalation was associated with the resolution of side-effects in half the patients. A CRP of less than 3-5 mg/L at time of de-escalation was the only independent predictor of sustained remission. Dose de-escalation of adalimumab from every week to every other week was assessed in a separate retrospective study in Crohn's disease, and was successful in 63% of patients.[75]

STRATEGY THREE: EARLY DETECTION AND TREATMENT OF RELAPSE

Careful objective monitoring for relapse is important following drug withdrawal because disease relapse might occur without clinical symptoms and both patients and health-care professionals might underestimate the relevance of mild symptoms.[76] The risk of relapse is highest in the first

year following drug withdrawal; therefore, more intensive monitoring is appropriate.[60] Despite substantial variability, secondary analysis of the STORI trial showed a higher median CRP concentration among patients who relapsed, with a concentration of more than 5 mg/L associated with a HR for relapse of 4·2 (95% CI 1·9-9·2; p<0·001).[77] Serial monitoring of faecal calprotectin is also of value in predicting relapse following withdrawal of anti-TNF, based on data from a prospective multicentre study[78] of patients with both Crohn's disease and ulcerative colitis.[78] Faecal calprotectin was found to increase up to 6 months before evidence of endoscopic relapse, with consistently low concentrations associated with sustained remission following drug withdrawal. Median concentrations consistently more than 120 pg/g were seen in patients who relapsed, which is substantially lower than the threshold of 250 pg/g reported as an independent predictor of relapse in the STORI trial (HR 6·5 [95% CI 2·7-15·6]; p<0·001), but this outcome might reflect the observation that baseline concentrations were also significantly higher in the STORI trial.[49,77]

An important consideration following de-escalation is whether the patient's response can be safely recaptured in the event of a relapse. In a multicentre UK study, reintroduction of thiopurine following a previous treatment regimen with thiopurine—lasting a median duration of 6 years—was successful in 31 (74%) of 42 patients with Crohn's disease and in 22 (92%) of with ulcerative colitis.[64] Two-thirds of patients with Crohn's disease and half of those with ulcerative colitis also required systemic steroids to reinduce remission. It is notable that 25 (86%) of 29 patients with Crohn's disease and moderate-to-severe relapse within 12 months of azathioprine withdrawal required systemic steroids, anti-TNF, or hospital admission, with five of these patients requiring surgical resection. In an earlier study, remission was recaptured in 22 (96%) of 23 patients with Crohn's disease in an earlier study, although alternative therapy was chosen in nine (28%) of the 32 patients who initially relapsed following azathioprine withdrawal.[31] Favourable proportions of patients who recaptured remission are also reported for anti-TNF therapy (table 4). A meta-analysis of retreatment with the same anti-TNF in 290 patients with IBD found the rate of recapture of remission to be 80% (95% CI 68-91; p<0.00001), with response rates similar for both Crohn's disease and ulcerative colitis.[57] This rate is similar to that reported in two prospective studies, including the STORI trial.[49,81] Higher early trough concentrations of infliximab upon reintroduction have been associated with long-term response.[82] Continued use of immunomodulators during the period of anti-TNF drug withdrawal in most patients is likely to protect against immunogenicity that would lead to loss of response and infusion reactions when the drug is reintroduced.[60]

Data from 2017 suggest promising rates of recapture of response and a much lower risk of immunogenicity with vedolizumab.[83] Interim analysis of the GEMINI longterm safety study[83] shows that remission rates improved from 9% to 48% at week 28 of retreatment for patients with Crohn's disease who withdrew early from the GEMINI2 placebo maintenance phase because of relapse or non-medical reasons.

Interest in the concept of drug holidays is growing, with the recognition that although therapies do not cure the underlying disease—meaning that relapse is common—the natural history of IBD is cyclical. Consequently, patients might experience long periods of remission after drug withdrawal once they have reached deep remission.[17,49,84] Even transient drug withdrawal might be beneficial, reducing the total lifetime treatment burden and potentially reducing adverse

events and cost.[47] In cases of borderline pharmacokinetics and low adherence with biological therapy, temporary drug cessation might also be less immunogenic.[84]As retreatment appears safe and effective in the majority of patients, this approach shows considerable promise and is the subject of ongoing research.[46,49,57,85]

CLINICIAN AND PATIENT PERSPECTIVES TO DE-ESCALATION

When considering de-escalation, the views of both the clinicians and the patients must be taken into account. Two surveys published in 2017[86] and 2018[87] are particularly illuminating with regard to this aspect of management. The first study, from the BIOCYCLE group,[86] reported that gastroenterologists were significantly more likely to stop immunomodulator use (75% in Europe and 61% in the USA; p=0.05) than biological therapy (23% in Europe and 29% in the USA) for patients in with Crohn's disease who are in remission. The risk of malignancy was regarded to be the most important reason for stopping immunomodulator therapy, with cost being the primary reason for stopping biological therapy. Importantly, there were clear cultural differences, with European gastroenterologists more likely than their US counterparts to recommend stopping combination therapy (44% in Europe *vs* 18% in the USA; p<0.05).[86]

A second survey[87] explored patient attitudes to de-escalation of combination therapy in Crohn's disease in both France and the USA. Substantially more patients preferred to stop the immunomodulator regimen (53% in the USA *vs* 47% in France) than anti-TNF therapy (26% in the USA *vs* 28% in France). Importantly, 26% of all patients would not accept any de-escalation if the process increased the risk of an acute flare, and 56% of all patients were more concerned by Crohn's disease activity than the risk of treatment-associated malignancy. Once again cultural differences were reported, with French patients more likely than US patients to consider stopping combination therapy if recommended by their clinician (69% in France *vs* 48% in the USA; p=0.04).[87]

Current recommendations on the elective withdrawal of medical therapy for patients with IBD in remission

In 2018, the European Crohn's and Colitis Organisation (ECCO) published guidance on treatment withdrawal in IBD.[60] The importance of individualising any withdrawal decision is emphasised, taking into account the views of the patient. When considering withdrawal of therapy, remission should be confirmed with a combination of clinical, biochemical, endoscopic, and imaging parameters, and predictors of relapse carefully considered.

For immunomodulator monotherapy, the ECCO guidance suggests that the risks and benefits of continued treatment should be discussed after 3-4 years for those in established remission. When used in combination, withdrawal of the immunomodulator is considered unlikely to increase relapse rates in Crohn's disease over the following 2 years, but this action might be inappropriate in patients with previously challenging disease or at high risk of unsuccessful biological treatment, including low infliximab trough concentrations. Anti-TNF withdrawal should typically only be considered in patients in deep remission, and maintenance

immunomodulator therapy might be appropriate to reduce risk of relapse. Anti-TNF discontinuation is not recommended in patients with perianal fistula given the high risk of relapse. Monitoring with serial faecal calprotectin and CRP is advised following treatment withdrawal, together with reassessment with imaging and endoscopy. More intensive monitoring is recommended in the first year after withdrawal of anti-TNF given the high relapse rates. In the UK, the National Institute for Health and Care Excellence recommends that patients with IBD on anti-TNF therapy should be reassessed at least annually, with a trial of treatment withdrawal considered if the patient is in stable remission, but no further specific guidance on patient selection or subsequent monitoring is provided.[88,89]

A proposed withdrawal strategy

The ECCO expert consensus provides valuable guidance for decision making.[60] We agree that consideration of drug withdrawal should be made on a case-by-case basis and careful counselling of the patient is essential, including an explanation that the current predictors of outcome are not perfect. However, patients should also be reassured that they will be closely monitored following de-escalation, allowing early detection of relapse, and that clinical response will most likely be recaptured if therapy is restarted. Although the optimal frequency of monitoring has not been established, faecal calprotectin and CRP measurement every 3 months might be appropriate initially, allied with close observation of symptoms, recognising that the highest risk of relapse is in the first year. Following drug withdrawal any concern should prompt formal reassessment with endoscopy or imaging or both (figure). We emphasise the importance of carefully considering the consequences of relapse that might argue against de-escalation, even when risk of relapse is low.

Future perspectives

UNMET RESEARCH NEEDS

Much of the data on drug de-escalation is from retrospective studies; therefore, high-quality RCTs are needed to guide decision making, several of which are underway. The standard-of-care for moderate-to-severe Crohn's disease is combined therapy with an immunomodulator and biological therapy, but the SPARE study (NCT02177071), which forms part of the BIOCYCLE project, aims to definitively answer whether monotherapy is feasible. This multicentre European study will enrol 225 patients with Crohn's disease in stable remission to one of three groups: continuation of both immunomodulator and biological, continuation of only immunomodulator, or continuation of only biological therapy. The efficacy of each treatment group to maintain remission will be assessed. Further data on the discontinuation of infliximab in Crohn's disease will be provided by the STOP IT trial,[90] while the BIOSTOP trial (EudraCT number 2016-001409-18) will assess the effects of anti-TNF withdrawal in patients with ulcerative colitis and explore the feasibility of drug holidays, as the protocol allows for the anti-TNF to be restarted in the event of relapse.

Figure: An algorithm to guide decision making in drug de-escalation

CDAI=Crohn's Disease Activity Index. CDEIS=Crohn's Disease Endoscopic Index of Severity. CRP=C-reactive protein. SES-CD=Simple Endoscopic Score for Crohn's Disease. SCAAI=Simple Clinical Colitis Activity Index.
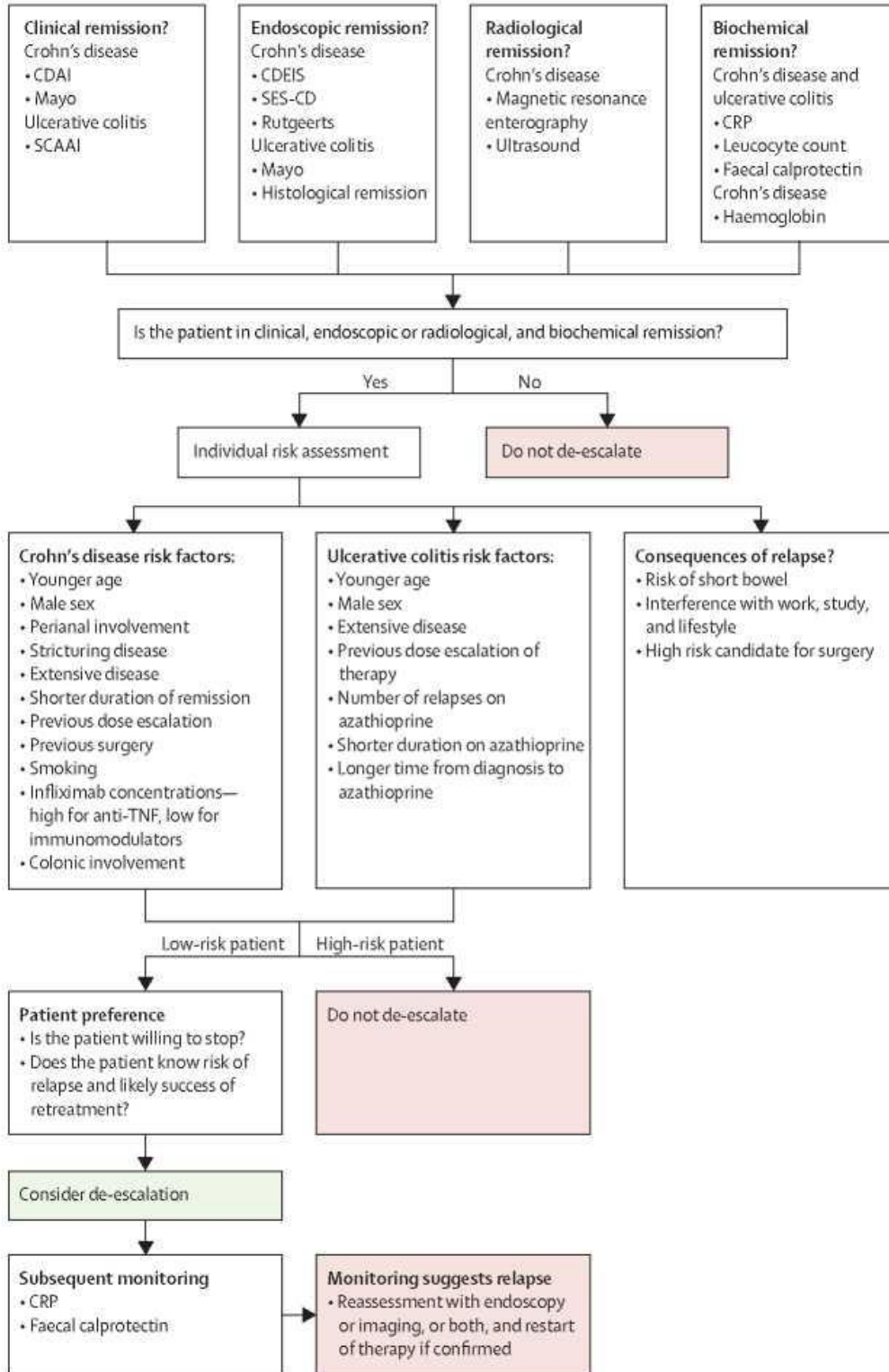
PERSONALISATION OF APPROACH

A core aim of the SPARE study is the identification of new biomarkers to predict the risk of relapse. This personalised approach to de-escalation of therapy is essential, as currently patients cannot be precisely stratified into appropriate treatment pathways. The use of molecular profiling to identify predictive biomarkers of disease course and treatment response is now of considerable research interest. In addition to HLA-DQA1*05, a number of other polymorphisms predict development of anti-drug antibodies, suggesting an additional benefit to determining a personalised gene expression signature for patients with IBD.[35,91-93] Other genomics strategies are also under evaluation, including methylation, transcription, and protein glycosylation profiling. Additionally, the development of telemedicine systems promises closer monitoring of disease activity, and might enable earlier detection of relapse following treatment de-escalation in the future.[94-97]

THE EFFECT OF EMERGING MEDICATIONS

Novel therapies will probably substantially affect the clinician's approach to drug withdrawal. No data are available for relapse rates following withdrawal of newer biologicals, like vedolizumab and ustekinumab, but the low risk of immunogenicity to these agents might simplify drug cycling. The emergence of small molecule inhibitors, such as the JAK inhibitors tofacitinib and filgotinib, is very relevant.[98] These agents pose no risk of immunogenicity and act rapidly, with data suggesting that drug holidays are highly feasible. Data from the OCTAVE trials[99] found that in patients who had previously responded to tofacitinib, retreatment following a treatment interruption during the placebo phase of up to 44 weeks was effective in 75 (76%) of 99 patients at 2 months.

Search strategy and selection criteria

We searched the PubMed database to identify relevant manuscripts from inception until March 31, 2019. The search combined the MeSH terms "inflammatory bowel disease", "Crohn's disease" and "ulcerative colitis" with the subheadings "de-escalation", "therapy withdrawal", "immunomodulator withdrawal", "biologic withdrawal", "dose reduction", "therapeutic drug monitoring", "drug holiday", "risk of relapse", "cost saving", "lymphoma", "severe infection", "opportunistic infection", and "patient preference". We also reviewed bibliographies of the included studies to identify additional important data. We also assessed recent guidelines and topical reviews. Only papers published in English were reviewed, with priority given to randomised clinical trials and meta-analyses.

Conclusion

In summary, there remains much to learn about the appropriate and individualised de-escalation of therapy in IBD. It is a highly important area in clinical practice, and worthy of greater research focus. With the emergence of stratified medicine, the next decade promises a potential transformation of both our understanding of IBD and the tools at our disposal, providing hope of greater precision in this challenging area of care

CONTRIBUTORS

JS, J-FC, and EL conceived the idea, TPC and CFG drafted the Review, and JS, J-FC, and EL made important revisions and intellectual contributions.

DECLARATION OF INTERESTS

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Table 1: *Randomised controlled trials of immunomodulator withdrawal*

	Participants and duration of follow-up	Definition of remission before de-escalation	Definition of relapse	Treatment group	Relapse rate				Time to relapse	Notes
					6 months	12 months	18 months	24 months		
Wenzl et al (2014)[16]	Crohn's disease (N=52); 24 months	Clinical remission in 12 months before enrolment, and CDAI <150 at baseline; >4years azathioprine	Clinical relapse (CDAI >150 with an increase of 60, new fistula development in a patient without fistula at enrolment; increase in PDAI by >4; hospitalisation for active Crohn's disease; oral steroids or anti-TN F or surgery)	Placebo (n=26); azathioprine (n=26)	8% for placebo; 0%for azathioprine	23% for placebo; 4% for azathioprine	31% for placebo; 12% for azathioprine	31% for placebo; 15% for azathioprine	197 months for placebo; 22-3 months for azathioprine	
Lemann et al (2005)[17]	Crohn's disease (N=83); 18 months	Clinical remission (CDAI <150)and no need for medical or surgical treatment in previous 42 months; >3-5 years azathioprine	Clinical relapse (CDAI >250; CDAI 150-250 on 3 consecutive weeks with an increase of 75; need for surgery for Crohn's disease [except limited perianal disease])	Placebo (n=43); azathioprine (n=40)	NA	16.5% (SE 5.7) for placebo; NA for azathioprine	21-3% (SE 6.3) for placebo; 7.9% (SE 4.4) for azathioprine	NA	15-9 months (SE0.9) for placebo; 17-3 months (SE 0.5) for azathioprine	Non-inferiority RCT; azathioprine withdrawal was not equivalent to continuation of azathioprine therapy in maintaining Crohn's disease remission
Vilien at al (2004)[18]	Crohn's disease (N=29);* 12 months	Clinical remission >2 years azathioprine	Clinical relapse (CDAI >150, CDAI rise by >75, or disease activity requiring intervention)	Discontinuation (n=15); continuation (n=13)	NA	53% for discontinuation; 15% for continuation	NA	NA	NA	Not placebo controlled

Hawthorne et al (1992)[19]	Ulcerative colitis (n=67); 12 months	Steroid free clinical remission and Baron 0-1 >6 months azathioprine	Clinical or endoscopic relapse	Placebo (n=34); azathioprine (n=33)	NA	59% for placebo; 36% for azathioprine	NA	NA	NA	Results from the longterm remission patients: 61% for placebo vs 31% for azathioprine
O'Donoghue et al (1978)[20]	Crohn's disease (N=51); 12 months	Clinical remission >6 months azathioprine	Clinical relapse	Placebo (n=24); azathioprine (n=27)	25% for placebo; 0%for azathioprine	33% for placebo; 4% for azathioprine	NA	NA	NA	Low dose steroids allowed in definition of stable disease
RCT=randomised controlled trial. CDAI=Crohn's Disease Activity Index. PDAI=Perianal Disease Activity Index. NA=not applicable. Unless otherwise specified the duration of follow-up was the same at the duration of the RCT and is the same for all participants. *29 patients recruited, but only 28 completed the study or relapsed.										

Table2: *Studies of immunomodulator withdrawal from combination therapy*

	Participants and duration of follow-up	Definition of remission before de-escalation	Definition of relapse	Relapse rate				Time to relapse	Notes
				7 months	12 months	24 months	Other timepoint		
Roblin et al (2017)[21]; RCT	IBD (N=81; Crohn's disease [n=45]; ulcerative colitis [n=36]); 12 months	Clinical or endoscopic remission >6 months (Crohn's disease: CDAI <150, faecal cal protectin n <250 pg/g; ulcerative colitis: Mayo score < 3, endoscopic subscore 0-1, and stool subscore 0); >1year infliximab and azathioprine	Clinical relapse and any change in IBD therapy	NA	30.8% for azathioprine discontinuation; 11.9% for azathioprine reduction; 17.9% for azathioprine continuation	NA	NA	NS	Dose reduction but not discontinuation appeared to be as effective as continuation of azathioprine at full dose, but not statistically significant

Fischer et al (2017)[22]; retrospective	Crohn's disease (N=43); median 62.5 months	Clinical remission >5-4 months; >4 months infliximab and immunomodulators	Clinical relapse and the need for steroids, anti-TNF switch, hospitalisation, or retreatment with immunomodulators	NA	NA	NA	At end of follow-up 72-1% for the discontinuation group	Median 28.1 months	No difference was found between those who stopped or de-escalated therapy in terms of the length of time to relapse
Kierkusetal (2015)[23]; RCT	Crohn's disease (N=84); 7 months	Clinical remission >4 months (PCDAI <30 and PCDAI drop >15 since infliximab started); >6.5 months infliximab and azathioprine	Clinical relapse or loss of response to anti -TN F	35.9% for the discontinuation group; 33.3% for the continuation group	NA	NA	NA	NS	High risk of bias: no placebo and no blinding
Filippi et al (2015)[24]; retrospective	Ulcerative colitis (N=82); median 22.3 months (SD14 months)	Clinical remission >6 months infliximab and azathioprine	Clinical relapse requiring a change of treatment, unsuccessful inflixiab regimen, or colectomy	NA	NA	NA	12% by trimester for the discontinuation group; 3% for the continuation group	Mean 7 months for the discontinuation group; mean 16.6 months for the contin-uation group	None
Drobne et al (2015)[25]; retrospective	Crohn's disease (n=117); median 29 months	Clinical and biochemical remission >6 months (low CRP [<10 mg/L], persistent improvement of IBD symptoms) >6-5 months infliximab and immunomodulators	Clinical and biochemical relapse	NA	NA	NA	At end of follow-up 38% for the discon-tinuation group	Median time to infliximab dose escalation 42.9 months	None

Choi et al (2010)[26]; retrospective	Crohn's disease (N=22); 12 months (mean or median not specified)	Controlled disease for 2 months infliximab, NS azathioprine	Recurrence requiring steroids or surgery	NA	42.8% for the discontinuation group; 40% for the continuation group	NA	NA	NS	No information on definition of remission
Oussalah et al (2010)27; retrospective	Crohn's disease (N=48); median 14 months	Clinical remission (CDAI <150); >6 months infliximab and azathioprine	Infliximab failure, intensification of dosing or switch to adalimumab, infliximab intolerance, or major surgery	NA	15% for the discontinuation group	59% for the discontinuation group	At end of follow-up 27% for the discontinuation group	Median time before infliximab failure 23 months	Duration of combination therapy <27 months predictive of infliximab failure on azathioprine withdrawal
Sokol et al (2009)28; retrospective (abstract)	IBD (N=118); NS	Controlled disease duration before drug therapy N S	Intensification of infliximab dosing	NA	38'8% for the discontinuation group; 40'6% for the continuation group	NA	NA	NS	None
Van Assche et al (2008)29; RCT	Crohn's disease (N=80); 24 months	Clinical remission (absence of intestinal or extra-intestinal symptoms); >6 months infliximab and immunomodulators	Clinical relapse (CDAI increase by >70 leading to change in infliximab dosing or infliximab stopped for any reason)	NA	NA	55% for the discontinuation group; 60% for the continuation group	NA	NS	No placebo and no blinding

RCT=randomised controlled trial. IBD=inflammatory bowel disease. CDAI=Crohn's Disease Activity Index. NA=not applicable. NS=not specified. CRP=C-reactive protein. PCDAI=Paediatric Crohn's Disease Activity Index. Unless otherwise specified the duration of follow-up was the same at the duration of the RCT and is the same for all participants.

Table 3: *Studies of withdrawal of biological therapy*

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	Participants and duration of follow-up	Proportion given immuno modulators (%)	Definition of remission before de-escalation	Definition of relapse	Relapse rate			Long-term outcome	Time to relapse	Notes
					6 months	12 months	24 months			
Casanova et al (2017)[51]; retrospective	IBD (N=1055; Crohn's disease [n=731]; ulcerative colitis [n=324]); median 19 months (>6 months)	68% (after biological withdrawal)	Clinical remission (luminal Crohn's disease: Harvey-Bradshaw Index ≤4; perianal Crohn's disease: absence of fistula drainage ulcerative colitis: partial Mayo score ≤2) duration before drug therapy NS	Clinical, biochemical, endoscopic, or radiological activity leading to therapeutic intervention (medical or surgery)	15% for the discontinuation group	24%	38%	46% relapse at 3 years; 56% at 5 years	Median time 11 months (range: 1-140)	The IBD subtype was not associated with risk of relapse; in patients classified as being in deep remission, the rate of re lapse was still similar (22% for Crohn's disease and 20% for ulcerative colitis after 1 year)
Reenaers et al (2018)[50]; retrospective	Crohn's disease (N=102); median 83 months	100% (after biological withdrawal)	Clinical remission (CDAI <150) >12 months infliximab and immunomodulators	Need to restart biological, major complications (surgery, complex perianal lesions)—so called infliximab failure	NA	NA	NA	78·4% restarted biological or had major complications and 34% had infliximab failure	Median time to infliximab retreatment: 13 months	Two-thirds of patients were successfully deescalated, a fifth of patients never restarted biological therapy
Kennedy et al (2016)[46]; retrospective	IBD (N=166; Crohn's disease [n=146; median follow-up 24 months]; ulcerative colitis or IBD unclassified	66.3% with IBD: 66% with Crohn's disease and 75% with ulcerative colitis	Steroid free clinical remission >6 months, >12 months anti-TN F with or without immunomodulators	Need for steroids, surgery, retreatment with biological, hospitalisation, or immunomodulators	NA	3 6.2% for Crohn's disease; 41-8% for ulcerative colitis	55.7% for Crohn's disease; 47.1% for ulcerative colitis	At end of follow-up 51-3% of patients with Crohn's disease relapse; 45% for ulcerative	NS	Approximately a third of patients with IBD flared within 12 months of withdrawal of anti- TNF

	[n=20; [median follow-up 23 months])							colitis		
Papamichael et al (2015)[52] ; retrospective	Crohn's disease (N=100); median 9.7 years	84%	Clinical remission (PGA); with median infliximab 73 months (IQR 1.4-16.2 months)	Need for steroids, surgery or retreatment with anti-TNF, retreatment or need for thiopurine	NA	4% for the discontinuation group	7% for the discontinuation group	12% of patients relapsed at 3 years, 27·2% at 5 years, and 48% at end of follow-up	NS	Lowest rates of relapse reported; many patients included were treated episodically
Dai et al (2014)[53]; prospective	IBD (N=216; Crohn's disease [n=109]; ulcerative colitis or IBD unclassified [n=107]); 12 months	30·6% with IBD: 41% with Crohn's disease and 20% with ulcerative colitis	Clinical remission duration before drug therapy NS	Clinical relapse (Crohn's disease: CDAI rise of >100 and CDAI >150; ulcerative colitis: partial Mayo >3)	NA	21.1% for Crohn's disease; 14% for ulcerative colitis	NA	NA	Median time: 4.8 months for Crohn's disease and 67 months for ulcerative colitis	NA
Farkas et al (2014)[54]; prospective	IBD (N=47; Crohn's disease [n=35]; ulcerative colitis [n=12]); 12 months	81%	Clinical remission (Crohn's disease: CDAI <150 ulcerative colitis: Mayo <2) >12 months infliximab or adalimumab with or without	Clinical relapse (Crohn's disease: CDAI rise of >100 and CDAI >150 points ulcerative colitis: partial Mayo >3)	NA	61.7% for the discontinuation group	NA	NA	NS	Relapse rate combined for ulcerative colitis and Crohn's disease

			immunomodulators							
Chauvin et al (2014)[55]; prospective	Crohn's disease (N=92); median 384 months for the maintenance group; median 55 months for the induction group	100%	Clinical remission (Harvey- Brad shaw Index <4): maintenance group ≥1 year infliximab and immuno-modulators; induction group >8 weeks infliximab and immunomodulators	Clinical relapse	NA	44% for the maintenance group; 22% for the induction group	64% for the maintenance group; 40% for the induction group	NA	Median time 15.9 months for the main-tenance group; 327 months for the induction group	Compared relapse rate after two different infliximab treatment strategies: induction or maintenance for at least 1 year
Molnar et al (2013)[56]; prospective	Crohn's disease (N=121); 12 months	83'6%	Clinical remission (CDAI <150) >52 weeks infliximab or adalimumab with or without immunomodulators	Clinical relapse (CDAI rise >100 and CDAI >150)	NA	45%fort he discontinuati on group	NA	NA	Median time 6 months	Biological therapy was restarted a median of 6 months after anti- TNF discontinuation in almost half of patients with Crohn's disease
Louis et al (2012)[49]; prospective	Crohn's disease (N=115); median 12 months	100%	Steroid-free remission (>6 months); >12 months infliximab and immunomodulators	Clinical relapse (CDAI >250 or CDAI 150-250 with >70 rise from baseline over two consecutive evaluations)	NA	43-9% (SD 5) for the discon-tinuation group	52-2% (SD 5-2) for the discon-tinuation group	NA	Median time 16-4 months	Approximately a half of patients with Crohn's disease treated with at least 1 year of combination therapy relapsed within 1 year of anti-TNF withdrawal

Steenholdt et al (2012)[43]; retrospective	Crohn's disease (n=53); ulcerative colitis or IBD unclassified (n=28); median 17-6 months for the Crohn's disease group; median 28-9 months for the ulcerative colitis group	864% (86'8% with Crohn's disease and 85'7% with ulcerative colitis)	Clinical relapse (PGA and steroid-free stable disease, no fistula secretion or signs of perianal inflammation or complete fistula closure); median infliximab infusions: 3 (IQR Crohn's disease 3-5, ulcerative colitis3-4)	Re-treatment with biological, systemic steroid, or surgery	NA	39% for Crohn's disease; 25% for ulcerative colitis	NA	At end of follow-up 68% of patients with Crohn's disease relapse; 36% for ulcerative colitis	NS	NA

IBD=inflammatory bowel disease. CDAI=Crohn's Disease Activity Index. PGA=patient global assessment. NA=not applicable. NS=not specified. Unless otherwise specified the duration of follow-up was the same at the duration of the RCT and is the same for all participants.

Table 4: Studies of re-treatment with anti-TN F agents

	Participants	Concurrent immunomodulators (%)	Time to relapse	Re-treatment with biological agent(%)	Achieved remission and the time to remission (%)	Adverse effects	Notes
Casanova et al (2017)[51]; retrospective	IBD (N=1055; Crohn's disease [n=731] and ulcerative colitis [n=324])	68% (after biological withdrawal)	Median of 11 months	78%	67% clinical remission at 14 weeks and 75% in clinical remission and 13% partial response at end of follow-up (median follow-up time 19 months)	Allergic reactions (5%)	3% of patients who relapsed went to surgery; similar results were found in patients in deep remission: 78% in clinical remission and 15% partial response at end of follow-up
Reenaers et al (2018)[50]; retrospective	Crohn's disease (n=102)	100% (after biological withdrawal)	Median of 13 months	71%	66% of those without infliximab restart failure (no acute or delayed infusion reaction, non-response, loss of response, or infliximab-	NS	18 patients had major complications a median of 50 months after stopping infliximab; 22 did not restart infliximab or need another biological (follow-up

				related sideeffects); timepoint NS		78 months)
Kennedy et al (2016)[46]; retrospective	IBD (N=166; Crohn's disease [n=146] and ulcerative colitis or IBD unclassified [n=20])	66.3% with IBD: 66% with Crohn's disease and 75% with ulcerative colitis	NS	75% of those with Crohn's disease and 33% of those with ulcerative colitis	93% successful in those with Crohn's disease and 67% successful of those with ulcerative colitis; timepoint NS	NS	40% of patients with Crohn's disease needed steroids and 4% surgery
Monterubbianesi et al (2015)[79]; retrospective	Crohn's disease (N=58)	66%	NS	52%	633% clinical remission; time point NS	Loss of response in 27% and infusion reaction in 10%	NA
Dai et al (2014)[53]; prospective	IBD (N=218; Crohn's disease [n=109]; ulcerative colitis or IBD unclassified [n=107))	30.6% with IBD: 41% with Crohn's disease and 20% with ulcerative colitis	Median of 4'8 months for those with Crohn's disease; median of 6-7 months for those with ulcerative colitis	100% for both groups	783% clinical response (mean 3 months) in those with Crohn's disease; 667% clinical response (mean 3 months) in those with ulcerative colitis	NS	NA
Farkas et al (2014)[54]; prospective	IBD (N =47; Crohn's disease [n=35]; ulcerative colitis [n=12])	81%	NS	NS	81% clinical response in those with Crohn's disease; 54% clinical response in those with ulcerative colitis (2 months)	NS	NA

Chauvin et al (2014)[55]; prospective	Crohn's disease (N=92)	100%	Median of 327 months for the induction group; median of 15-9 months for the maintenance group	80%	89% clinical remission, 72% remained in steroid-free remission (median l.2years[IQR 0.3-2.4])	NS	NA
Brooks et al (2014)[5o]; prospective	Crohn's disease (N=86)	80%	Mean of 7-5 months	86%	93% initial response and 92% in clinical remission after 1 year of follow-up	Neutropenia (in two patients)	NA
Molander et al (2014)[44]; prospective	IBD (N=52; Crohn's disease [n=17]; ulcerative colitis or IBD unclassified [n=35])	71% with Crohn's disease; 86% with ulcerative colitis	NS	88%	93% in clinical remission (3 months); 90% clinical remission (12 months) for both groups of patients	No serious adverse effects	NA
Molnaretal (2013)[56]; prospective	Crohn's disease (N=121)	83.6%	Median of 6 months	100%	547% clinical remission	Mild side-effects in 4% and infusion reaction in 6%	NA
Louis et al (2012)[49]; prospective	Crohn's disease (N=115)	100%	Median of 16.4 months	100%	Before third infliximab infusion: 88% (38/43) clinical remission and 98% (42/43) clinical response	NS	NA

IBD=inflammatory bowel disease. NS=not specified. NA=not applicable.

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