ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 April 26; 11(12): 2582-2854

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

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PUBLICATION DATE
April 26, 2023

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World Journal of Clinical Cases

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World J Clin Cases 2023 April 26; 11(12): 2657-2669

DOI: 10.12998/wjcc.v11.i12.2657

ISSN 2307-8960 (online)

MINIREVIEWS

Exit strategies in inflammatory bowel disease: Looking beyond anti-tumor necrosis factors

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Li J, China; Skok P, Slovenia

Received: January 20, 2023
Peer-review started: January 20, 2023
First decision: February 22, 2023
Revised: March 10, 2023
Accepted: March 29, 2023
Article in press: March 29, 2023
Published online: April 26, 2023

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Abstract

The long-term management of patients with inflammatory bowel disease (IBD) is still a matter of debate, and no clear guidelines have been issued. In clinical practice, gastroenterologists often have to deal with patients in prolonged remission after immunomodulatory or immunosuppressive therapies. When planning an exit strategy for drug withdrawal, the risk of disease relapse must be balanced against the risk of drug-related adverse events and healthcare costs. Furthermore, there is still a dearth of data on the withdrawal of novel biologics, such as the anti-α4β7 integrin antibody (vedolizumab) and anti-IL12/23 antibody (ustekinumab), as well as the small molecule tofacitinib. Models for estimating the risk of disease relapse and the efficacy of retreatment should be evaluated according to the patient's age and IBD phenotype. These models should guide clinicians in programming a temporary drug withdrawal after discussing realistic outcomes with the patient. This would shift the paradigm from an exit strategy to a holiday strategy.

Key Words: Exit strategy; Biologic withdrawal; Drug holiday; Vedolizumab; Ustekinumab; Tofacitinib

Core Tip: Clinicians are still uncertain about whether and when to consider stopping conventional therapies in inflammatory bowel disease (IBD) for fear of disease relapse. Our review aims to shed light on the optimal discontinuation strategies for biologics and the small molecule tofacitinib in IBD.

Citation: Crispino F, Michielan A, Grova M, Tieppo C, Mazza M, Rogger TM, Armelao F. Exit strategies in inflammatory bowel disease: Looking beyond anti-tumor necrosis factors. *World J Clin Cases* 2023; 11(12): 2657-2669
URL: https://www.wjgnet.com/2307-8960/full/v11/i12/2657.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i12.2657

INTRODUCTION

Early initiation of immunosuppressive treatment and rapid escalation of therapy in the course of inflammatory bowel disease (IBD) appear to improve disease outcomes by tightly controlling inflammation[1-3]. However, once remission has been achieved, both clinicians and patients are faced with the thorny issue of the feasibility and timing of discontinuing therapy.

Undoubtedly, there has been a tendency in recent years to continue immunosuppressive treatment indefinitely in IBD patients in remission, fearing the detrimental effects of loss of disease control, impairment of previous drug efficacy, and adverse events after retreatment[4-5]. However, the risk of disease relapse must be balanced against the risk of immunosuppressive-related adverse events, particularly opportunistic infections[6-8] and malignancies[9,10].

In addition to safety issues, the cost of biological therapy must also be considered. The cost of medications represents an increasing proportion of the total cost of IBD treatment and has gradually surpassed the costs of surgery and hospitalization[11]. Thus, as expected, a de-escalation strategy for IBD patients in remission has resulted in significant cost savings, even with the advent of biosimilar drugs[12,13]. Consequently, there are both individual and societal reasons to re-examine the indefinite use of immunosuppressive drugs in IBD patients[14,15]. This is especially true as the number of available therapies has doubled in the last decade with the introduction of novel biologics, such as anti-α4β7 integrin and anti-IL12/23 antibodies, and the approval of small molecules. As a result of this vast treatment landscape, the evaluation of less expensive and safer withdrawal strategies is paramount to providing personalized and appropriate IBD treatment.

SELECTING THE IDEAL CANDIDATE FOR THERAPY WITHDRAWAL

Patient selection must take into account patient demographics and clinical characteristics, as these are crucial when considering discontinuation of IBD therapy. The most predictive factors of relapse after treatment withdrawal are the presence of poor prognostic features, challenging disease control prior to discontinuation, or biochemical disease activity[5,14-17] (Table 1). To date, CRP and fecal calprotectin have been recognized as the best biomarkers for assessing the risk of short-term (< 6 mo) relapse after stopping biologics[18-20]. Using mass spectrometry-based proteomics on the basal serum of Crohn's disease (CD) patients from the STORI trial[5] at the time of infliximab (IFX) discontinuation, Pierre *et al* [21] recently identified two protein panels (15 and 17 proteins) associated with short-term and mid- to long-term relapse (> 6 mo), respectively, reflecting two distinct pathophysiological processes. Notably, the discriminatory probability of these novel biomarkers to predict relapse in CD patients following the discontinuation of anti-tumor necrosis factors (TNF) therapy was superior to that of C-reactive protein (CRP) and fecal calprotectin[22,23].

Furthermore, evidence of mucosal healing at either imaging or endoscopy is a key element associated with a reduced risk of relapse after discontinuation of biologic therapy: Several studies in CD and ulcerative colitis (UC) have shown that relapse rates are higher when anti-TNF is discontinued based solely on clinical remission, without taking into account endoscopic remission[14,15] (Table 1).

Some studies have also shown that CD patients who achieved transmural healing, as assessed by either bowel ultrasound or magnetic resonance imaging, had a lower risk of relapse after drug discontinuation and better 1-year clinical outcomes than those with endoscopic mucosal healing[24,25] (Table 1). This finding is not surprising, as it is consistent with evidence suggesting that transmural healing is associated with improved clinical outcomes and reduced long-term disease complications compared to mucosal healing, with some suggesting that it should be considered a deeper therapeutic target in the treatment of CD[26].

There is also a growing body of evidence demonstrating the link between histologic healing and a lower risk of clinical relapse in UC patients[27-29], although not all research points in this direction[30].

Table 1 Predictive factors for disease recurrence after therapy withdrawal

Poor disease prognostic features	CD/UC: Young age at diagnosis and male sex
	CD: Ileal, colonic or perianal disease; stricturing/penetrating disease
	UC: Pancolitis
Challenging disease control before withdrawal	Many relapses requiring add-on steroids
	Anti-TNF escalation while already on
	Need for surgery or anti-TNF post-operative prophylaxis
Biochemical disease activity	High CRP levels
	Elevated fecal calprotectin
	Elevated white cells or neutrophil count
	Low hemoglobin levels
Endoscopic disease activity	No mucosal healing
Radiological CD activity	No transmural healing
IFX trough levels	High IFX trough levels in monotherapy
	Low IFX trough levels in combination therapy with an imunomodulator

CD: Crohn's disease; UC: Ulcerative colitis; TNF: Tumor necrosis factor; CRP: C-reactive protein; IFX: Infliximab.

Infliximab (IFX) trough levels have also been shown to be inversely associated with the risk of relapse, depending on whether IFX monotherapy or immunomodulator combination therapy is discontinued. Low IFX trough concentrations predict a lower risk of relapse when the drug is discontinued[5, 31], suggesting that patients in whom anti-TNF was the main contributor to remission are at a higher risk of relapse after discontinuation. Conversely, in patients receiving combined IFX and immunomodulator therapy, a higher IFX trough concentration predicts a lower relapse rate when the immunomodulator is withdrawn[32] (Table 1).

Several pharmacogenetic studies have shown an association between certain genetic polymorphisms, particularly those in the anti-TNF pathway, and response to biologic therapy[33]. It is therefore reasonable to assume that there is also a correlation with the outcomes of exit strategies, giving the genetic biomarkers a role in the selection of the most suitable IBD patient for therapy withdrawal.

To date, there are no recommendations for gene searches as part of therapy optimization or discontinuation. However, they seem very promising for a future tailored approach.

Although the predictors of the risk of relapse after discontinuation of therapy are well known, they may not be sufficiently weighted at the individual patient level. The landmark STORI trial, conducted on CD patients on combination therapy who discontinued anti-TNF, identified a predictive model (corticosteroid use 6–12 mo prior to anti-TNF withdrawal, no previous surgery, male sex, hemoglobin < 145 g/L, leukocyte count > 6 × 10^9/L, Crohn's Disease Endoscopic Index of Severity score > 0, CRP ≥ 5 mg/L, IFX trough level ≥ 2 mg/L, and fecal calprotectin ≥ 300 μg/g), in which patients with fewer than 3 risk factors had a significantly lower risk of relapse within 1 year than patients with 4, 5-6, or more than 6 factors[5]. However, when validated in an individual participant data meta-analysis of 1317 CD patients in remission, it showed poor discriminative ability (C-statistic, 0.51). The model performance for the risk of relapse after anti-TNF withdrawal improved (C-statistic, 0.59) when other risk factors were considered (clinical symptoms at withdrawal, no concomitant immunosuppressants, adalimumab, second-line anti-TNF, younger age at diagnosis, smoking, upper gastrointestinal tract involvement, younger age at withdrawal, longer disease duration, and C-reactive protein), and when fecal calprotectin was added to them (C-statistic, 0.63)[34]. It would be interesting to investigate whether this clinical score would be superior or complementary to the aforementioned proteomic biomarkers from the study by Pierre *et al*[21]. Moreover, it is worth noting that none of these scores have ever accounted for radiological activity in CD or histologic activity in UC.

In conclusion, stable deep remission (clinical, biochemical, and endoscopic remission) is the key requirement when considering discontinuation of therapy. It is expected that radiological and histological remission, along with novel biochemical and genetic biomarkers, will soon contribute to better patient profiling for a tailored approach.

DISCUSS EXIT STRATEGIES WITH THE PATIENT

The decision to discontinue treatment should be shared with the patient, who should be advised of the pros and cons. A given risk of relapse over time may be acceptable for one patient but not for another; therefore, individual patient preference is critical in formulating a treatment exit strategy.

An interesting survey found that about one-third of patients would not accept any de-escalation if it increased the risk of disease flare-up, and nearly half of them were more concerned about CD activity than the risk of treatment-related malignancy[14,35].

Evidence-based estimates of the risk of relapse after withdrawal and the efficacy of retreatment are discussed separately for each drug in the next section and are summarized in Table 2.

WITHDRAWAL, DE-ESCALATION AND RE-TREATMENT

Research results on immunosuppressive drug withdrawal, de-escalation, and retreatment are presented and discussed in the following subsections. Discontinuation of 5-aminosalicylate in UC patients is beyond the scope of this review and will not be discussed.

Immunomodulator monotherapy

Several randomized controlled trials (RCTs) and observational studies have shown that the withdrawal of immunomodulator monotherapy (thiopurine in CD/UC or methotrexate in CD) is associated with a substantial risk of relapse (30% at 2 years and 50%-75% at 5 years)[15]. A multicenter, double-blind, non-inferiority withdrawal study on CD patients showed that such high relapse rates occur even after long periods (> 3-5 years) of steroid-free clinical remission[36,37]. More importantly, similar recurrence rates (CD 30.8% and UC 58.1% within a median of 15 mo) were observed in a recent prospective study of IBD patients who discontinued azathioprine (AZA) after at least 5 years of treatment, despite being in deep extended remission (normal clinical, endoscopic, fecal calprotectin, CPR, and histologic indexes)[38]. However, the increased risk of potential drug-related lymphoma after long-term immunosuppressive therapy must be considered (incidence rate 0.90 per 1000 patient-years)[9]. Therefore, many authors suggest that the risks and benefits of continued immunomodulatory therapy should be discussed with the patient at least after 3-5 years of stable remission, along with the suggestion that a period off therapy would significantly reduce the risk of lymphoproliferative disorders[14,15].

There is a paucity of evidence on the efficacy of retreatment for relapse after immunosuppression withdrawal, and no study has ever evaluated AZA metabolite concentrations, which may be important in predicting relapse after discontinuation or de-escalation of immunosuppressive monotherapy. Recapture data were reported by Treton *et al*[42] in a small study in which 23 of 32 CD patients who relapsed after AZA withdrawal were retreated with AZA, and all but one achieved clinical remission at a median follow-up of 28 mo[34]. Similarly, high AZA recapture rates were demonstrated in a subsequent multicenter retrospective cohort study in which 74% of CD and 92% of UC patients who resumed AZA at the time of relapse regained and maintained clinical remission, although mostly in combination with systemic steroid re-induction[39]. It should be noted that in both studies, besides the need for corticosteroids, a non-negligible percentage of patients who discontinued AZA required biologic therapy, hospitalization, and/or resectional surgery.

As regards immunosuppressive de-escalation, there are no data on the efficacy and safety of low-dose immunomodulators as monotherapy in IBD. A dose-dependent relationship between AZA and non-Hodgkin's lymphoma and 6-thioguanine nucleotide (6-TGN) concentrations and skin cancer in transplant patients has been shown[40,41].

Anti-TNF monotherapy

Withdrawal of anti-TNF monotherapy (IFX or adalimumab) is associated with a high risk of relapse (between 30%-40% at 6 mo/1 year and > 50% beyond 2 years)[14,15], which is quite significant given that the clinical benefits of discontinuing anti-TNF, such as reduced risk of infection or malignancy, are hypothetical as no controlled study has ever been conducted. The aforementioned STORI trial, which was designed to assess the prevalence of clinical relapse after discontinuation of anti-TNF in quiescent CD while on immunosuppressants, revealed that 44% and 52.2% of patients relapsed one year and two years after discontinuation, respectively[5]. A subsequent meta-analysis by Gisbert *et al*[47] showed that the overall risk of relapse after discontinuation of anti-TNF was 44% for CD and 38% for UC[42].

The more recent STOP-IT RCT showed significantly lower relapse-free survival rates at 48 wk in CD patients who discontinued IFX compared to those who continued IFX (51% *vs* 100%), regardless of deep remission at baseline[43]. In UC patients, the HAYABUSA RCT also showed a significant difference in clinical remission rates (80% *vs* 54%) between the IFX continuation group and the IFX discontinuation group at 48 wk after randomization, even after adjustment for the Mayo endoscopic subscore[44]. The studies that also focused on treatment reported favorable recapture rates (up to 80%-90%) with an acceptable rate of infusion-related reactions[5,40,42]. In terms of efficacy and safety, such findings contrast with the proven increased risk of anti-drug antibody (ADA) development after retreatment[45,

Table 2 Summary of the available evidence for withdrawal of immunosoppressive drugs in inflammatory bowel disease

Drug	Minimum therapy duration before withdrawal, yr	Estimated risk of disease relapse after withdrawal	Therapeutic drug monitoring before withdrawal	Estimated efficacy of re-treatment	De-escalation
Immunomodulators (thiopurine in CD/UC or methotrexate in CD)	3-5	30% by 2, 50%–75% by 5 yr	No data available	75%-90% (often in combination with steroids)	Possible in combination therapy
Anti-TNF	1-2	30%–40% at 6 mo/1 year and > 50% by 2 yr	Possible	80%-90%	Possible (TDM suggested)
Vedolizumab	No data available	65% by 1.5 yr	No data available	50%-65%	No IBD data available beyond 8 wk
Ustekinumab	No data available	59.5% by 1 yr in registrative studies	No data available	39.2%-64% in registrative studies	No IBD data available beyond 12 wk
Tofacitinib	No data available	65 % by 6 mo, 80 % by 1 yr in registrative studies	No data available	75% after 2 months and 50 % after 3 yr in registrative studies	No IBD data available for dosage < 5 mg bid

CD: Crohn's disease; UC: Ulcerative colitis; TDM: Therapeutic drug monitoring.

46], which is associated with infusion-related reactions and long-term loss of response due to faster clearance and lower drug concentrations[47]. Nevertheless, the effect of concomitant immunomodulators, which have been widely used in most studies during drug holidays and retreatment, cannot but be considered since several studies have shown that they are associated with reduced immunogenicity effects[48-49]. The recent REGAIN study showed that early detection of ADAs (week 0 and week 4) after IFX reintroduction can predict subsequent failure and infusion reactions, regardless of the reason for prior discontinuation[50].

Both decreasing the dose of anti-TNF and lengthening the interval between doses have been proposed to de-escalate the drug prior to withdrawal. Whether de-escalation should be guided by clinical/biochemical assessment or by therapeutic drug monitoring (TDM) is still a matter of debate because of the controversial nature of the available results. In the TAXIT study, dose reduction in clinically stable patients with supra-optimal IFX levels (> 7 mg/L) did not lead to flare-ups or elevated inflammatory markers compared to patients whose dosing was based on clinical symptoms; this resulted in significant cost savings[12]. Furthermore, in a subsequent study, trough levels before or after anti-TNF interval prolongation were not significantly associated with the success of the spaced schedule [51], but in a French study, de-escalation based on trough levels was associated with a lower risk of relapse[52]. In any case, it remains unclear whether lower anti-TNF doses lead to fewer anti-TNF-related adverse events in both the IBD and rheumatological fields[53-56].

Combined immunomodulatory and anti-TNF therapy

Withdrawal of immunomodulators in CD patients treated with combination therapy for more than 6 months does not increase the relapse rate compared to continued combination therapy[14,15], as recently confirmed by the SPARE trial[57]. On the other hand, the risk of relapse over 1 to 2 years is between 40% and 50% when the biologic is stopped[5,40].

A topical review by the European Crohn's and Colitis Organization (ECCO) suggests that the decision to discontinue the immunomodulator should also be guided by the anti-TNF TDM[14].

A single small randomized study has found that AZA dose reduction, but not withdrawal, resulted in similar IFX trough levels and relapse rates in patients receiving combination therapy, also supporting a dose de-escalation strategy[58].

Anti-α4β7 integrin antibody: Vedolizumab

Only one observational study has evaluated the risk of relapse after vedolizumab withdrawal, showing a relapse rate of 64% at 18 mo after therapy discontinuation[59]. Although there is no evidence that a longer duration of biologic therapy promotes a lower risk of relapse, it should be noted that most anti-TNF withdrawal studies included patients treated with IFX or adalimumab for at least 2 years, whereas the median duration of vedolizumab therapy in this study was only 14.5 mo. This finding is even more significant when considering vedolizumab's slow onset of action during the induction phase. In addition, most of the patients in this study were previously treated with immunomodulators and anti-TNF, which was not the case in patients who discontinued anti-TNF. Following the reintroduction of vedolizumab, 24 of 61 patients who experienced a clinical relapse were retreated with vedolizumab, and as many as two-thirds of them achieved steroid-free clinical remission at week 14 and during the 11-

month follow-up period. However, it should be noted that patients who were not retreated with vedolizumab (60.7%) underwent surgery or started other biologics, mostly ustekinumab.

In the GEMINI long-term safety study, CD patients on drug holidays for up to one year were retreated with VDZ every 4 wk and experienced clinical benefits: Patients with early withdrawal from GEMINI 2 had an improved remission rate (from 9% to 48% at week 24), while patients who completed the GEMINI 2 maintenance phase on a placebo improved from 53% to 63% at week 52[60]. In this cohort, the percentage of patients who developed ADAs was consistent regardless of the duration of the drug holiday. A subsequent study evaluating the immunogenicity of vedolizumab showed that treatment interruption resulted in a significant increase in the rate of ADAs compared to continuous therapy (19.4% *vs* 2.4%), which was lower when concomitant immunomodulators were used (0.8% *vs* 10.8%)[61]. However, no association between immunogenicity and infusion□related reactions was observed, consistent with previous reports[62,63]. Given that ADAs also do not appear to play a major role in the efficacy of vedolizumab[64], even in patients who discontinue and later restart treatment[65, 66], the addition of an immunosuppressant upon resumption of vedolizumab seems to be unnecessary.

Regarding vedolizumab de-escalation, Vermeire *et al*[67] recently reported that changing the dosing interval from 4 to 8 wk maintained clinical efficacy with high persistence rates after 2 years of follow-up. These results are consistent with those from registrational clinical trials[68,69] and a previously published vedolizumab dose-lengthening study in a subset of patients from the GEMINI study[70], especially when accounting for the unproven exposure-efficacy relationship for vedolizumab in the maintenance phase[71].

Further data are needed to identify de-escalation strategies for vedolizumab, including extending the dosing interval beyond 8 wk, given that current evidence is limited.

Anti-IL12/23 antibody: Ustekinumab

There is a paucity of data on ustekinumab withdrawal and retreatment in IBD, given that it was originally used as second- and third-line therapy in refractory and usually complex patients. In the UNIFI trial, 42 UC patients, among those who responded to ustekinumab induction and were randomized to placebo at maintenance, were retreated with subcutaneous ustekinumab every 8 wk during the long-term extension study[72]. Of these, 16 of the 25 patients (64.0%) who had clinical symptoms successfully regained clinical remission after 16 wk of dose adjustment. Although the incidence of ADAs was higher in the placebo dose adjustment group (13.2%), the safety profile was consistent with that observed in patients randomized to ustekinumab maintenance[73]. Good recapture rates (39.2%) were also observed in the IM-UNITI study, in which 51 CD patients randomized to placebo after responding to induction were retreated with subcutaneous ustekinumab every 8 wk after meeting loss-of-response criteria[74]. This finding is consistent with other studies that have also evaluated the efficacy of intravenous reinduction of ustekinumab in CD patients who lost response to ustekinumab maintenance therapy alone[75].

To gain a sense of the relapse and recapture rates following ustekinumab withdrawal and retreatment, it is also worth looking at the larger data set of patients with moderate to severe plaque psoriasis. In the phase 3 PHOENIX 1 trial, the median time to loss of 75% of the Psoriasis Area and Severity Index (PASI 75) was 15 wk after ustekinumab withdrawal. Twelve weeks after retreatment, most patients achieved a PASI 75 response[76]. Similar findings were observed in the ACCEPT study, where the median time to clinical relapse was 14.4-18.1 wk and recapture rates were 80-90% at 12 wk after the initial retreatment dose[77]. An eight-year observational multicenter study also showed very low cumulative probabilities of being psoriasis relapse-free, with a median time to loss of PASI 50 after treatment withdrawal of 24 wk[78], in line with another previous observational study[79].

As for treatment de-escalation, there are no criteria to decide whether IBD patients should receive ustekinumab every 8 wk or every 12 wk (Q12W)[80,81]. For instance, in the SUSTAIN study, a history of perianal surgery was the only reason CD patients received ustekinumab every 8 wk. In this study, 6.2% of patients with stable remission had their ustekinumab dosage reduced from every 8 wk to every 12 wk, and 65.2% of these patients maintained remission over time[82]. A recent prospective study investigated the clinical response rates in psoriatic patients with extended ustekinumab maintenance dosing intervals (up to every 16-24 wk) and found that a subset of patients with early, high-level responses while on Q12W therapy were more likely to extend the dosing interval and maintain response without experiencing an increase in ADA development[83].

JAK inhibitors: Tofacitinib

The OCTAVE Sustain study demonstrated that clinical response and remission were maintained in nearly one-third and one-fifth of placebo-treated UC patients after interruption of tofacitinib 10 mg twice daily (b.d.) at 24 and 52 wk, respectively. The median time to treatment failure after tofacitinib withdrawal was 169 and 123 days for induction remitters and induction responders, respectively[84]. Following tofacitinib retreatment, clinical response and remission rates were 74.0% and 39% after 2 mo and 37.4% and 48.5% after 36 mo, respectively. The predictors of recapture efficacy following retreatment were less severe disease at the time of retreatment, increased age, no prior use of immunosuppressants, and no use of corticosteroids at induction study baseline, regardless of prior anti-TNF status[72].

The OCTAVE clinical trials also evaluated the effect of dose reduction on the efficacy of tofacitinib. Among patients who received a high dose of tofacitinib (15 mg b.d. or 10 mg b.d.) in OCTAVE Induction 1 and 2 and re-randomization to receive tofacitinib 5 mg b.d. in OCTAVE Sustain, 32.4% of patients were in remission at week 52[85]. An additional post-hoc analysis evaluated the effect of dose reduction in patients in remission treated with tofacitinib 10 mg b.d. for 52 wk, followed by 5 mg b.d. in OCTAVE Open. After tofacitinib dose reduction, clinical response was maintained in 92.4% and 84.1% of patients at months 2 and 12, respectively[86].

The RIVETING trial also showed that most patients in stable remission on tofacitinib maintenance therapy at 10 mg b.d. maintained remission following dose de-escalation to 5 mg twice daily[87]. These data are consistent with previous observational and long-term extension studies of tofacitinib discontinuation and dose reduction in rheumatoid arthritis[88,89].

OPTIMAL MONITORING AFTER THERAPY WITHDRAWAL

Although no specific study has evaluated the optimal strategy for monitoring disease activity after treatment withdrawal, noninvasive markers (ESR, CRP, and fecal calprotectin) may be a more reliable tool than clinical activity[90]. The efficacy of biomarker-driven monitoring in IBD was also demonstrated in the CALM trial, in which patients on tight control had superior clinical and endoscopic outcomes than those managed with a symptom-driven strategy[19].

In particular, fecal calprotectin demonstrated better performance compared to CRP[92], and its elevation (with different cut-offs depending on the study) seems to precede the short-term clinical and endoscopic relapse in patients who discontinued anti-TNF therapy[18-20]. Buisson *et al*[91] also found that calprotectin levels were higher in patients who relapsed after therapeutic de-escalation (which included both a reduction in the drug dose and an increase in the interval between infusions).

Intestinal ultrasound has gained ground in the management of IBD patients due to its reproducibility, lack of risk, and general patient acceptance[92]. Theoretically, these features make ultrasound very appealing for monitoring patients with IBD; however, to date, no study has been undertaken to investigate its role in this specific setting.

The optimal timing for disease monitoring after therapy withdrawal remains to be determined.

As in the HAYABUSA study, the difference between patients who discontinued anti-TNF and those who did not was significant as early as 16 wk after withdrawal, and relapse seems to be more likely to occur in the first months after treatment discontinuation[44].

Based on this scarce evidence, patients discontinuing biologic or immunosuppressive therapy should be closely monitored for disease activity, especially during the first 6-12 mo after therapy withdrawal. Monitoring should include a thorough clinical assessment and repeated measurements of noninvasive biomarkers[14]. Current clinical practice suggests that in the event of biomarker elevation and/or symptom recurrence, a repeat endoscopic or radiological assessment should be performed promptly to rapidly diagnose recurrence and re-establish disease control. No ad hoc studies have examined the role of specific therapeutic interventions (*i.e.*, concomitant drug optimization or new drug introduction) as maintenance therapy after biologic withdrawal.

CONCLUSION

The management of IBD patients in remission remains an important research gap, as stated in the ECCO guidelines[93]. First, as remission is an evolving concept, it should be noted that early studies only included patients in steroid-free clinical remission, without considering biochemical and/or endoscopic remission. Second, the duration of remission itself before therapy discontinuation remains controversial. Little is also known regarding the optimal therapy duration prior to withdrawal: It is interesting to note that, despite the fact that longer durations of immunosuppressive therapy have not been shown to reduce the risk of relapse, the majority of studies included patients treated with biologics for just 1-2 years. Furthermore, although there is a large body of evidence on anti-TNF, there is still very limited real-world data on the withdrawal of novel biologics, such as the anti- α4β7 integrin antibody (vedolizumab) and anti-IL12/23 antibody (ustekinumab), and the small molecule tofacitinib.

Future studies should focus on resolving these issues and identifying predictive factors for relapse after therapy withdrawal in the perspective of a personalized approach for IBD patients.

To date, immunomodulators, anti-TNF, and vedolizumab have demonstrated good recapture rates after retreatment. In light of this evidence, the concept of a holiday strategy/therapy cycling (*i.e.*, planned therapy interruption, close monitoring, and prompt resumption of therapy before the onset of clinical symptoms), rather than a definitive exit strategy, appears to be more realistic when discussing long-term management with patients.

FOOTNOTES

Author contributions: Crispino F, Michielan A designed the study; Grova M, Tieppo C, Mazza M, Rogger TM, Armelao F analysed and interpreted data; Crispino F, Grova M, Michielan A drafted the manuscript; Tieppo C, Mazza M, Rogger TM study supervision; Armelao F critically revised the manuscript for important intellectual content; Crispino F, Grova M, Armelao F, Tieppo C, Mazza M, Rogger TM, Michielan A approved the manuscript.

Conflict-of-interest statement: Dr. Michielan has nothing to disclose.

Country/Territory of origin: Italy

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S-Editor: Ma YJ
L-Editor: A
P-Editor: Chen YX

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