**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 91615

**Manuscript Type:** MINIREVIEWS

**Discontinuation of therapy in inflammatory bowel disease: Current views**

Meštrović A *et al.* Discontinuation of therapy in IBD

Antonio Meštrović, Marko Kumric, Josko Bozic

**Antonio Meštrović,** Department of Gastroenterology, University Hospital of Split, Split 21000, Croatia

**Marko Kumric, Josko Bozic,** Department of Pathophysiology, University of Split School of Medicine, Split 21000, Croatia

**Author contributions:** Meštrović A, Kumric M and Bozic J wrote the manuscript. All authors have read and approve the final manuscript.

**Corresponding author: Josko Bozic, MD, PhD, Associate Professor,** Department of Pathophysiology, University of Split School of Medicine, Soltanska 2, Split 21000, Croatia. josko.bozic@mefst.hr

**Received:** December 31, 2023

**Revised:** February 25, 2024

**Accepted:** March 14, 2024

**Published online:**

**Abstract**

The timely introduction and adjustment of the appropriate drug in accordance with previously well-defined treatment goals is the foundation of the approach in the treatment of inflammatory bowel disease (IBD). The therapeutic approach is still evolving in terms of the mechanism of action but also in terms of the possibility of maintaining remission. In patients with achieved long-term remission, the question of de-escalation or discontinuation of therapy arises, considering the possible side effects and economic burden of long-term therapy. For each of the drugs used in IBD (5-aminosalycaltes, immunomodulators, biological drugs, small molecules) there is a risk of relapse. Furthermore, studies show that more than 50% of patients who discontinue therapy will relapse. Based on the findings of large studies and meta-analysis, relapse of disease can be expected in about half of the patients after therapy withdrawal, in case of monotherapy with aminosalicylates, immunomodulators or biological therapy. However, longer relapse-free periods are recorded with withdrawal of medication in patients who had previously been on combination therapies immunomodulators and anti-tumor necrosis factor. It needs to be stressed that randomised clinical trials regarding withdrawal from medications are still lacking. Before making a decision on discontinuation of therapy, it is important to distinguish potential candidates and predictive factors for the possibility of disease relapse. Fecal calprotectin level has currently been identified as the strongest predictive factor for relapse. Several other predictive factors have also been identified, such as: High Crohn's disease activity index or Harvey Bradshaw index, younger age (< 40 years), longer disease duration (> 40 years), smoking, young age of disease onset, steroid use 6-12 months before cessation. An important factor in the decision to withdraw medication is the success of re-treatment with the same or other drugs. The decision to discontinue therapy must be based on individual approach, taking into account the severity, extension, and duration of the disease, the possibility of side adverse effects, the risk of relapse, and patient’s preferences.

**Key Words:** Inflammatory bowel disease; Therapy discontinuation; Therapy de-escalation; Ulcerative colitis; Crohn’s disease

Meštrović A, Kumric M, Bozic J. Discontinuation of therapy in inflammatory bowel disease: Current views. *World J Clin Cases* 2024; In press

**Core Tip:** Tailoring treatment for inflammatory bowel disease (IBD) hinges on timely drug initiation aligned with treatment objectives. While therapy approaches evolve, achieving and sustaining remission prompts discussions on de-escalating or halting treatment, weighed against long-term therapy risks. With each IBD drug category, relapse risks persist post-discontinuation, impacting over 50% of patients. Withdrawal following combination therapies shows prolonged relapse-free periods, yet randomized trials on medication cessation are limited. Identifying relapse predictors and suitable candidates is pivotal. Re-treatment success underpins therapy withdrawal decisions. Individualized assessments, considering disease severity, duration, side effects, relapse risk, and patient preferences all guide prudent discontinuation choices.

**INTRODUCTION**

Inflammatory bowel disease (IBD) is characterized by chronic, lifelong intestinal inflammation, often displaying alternate periods of remission and relapse[1,2]. Clinically, we distinguish two subtypes of IBD: Ulcerative colitis (UC) and Crohn’s disease (CD). The etiology of IBD is ambiguous and is considered a combination of genetic, environmental, dietary, microbial, and immunological factors. While the exact origin of the disease remains uncertain, both UC and CD are characterized by the presence of common pathogenesis resulting from an unregulated immune response to antigenic components of the normal commensal microbiota found within the intestine[3].

IBD globally impacts various age groups with a rising incidence in developing countries, posing a significant strain on healthcare systems[4]. It commonly manifests during adolescence or childhood, with around a quarter of patients experiencing onset before the age of 20[5,6]. Although IBD predominantly affects young adults, it can occur at any age. Approximately 20% of children will present with IBD before reaching 10 years of age, and approximately 5% will present even before reaching 5 years of age, showing a varied age range for its occurrence[5,6]. As IBD is a chronic disease which usually appears at a young age, it implies the need for long-term treatment, often accompanied with high financial costs.

The treatment of IBD has evolved in recent decades. The increased introduction of therapy still represents the basis of a rational approach to the treatment of each IBD patient individually, contributing to the severity and extension of the disease[7,8]. Treatment includes anti-inflammatory drugs, immunomodulators and, most recently, biological therapy, with the introduction of small molecule therapy several years ago[7,8]. The field of IBD is very attractive to drug researchers, which is evident in numerous ongoing clinical studies exploring new medications primarily targeting immune response mechanisms. This underscores the persistent presence of patients who are facing challenges in achieving and sustaining adequate remission, partly due to the loss of response to the treatment. Traditionally, treatment goals centred on clinical remission, inflammation reduction, and mucosal healing. However, recent focus has shifted towards the overarching objective of enhancing quality of life, recognizing the substantial impact of IBD on both physical and mental well-being[9,10].

For certain IBD patients, the treatment efficiently keeps them in long-term remission, posing a dilemma for clinicians on the necessity and duration of continued treatment. However, current guidelines do not anticipate when therapy should be discontinued[7,8]. Furthermore, the continuation of biological treatment for an indefinite time is encouraged, with the aim of maintaining remission for as long as possible[7,8].

Weighing the possibility of relapse and lack of response to reintroduction of therapy against the risk of side effects such as infections and the risk of inducing malignant diseases due to prolonged use of immunomodulators and immunosuppressive therapy is crucial when considering the possible cessation of treatment. Apart from health risks, the financial aspect of treatment is also relevant. The continuous introduction of advanced medications incurs expenses for the healthcare system, which now surpass the costs associated with surgical procedures and hospital stays[11-14].

The outlined complexities underscore the necessity for a tailored approach to treating IBD patients—one that aligns with medical and financial rationale while also meeting the patient's needs and preferences.

***Therapy goals in the treatment of IBD***

The International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) in 2021 updated the previous goals for the treatment of IBD from 2015, known as the Initiative to Select Therapeutic Targets in Inflammatory Bowel Diseases (STRIDE)[9,10]. STRIDE represents a treat-to-target strategy based on evidence and consensus, which foresees an individual approach to patients according to local possibilities, all with the aim of improving treatment outcomes[9,10]. A systematic review included 435 relevant papers from a pool of 11278 manuscripts[10]. The original STRIDE recommendations (STRIDE I) defined the following important treatment goals: Clinical response and remission, endoscopic healing, and normalization of C-reactive protein (CRP, or rate of erythrocyte sedimentation rate) and calprotectin[9].

STRIDE II reaffirmed these goals while adding long-term objectives like absence of disability, improvement in quality of life, and maintaining normal growth in children[10]. Improvement in symptoms and normalization of inflammatory parameters in serum (CRP/erythrocyte sedimentation rate) and stool (fecal calprotectin) are proclaimed short-term treatment goals[10]. However, transmural healing in CD and histological healing of the mucosa in UC are not considered final treatment goals, but represent a measure of the magnitude of remission[10].

The absence of disability and normalization of health-related quality of life is the long-term goal of treatment, according to the IOIBD recommendations[10]. However, it should be emphasized that the quality of life should be the aim in each phase of treatment. The treatment goals are summarized in Table 1, with a strong recommendation to reassess therapeutic approaches if these goals are not achieved.

***Exit strategies in specific therapeutic approaches***

In 2017, a consensus expert panel convened by the European Crohn’s and Colitis Organization gave practical instructions for exit strategies in the treatment of IBD[11]. The likelihood of relapse with stopping a specific class of IBD therapy was also reviewed[11].

It is important to emphasize that each major class of IBD medications, whether used alone or combined (such as 5-aminosalicyclates, immunomodulators, biologic agents), confers a risk of relapse following reduction or discontinuation of treatment[11]. An individualized approach, involving shared decision-making with patients, is crucial. Decisions on discontinuation should consider relapse risks and treatment effectiveness upon re-initiation.

In particular, the actual disadvantage of withdrawal should not be recognized by the rate of relapse after discontinuation itself, but by the increase in the rate of relapse over the rate of relapse with continued therapy, because a considerable number of patients may still relapse even if therapy is continued[15].

***5-Aminosalicylates***

5-Aminosalicylates (5-ASA) are the cornerstone therapy for patients with mild to moderate UC[8]. Furthermore, it is estimated that 88%-97% of patients receive 5-ASA therapy within one year of the initial diagnosis, and 60%-87% continue to use it in the following 10 years[16,17]. 5-ASA is a widely prescribed drug and accounts for 25% of the total cost of treatment in patients with UC[18,19].

Contrary to the European Crohn’s and Colitis Organisation (ECCO) guidelines, 5-ASA are also frequently prescribed drugs in the treatment of CD[7]. Moreover, one-third of patients with CD receive long-term therapy with 5-ASA, despite the lack of proven benefit[7,20-22]. On the other hand, in UC, 5-ASA have been proven successful as well-tolerated drugs with a high safety profile[8]. The role of 5-ASA in the prevention of colorectal cancer, possibly due to its potential direct chemoprotective effect, should be especially highlighted[23].

A meta-analysis of 31 observational studies encompassing 2137 cases of colorectal neoplasia, 76% of which were cancer, revealed that therapeutic doses of 5-ASA were significantly associated with reduced neoplasia in UC [risk ratio (RR) 0.54, 95% confidence interval (95%CI): 0.38-0.64], but this effect was not observed in patients with CD (RR 0.76, 95%CI: 0.43-1.33). Notably, there was no observed benefit with sulfasalazine[24]. Additionally, a separate systematic review and meta-analysis involving 26 observational studies, incorporating 15460 subjects, highlighted the chemopreventive effect of 5-ASA on colorectal cancer (excluding dysplasia)[25]. This effect exhibited significance exclusively in clinical studies (OR = 0.51; 95%CI: 0.39-0.65) and among patients diagnosed with UC (OR = 0.46, 95%CI: 0.34-0.61). Moreover, the protective effect against colorectal cancer was notably more pronounced with a mesalazine dosage of 1.2 g/d compared to dosages below 1.2 g/d[25].

Ardizzone *et al*[26] conducted a comparison of 12-month relapse rates concerning the duration of remission before therapy withdrawal. Patients who had sustained remission for more than 2 years before discontinuing 5-ASA did not exhibit a significantly higher relapse rate compared to those who continued treatment. Conversely, patients in remission for 1-2 years prior to 5-ASA withdrawal demonstrated a notably higher relapse rate than the continuation group (49% *vs* 23%). The authors concluded that maintaining 5-ASA treatment is essential for patients who have been in remission for less than 2 years.

Regarding topical (rectal) 5-ASA therapy, existing studies provide compelling evidence. Six randomized clinical trials collectively revealed higher relapse rates in the placebo group vs the 5-ASA treatment group using topical monotherapy[27-32]. Reported relapse rates in the placebo group ranged from 52% to 85% at 12 months and up to 91% at 24 months. Conversely, relapse rates among patients continuing 5-ASA ranged from 20% to 48% at 12 months and reached 55% at 24 months. Authors across all studies uniformly concluded that discontinuing topical therapy in distal UC significantly increased the likelihood of disease relapse. Although studies analyzing dose de-escalation are lacking, reducing the frequency of administration is commonly practiced upon achieving remission[8].

Recent American Gastroenterological Association guidelines for managing moderate to severe UC propose the possibility of discontinuing 5-ASA therapy in patients achieving remission with biologic agents, immunomodulators, or tofacitinib[33]. A retrospective analysis utilizing two national databases in Denmark and the United States, comprising 3178 patients, compared adverse events among individuals who ceased oral 5-ASA within 90 d of commencing anti-tumor necrosis factor (TNF) therapy with those who maintained 5-ASA. Results indicated that discontinuing 5-ASA did not elevate the risk of adverse clinical events, corticosteroid usage, hospitalization, or surgery in either the United States or Danish cohort[34].

Moreover, Singh *et al*[35] conducted a pooled analysis of individual participant data from five infliximab and golimumab trials in UC, encompassing 2183 patients treated with infliximab or golimumab (78.6% receiving 5-ASA), aiming to evaluate whether concurrent 5-ASA use influences clinical outcomes in these patients. Their findings indicated that the concurrent use of 5-ASA did not correlate with increased odds of achieving clinical remission or mucosal healing. These outcomes remained consistent across trials for both induction and maintenance therapies and across infliximab and golimumab treatments[35]. Similarly, a retrospective observational cohort study focusing on vedolizumab, a monoclonal antibody targeting α4β7 Leukocyte integrin in UC patients, arrived at the same conclusion. Ma *et al*[36] reported that concomitant 5-aminosalicylate use among individuals treated with vedolizumab did not demonstrate significant differences in achieving clinical or endoscopic remission, sustained vedolizumab use, or secondary loss of response.

In general, discontinuing oral 5-ASA as a standalone therapy tends to result in a higher relapse rate. When considering the withdrawal of 5-ASA in UC patients, it’s crucial to approach it on a case-by-case basis, involving the patient in decision-making. This decision should hinge on the presence or absence of specific risk factors. However, for UC patients displaying high adherence to the drug, experiencing a mild disease course, showcasing low levels of fecal calprotectin, and/or demonstrating complete mucosal healing, a reduction in the maintenance dose of 5-ASA could be contemplated[8]. Conversely, patients diagnosed with left-sided and extensive colitis typically anticipate higher relapse rates, and these individuals might benefit from a higher maintenance dose of therapy.

***Immunomodulators***

As widely acknowledged, ECCO guidelines recommend thiopurine monotherapy to sustain remission in individuals with steroid-dependent UC or those unable to tolerate 5-ASA[8]. Additionally, thiopurines are endorsed for sustaining remission in steroid-dependent CD patients[7]. Nonetheless, concerns regarding the potential complications, including non-melanoma skin cancer, myeloproliferative, and lymphoproliferative disorders associated with long-term thiopurine use, raise substantial safety considerations[37-39].

The potential adverse effects of long-term immunomodulator therapy prompt consideration about its discontinuation and the optimal timing for such a decision. A comprehensive systematic review conducted by Torres *et al*[40] synthesized data from 69 studies comprising 4672 IBD patients, revealing that more than 50% of individuals discontinuing immunomodulators or biological-based therapies experienced disease relapse. Notably, randomized clinical trials investigating withdrawal possibilities and their impact on disease progression and relapse remain scarce. One of the early studies on immunomodulatory withdrawal in CD, led by Bouhnik *et al*[41], shed light on this aspect. Their retrospective analysis revealed that among patients continuing therapy, the cumulative probabilities of relapse at 1 and 5 years stood at 11% and 32%, respectively. Notably, female gender, younger age, and a longer time to achieve remission (over 6 months) were associated with a heightened risk of relapse in this cohort. In contrast, for patients who ceased therapy, the probabilities of relapse at 1 and 5 years were notably higher, at 38% and 75%, respectively. Factors such as male sex, younger age, and shorter duration of remission (less than 4 years) correlated with an increased risk of relapse in this group. The authors concluded that after 4 years of remission under these medications, the risk of relapse appeared comparable regardless of therapy continuation or cessation. This finding led to questioning the utility of prolonged immunomodulator use in such patients[41].

Further analyses dissuade the discontinuation of immunomodulators in the absence of long-term remission. French *et al*[42] conducted a meta-analysis involving five studies encompassing 256 CD patients and 168 controls. Their findings highlighted the benefits of continuing azathioprine or 6-mercaptopurine for a minimum of 18 months to uphold previously attained remission. The study revealed that maintaining thiopurine therapy reduced the relapse risk at 6, 12, and 18 months, displaying pooled odds ratios of 0.22, 0.25, and 0.35, respectively[42]. Similarly, in UC patients, although data are limited, comparable results have emerged. A sole published double-blind randomized clinical trial involving withdrawal of azathioprine in UC patients depicted one-year relapse rates of 59% after azathioprine withdrawal *vs* 36% with sustained therapy, particularly notable in patients experiencing short-term remission (less than 6 months)[43].

A multicentre observational Italian retrospective study concluded that discontinuation of azathioprine while UC is in remission is associated with a high rate of relapse. In a study with 127 patients who were followed for a median of 55 months or until relapse after drug withdrawal, one-third of the patients relapsed within 12 months, half within 2 years, and two-thirds within 5 years[44]. The BERENICE study yielded interesting results, providing insight into the risks after stopping medications[45]. In the above-noted study, the authors developed a model-based risk-benefit analysis of withdrawing thiopurines in CD patients in prolonged remission. For patients without extensive colitis, continuing thiopurines marginally increased life expectancy for 35-year-old men and women, but decreased life expectancy for 65-year-old men and women. According to the study findings, the withdrawal strategy became the preferred approach at approximately 40 years for men and approximately 45 years for women without extensive colitis. In patients with extensive colitis, the continuation strategy was favored regardless of age[45].

In a previously mentioned systematic review, Torres *et al*[40] clearly highlighted high rates of relapse in patients with CD or UC after stopping immunomodulator monotherapy. Roughly 75% of patients experienced relapse within 5 years after discontinuing therapy. However, in the case of combination therapy (immunomodulator + anti-TNF therapy) in patients with CD, discontinuing the immunomodulator do not affect the relapse rate compared to those who continued the drug. Analysis of multiple studies showed that 55%-60% experienced disease relapse 24 months after stopping the immunomodulator. The only study in patients with UC supported the ongoing use of immunomodulators[40]. In the same systematic review, the authors identified factors associated with a higher risk of CD relapse: Elevated CRP, increased leukocyte or neutrophil count, low hemoglobin levels, high-risk disease (perianal involvement), younger age, male gender, short duration of remission, a shorter time since the last steroids, higher dose of azathioprine, thiopurine reduction before de-escalation, and smoking cessation[40].

The factors linked to an increased risk of relapse in UC were outlined as follows: Increased leukocyte count, extensive disease (pancolonic/extensive), younger age, male sex, number of relapses with azathioprine, shorter duration of azathioprine, and longer time from diagnosis to azathioprine. From this, we can deduce that higher disease activity, poor prognostic factors, and a complex or recurring disease course are correlated with future relapse[40]. These findings underscore the necessity for an individualized approach in deciding whether to discontinue therapy, contingent upon each patient’s disease course and severity.

Concerning exit strategies, the ECCO review board concluded that there is a cumulative risk of relapse over time after immunomodulatory monotherapy withdrawal in both CD and UC. It is estimated that approximately 30% of patients experience a relapse within 2 years, and between 50% to 75% relapse within 5 years[11]. The discontinuation of immunomodulator monotherapy is evidently associated with an increased risk of relapse. In a systematic review and meta-analysis encompassing ten randomized controlled trials with 587 included patients, Dohos *et al*[46] concluded that continued immunomodulator monotherapy should remain the preferred approach among patients with CD, despite concerns about long-term toxicity. However, the withdrawal of immunomodulator monotherapy did not exhibit a significantly higher risk of relapse within 24 months of follow-up in UC (RR = 1.39, 95%CI: 0.85-2.26, respectively). Moreover, discontinuing an immunomodulator in combination with biologics did not demonstrate a higher risk of relapse compared to continuing both drugs (RR = 1.30, 95%CI: 0.81-2.08)[46].

As previously mentioned, the removal of the immunomodulator from a combination with anti-TNF treatment do not yield a significantly higher relapse rate. In the study conducted by van Assche *et al*[47], continuing combination therapy showed no evident clinical benefit. Nonetheless, concurrent therapy involving any immunomodulators affects the pharmacokinetics of antibodies against infliximab and adalimumab[48,49]. Moreover, a comprehensive meta-analysis indicated that combination therapy correlates with reduced immunogenicity[50]. The potential withdrawal of immunomodulators from the combination regimen might lead to a heightened risk of antidrug antibody formation, although its impact on clinical outcomes might take more than a year to manifest[46].

In short, the decision to withdraw immunomodulators in IBD treatment is complex, as studies show varying relapse rates upon discontinuation. While discontinuing immunomodulator monotherapy in both CD and UC correlates with an increased risk of relapse, the withdrawal from combination therapy with anti-TNF treatment doesn't significantly heighten relapse rates. However, the removal of immunomodulators from these combined regimens could potentially impact antibody formation, affecting the long-term clinical outcomes of IBD treatment.

***Biological therapy***

Biological therapy has emerged as a primary treatment for moderate to severe CD and UC, aligning with established guidelines[7,8]. An extensive examination of healthcare expenditures in IBD was conducted among 1289 patients across 21 countries over a 5-year span, revealing a substantial rise in the costs attributed to biological treatments, comprising 73% in CD and 48% in UC cases[13]. While a test-based de-escalation approach demonstrated potential cost savings for CD patients in remission on optimized infliximab, it underscores the necessity for rethinking subsequent therapy management[51]. Presently, there is insufficient data supporting a clear recommendation for maintaining or stopping anti-TNF therapy upon achieving prolonged remission in IBD patients, and the absence of randomized trials complicates the decision-making process. Observational studies hint that discontinuing anti-TNF therapy might lead to a higher relapse risk compared to immunomodulators, with approximately 50% of patients experiencing relapse within two years, emphasizing the crucial role of clinical judgment in withdrawal decisions[11,51].

The STORI trial, the initial prospective study observing infliximab withdrawal after a year of remission in 115 CD patients on concurrent immunomodulatory therapy, noted relapse in 44% of patients within the first year[52]. Identified risk factors for relapse in the multivariate analysis included male gender, lack of surgical resection, elevated white blood cell count (> 6.0 × 109/L), lower hemoglobin (≤ 145 g/L), normal CRP levels (< 5.0 mg/L), and higher fecal calprotectin (≥ 300 µg/g)[52]. In the extended follow-up of the STORI trial, among patients maintaining remission on combined infliximab and immunomodulators, around 70% did not experience treatment failure even seven years after withdrawing infliximab. Yet, a fifth of these patients encountered significant complications over the same period[53].

In a comprehensive meta-analysis spanning 27 studies focusing on infliximab and adalimumab, Gisbert *et al*[54] found that after discontinuing anti-TNF therapy, the overall relapse risk stood at 44% for CD and 38% for UC patients. Within a year, 40% of CD and 28% of UC patients relapsed. For CD patients achieving endoscopic remission alongside clinical remission before stopping anti-TNF therapy, the relapse rate dropped notably to 26% after one year. Importantly, the study highlighted a positive response to retreatment using the same anti-TNF medication. Factors associated with a higher risk of relapse encompassed younger age, smoking habits, longer disease duration, perianal CD fistulization, and specific laboratory markers such as low hemoglobin, elevated CRP levels, and high fecal calprotectin. Conversely, lower serum anti-TNF levels and mucosal healing appeared linked to a decreased risk of relapse following anti-TNF discontinuation[54].

When deciding to discontinue therapy, the question arises regarding the success of reintroducing therapy in case of disease relapse. The multicentre retrospective EVODIS study, which enrolled 1055 patients with CD and UC, with a median follow-up of 34 months, assessed the risk of long-term relapse after the discontinuation of anti-TNF[55]. The results showed that the cumulative incidence of relapse was 50%: 19% in year one and 48% in 5 years of follow-up[55]. However, of the 60% of patients who had been retreated with the same anti-TNF after relapse, 73% regained remission[55]. The introduction of vedolizumab further improved the effectiveness of the treatment of IBD. However, there is a lack of data in the literature on relapse after drug withdrawal. In one retrospective observational study, from 21 tertiary centers, Martin *et al*[56] assessed the risk of relapse after the vedolizumab therapy was discontinued. The results showed that two-thirds of the patients had relapse within the first year after discontinuation of vedolizumab[56]. Retreatment with vedolizumab was effective in two-thirds of patients. However, many of them were treated with anti-TNF before the first treatment with vedolizumab was introduced[56].

Information regarding the withdrawal of anti-IL12/23 antibody, specifically ustekinumab, is scarce primarily because it was predominantly utilized as secondary or tertiary treatment post previous therapy failures[57].

The OCTAVE Open investigation assessed tofacitinib retreatment effectiveness and safety in UC patients who previously experienced treatment failure after 8 wk[58]. Results showed that after discontinuation, the median treatment failure time was 169 d for induction remitters and 123 d for responders who did not achieve remission. Reintroducing 10 mg bid tofacitinib proved effective and safe, with clinical response rates in year 3 reaching 60.6% for induction remitters and 42.4% for induction responders who did not achieve remission[58].

According to the ECCO conclusion on exit strategy, individuals achieving clinical, biological, and endoscopic remission likely face reduced relapse risks upon stopping anti-TNF therapy, making them potential candidates for withdrawal[11]. However, patients with a previous need for anti-TNF dose increase seem to be at high risk of relapse after discontinuation[11]. On the other hand, continuing immunomodulator treatment post anti-TNF discontinuation seems to lower the relapse risk[11].

***Monitoring after withdrawal from therapy and predictive factors of relapse***

The ECCO topical review on exit strategies suggests close monitoring during the initial year post-withdrawal, as the majority of relapses, particularly with anti-TNF agents, tend to happen within 6 to 12 months after cessation[11]. In clinical practice, a fundamental concern revolves around post-withdrawal patient monitoring and, notably, identifying relapse risks. Consequently, monitoring approaches utilizing non-invasive markers have been suggested.

In a recent prospective study monitoring patients after withdrawing from immunomodulator monotherapy, fecal calprotectin emerged as the most sensitive biomarker for relapse compared to CRP and white blood cell count[59]. Other research also supports the pivotal role of fecal calprotectin, indicating its rise preceding clinical or endoscopic relapse[60]. This suggests the possibility of its use as a predictive marker for identifying patients requiring close follow-up[60]. This suggests its potential as a predictive marker for identifying patients needing closer monitoring[60]. Another prospective study by Molander *et al*[60] tracking patients after anti-TNF withdrawal found significant correlations between fecal calprotectin and later relapse in UC (RR: 3.3; 95%CI: 1.2-10) and CD patients (hazard ratio: 4.5; 95%CI: 1.4-12.5)[60]. However, maintaining normal levels during follow-up proved highly predictive of clinical and endoscopic remission[60].

In a study by Buisson *et al*[61], the predictive value of fecal calprotectin in assessing relapse risk after therapeutic de-escalation was confirmed. Using a receiver operating characteristic curve, the authors determined that a fecal calprotectin level > 100 µg/g was the optimal threshold for predicting clinical relapse after de-escalation (area under the curve = 0.84)[61]. Some authors proposed predictive models for relapse as clinical practice recommendations. In a meta-analysis involving 14 studies and 1317 patients, Pauwels *et al*[62] proposed a predictive model for CD relapse post-cessation of anti-TNF therapy. Several factors were identified as predictive of relapse strength: Clinical symptoms (*e.g.*, CD activity index of 150 or higher, Harvey Bradshaw index of 5 or higher, Physicians’ Global Assessment above 0), younger age (< 40 years), longer disease duration (> 40 years), smoking, age at diagnosis of 16 years, steroid use 6-12 months before cessation, absence of immunosuppressant use, age between 40-60 years, and disease duration of 30-40 years[61]. Figure 1 illustrates the most commonly recognized factors associated with risk of relapse.

After discontinuation of therapy, relapse can be expected in a large portion of patients within 6 to 12 months[11]. For this reason, strict monitoring of clinical and non-invasive parameters is recommended, especially within the first year[57]. The non-invasive parameters primarily include fecal calprotectin and CRP[11]. In case of withdrawal of the anti-TNF therapy, elevated CRP and fecal calprotectin level was observed even several months before the clinical relapse[57]. If elevated values are confirmed by retesting, for further research, in the form of endoscopic revaluation is requested.

Current knowledge from clinical practice dictates the need for endoscopic and/or radiological assessment in case of CRP and fecal calprotectin elevation during follow-up after drug withdrawal. Further studies are needed in order to establish the optimal monitoring interval of non-invasive markers and treatment algorithms during follow up, as well as the time of endoscopic re-evaluation. Timing of endoscopic re-evaluation in the situation of sustained clinical remission after withdrawal should also be clarified.

***Future directions***

It remains important to distinguish and select patients with the lowest risk of relapse after discontinuation or de-escalation of therapy. For this purpose, it would be valuable to design scoring systems to predict the possibility of relapse using various clinical, endoscopic, and laboratory parameters. As previously mentioned, the role of fecal calprotectin has been indisputably proven in this matter[59-61]. Future research is expected to focus on identifying the best non-invasive markers for assessing disease severity and predicting relapse after drug withdrawal[63]. There is considerable anticipation regarding the role of intestinal ultrasound as a convenient imaging method. Until now, intestinal ultrasound has been established as a cross-sectional imaging tool, accurate in assessing IBD activity in real time[64]. It not only positively impacts patient compliance but also aids in quick clinical decision-making[64]. It is worth highlighting the possibility of machine learning models that could be used for designing suitable algorithms for assessing the severity of the disease and the possibility of relapse. This is consistent with the increasingly present idea of using artificial intelligence in the field of IBD[65,66]. Additionally, the optimal and timely monitoring of patients after stopping IBD therapy is an important consideration. Current knowledge favors periodic fecal calprotectin checks every three months[59]. Larger randomized clinical studies are necessary to evaluate the possibility of relapse and the safety of drug withdrawal in both monotherapy and combination therapy models. Likewise, there is a lack of comprehensive studies on therapies involving anti-integrins, anti-IL12/23 drugs, and small molecules, particularly in primarily resistant cases, warranting further investigation.

**CONCLUSION**

According to the currently available data, patient in clinical, laboratory, and endoscopic remission, has a better chance of experiencing an extended period of remission. Since long-term immunosuppressive therapy might result in adverse events, it is reasonable to consider reducing or discontinuing treatment in some patients. In patients with a low risk of relapse, discontinuation of treatment can be recommended. While 5-ASA are recommended, mainly due to their chemoprotective effect, discontinuation of immunomodulators or biological therapy could be suggested, particularly in cases of combination treatment. Although reintroducing therapy within the same drug group can be successful, retreatment will not be effective in at least one third of patients. However, the key challenge in the clinical practice lies in identifying patients at risk of relapse. Therefore, there is a strong need to develop exit strategies tailored to individual patients.

**REFERENCES**

1 **Kobayashi T**, Siegmund B, Le Berre C, Wei SC, Ferrante M, Shen B, Bernstein CN, Danese S, Peyrin-Biroulet L, Hibi T. Ulcerative colitis. *Nat Rev Dis Primers* 2020; **6**: 74 [PMID: 32913180 DOI: 10.1038/s41572-020-0205-x]

2 **Torres J**, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017; **389**: 1741-1755 [PMID: 27914655 DOI: 10.1016/S0140-6736(16)31711-1]

3 **Lee SH**, Kwon JE, Cho ML. Immunological pathogenesis of inflammatory bowel disease. *Intest Res* 2018; **16**: 26-42 [PMID: 29422795 DOI: 10.5217/ir.2018.16.1.26]

4 **Ng SC**, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017; **390**: 2769-2778 [PMID: 29050646 DOI: 10.1016/S0140-6736(17)32448-0]

5 **Rosen MJ**, Dhawan A, Saeed SA. Inflammatory Bowel Disease in Children and Adolescents. *JAMA Pediatr* 2015; **169**: 1053-1060 [PMID: 26414706 DOI: 10.1001/jamapediatrics.2015.1982]

6 **Borowitz SM**. The epidemiology of inflammatory bowel disease: Clues to pathogenesis? *Front Pediatr* 2022; **10**: 1103713 [PMID: 36733765 DOI: 10.3389/fped.2022.1103713]

7 **Torres J**, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, Adamina M, Armuzzi A, Bachmann O, Bager P, Biancone L, Bokemeyer B, Bossuyt P, Burisch J, Collins P, El-Hussuna A, Ellul P, Frei-Lanter C, Furfaro F, Gingert C, Gionchetti P, Gomollon F, González-Lorenzo M, Gordon H, Hlavaty T, Juillerat P, Katsanos K, Kopylov U, Krustins E, Lytras T, Maaser C, Magro F, Marshall JK, Myrelid P, Pellino G, Rosa I, Sabino J, Savarino E, Spinelli A, Stassen L, Uzzan M, Vavricka S, Verstockt B, Warusavitarne J, Zmora O, Fiorino G. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *J Crohns Colitis* 2020; **14**: 4-22 [PMID: 31711158 DOI: 10.1093/ecco-jcc/jjz180]

8 **Raine T**, Bonovas S, Burisch J, Kucharzik T, Adamina M, Annese V, Bachmann O, Bettenworth D, Chaparro M, Czuber-Dochan W, Eder P, Ellul P, Fidalgo C, Fiorino G, Gionchetti P, Gisbert JP, Gordon H, Hedin C, Holubar S, Iacucci M, Karmiris K, Katsanos K, Kopylov U, Lakatos PL, Lytras T, Lyutakov I, Noor N, Pellino G, Piovani D, Savarino E, Selvaggi F, Verstockt B, Spinelli A, Panis Y, Doherty G. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. *J Crohns Colitis* 2022; **16**: 2-17 [PMID: 34635919 DOI: 10.1093/ecco-jcc/jjab178]

9 **Peyrin-Biroulet L**, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, D'Haens G, Dotan I, Dubinsky M, Feagan B, Fiorino G, Gearry R, Krishnareddy S, Lakatos PL, Loftus EV Jr, Marteau P, Munkholm P, Murdoch TB, Ordás I, Panaccione R, Riddell RH, Ruel J, Rubin DT, Samaan M, Siegel CA, Silverberg MS, Stoker J, Schreiber S, Travis S, Van Assche G, Danese S, Panes J, Bouguen G, O'Donnell S, Pariente B, Winer S, Hanauer S, Colombel JF. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol* 2015; **110**: 1324-1338 [PMID: 26303131 DOI: 10.1038/ajg.2015.233]

10 **Turner D**, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, Bettenworth D, Sandborn WJ, Sands BE, Reinisch W, Schölmerich J, Bemelman W, Danese S, Mary JY, Rubin D, Colombel JF, Peyrin-Biroulet L, Dotan I, Abreu MT, Dignass A; International Organization for the Study of IBD. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology* 2021; **160**: 1570-1583 [PMID: 33359090 DOI: 10.1053/j.gastro.2020.12.031]

11 **Doherty G**, Katsanos KH, Burisch J, Allez M, Papamichael K, Stallmach A, Mao R, Berset IP, Gisbert JP, Sebastian S, Kierkus J, Lopetuso L, Szymanska E, Louis E. European Crohn's and Colitis Organisation Topical Review on Treatment Withdrawal ['Exit Strategies'] in Inflammatory Bowel Disease. *J Crohns Colitis* 2018; **12**: 17-31 [PMID: 28981623 DOI: 10.1093/ecco-jcc/jjx101]

12 **Peyrin-Biroulet L**, Rahier JF, Kirchgesner J, Abitbol V, Shaji S, Armuzzi A, Karmiris K, Gisbert JP, Bossuyt P, Helwig U, Burisch J, Yanai H, Doherty GA, Magro F, Molnar T, Löwenberg M, Halfvarson J, Zagorowicz E, Rousseau H, Baumann C, Baert F, Beaugerie L; I-CARE Collaborator Group. I-CARE, a European Prospective Cohort Study Assessing Safety and Effectiveness of Biologics in Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* 2023; **21**: 771-788.e10 [PMID: 36152897 DOI: 10.1016/j.cgh.2022.09.018]

13 **Burisch J**, Vardi H, Schwartz D, Friger M, Kiudelis G, Kupčinskas J, Fumery M, Gower-Rousseau C, Lakatos L, Lakatos PL, D'Incà R, Sartini A, Valpiani D, Giannotta M, Arebi N, Duricova D, Bortlik M, Chetcuti Zammit S, Ellul P, Pedersen N, Kjeldsen J, Midjord JMM, Nielsen KR, Winther Andersen K, Andersen V, Katsanos KH, Christodoulou DK, Domislovic V, Krznaric Z, Sebastian S, Oksanen P, Collin P, Barros L, Magro F, Salupere R, Kievit HAL, Goldis A, Kaimakliotis IP, Dahlerup JF, Eriksson C, Halfvarson J, Fernandez A, Hernandez V, Turcan S, Belousova E, Langholz E, Munkholm P, Odes S; Epi-IBD group. Health-care costs of inflammatory bowel disease in a pan-European, community-based, inception cohort during 5 years of follow-up: A population-based study. *Lancet Gastroenterol Hepatol* 2020; **5**: 454-464 [PMID: 32061322 DOI: 10.1016/S2468-1253(20)30012-1]

14 **Park KT**, Ehrlich OG, Allen JI, Meadows P, Szigethy EM, Henrichsen K, Kim SC, Lawton RC, Murphy SM, Regueiro M, Rubin DT, Engel-Nitz NM, Heller CA. The Cost of Inflammatory Bowel Disease: An Initiative From the Crohn's & Colitis Foundation. *Inflamm Bowel Dis* 2020; **26**: 1-10 [PMID: 31112238 DOI: 10.1093/ibd/izz104]

15 **Miyatani Y**, Kobayashi T. Evidence-Based Approach to the Discontinuation of Immunomodulators or Biologics in Inflammatory Bowel Disease. *Digestion* 2023; **104**: 66-73 [PMID: 36450267 DOI: 10.1159/000527776]

16 **Lamb CA**, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee B, Lomer MCE, Parkes GC, Selinger C, Barrett KJ, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD, Parkes M, Sanderson J, Terry H; IBD guidelines eDelphi consensus group, Gaya DR, Iqbal TH, Taylor SA, Smith M, Brookes M, Hansen R, Hawthorne AB. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019; **68**: s1-s106 [PMID: 31562236 DOI: 10.1136/gutjnl-2019-318484]

17 **Fumery M**, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural History of Adult Ulcerative Colitis in Population-based Cohorts: A Systematic Review. *Clin Gastroenterol Hepatol* 2018; **16**: 343-356.e3 [PMID: 28625817 DOI: 10.1016/j.cgh.2017.06.016]

18 **Niewiadomski O**, Studd C, Hair C, Wilson J, McNeill J, Knight R, Prewett E, Dabkowski P, Dowling D, Alexander S, Allen B, Tacey M, Connell W, Desmond P, Bell S. Health Care Cost Analysis in a Population-based Inception Cohort of Inflammatory Bowel Disease Patients in the First Year of Diagnosis. *J Crohns Colitis* 2015; **9**: 988-996 [PMID: 26129692 DOI: 10.1093/ecco-jcc/jjv117]

19 **Ghosh N**, Premchand P. A UK cost of care model for inflammatory bowel disease. *Frontline Gastroenterol* 2015; **6**: 169-174 [PMID: 28839807 DOI: 10.1136/flgastro-2014-100514]

20 **Lichtenstein GR**, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol* 2018; **113**: 481-517 [PMID: 29610508 DOI: 10.1038/ajg.2018.27]

21 **Siegel CA**. Refocusing IBD Patient Management: Personalized, Proactive, and Patient-Centered Care. *Am J Gastroenterol* 2018; **113**: 1440-1443 [PMID: 30287877 DOI: 10.1038/s41395-018-0246-x]

22 **Klag T**, Stange EF, Wehkamp J. Management of Crohn's disease - are guidelines transferred to clinical practice? *United European Gastroenterol J* 2015; **3**: 371-380 [PMID: 26279846 DOI: 10.1177/2050640615580228]

23 **Chapman TP**, Frias Gomes C, Louis E, Colombel JF, Satsangi J. Review article: Withdrawal of 5-aminosalicylates in inflammatory bowel disease. *Aliment Pharmacol Ther* 2020; **52**: 73-84 [PMID: 32452591 DOI: 10.1111/apt.15771]

24 **Bonovas S**, Fiorino G, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with meta-analysis: Use of 5-aminosalicylates and risk of colorectal neoplasia in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2017; **45**: 1179-1192 [PMID: 28261835 DOI: 10.1111/apt.14023]

25 **Qiu X**, Ma J, Wang K, Zhang H. Chemopreventive effects of 5-aminosalicylic acid on inflammatory bowel disease-associated colorectal cancer and dysplasia: A systematic review with meta-analysis. *Oncotarget* 2017; **8**: 1031-1045 [PMID: 27906680 DOI: 10.18632/oncotarget.13715]

26 **Ardizzone S**, Petrillo M, Imbesi V, Cerutti R, Bollani S, Bianchi Porro G. Is maintenance therapy always necessary for patients with ulcerative colitis in remission? *Aliment Pharmacol Ther* 1999; **13**: 373-379 [PMID: 10102971 DOI: 10.1046/j.1365-2036.1999.00473.x]

27 **Miner P,** Daly R, Nester T. The effect of varying dose intervals of mesalamine enemas for the prevention of relapse in distal ulcerative colitis. *Gastroenterology* 1994; **106** Suppl 2: A736. Available from: https://eurekamag.com/research/033/787/033787186.php

28 **D'Arienzo A**, Panarese A, D'Armiento FP, Lancia C, Quattrone P, Giannattasio F, Boscaino A, Mazzacca G. 5-Aminosalicylic acid suppositories in the maintenance of remission in idiopathic proctitis or proctosigmoiditis: A double-blind placebo-controlled clinical trial. *Am J Gastroenterol* 1990; **85**: 1079-1082 [PMID: 2202199]

29 **Hanauer S**, Good LI, Goodman MW, Pizinger RJ, Strum WB, Lyss C, Haber G, Williams CN, Robinson M. Long-term use of mesalamine (Rowasa) suppositories in remission maintenance of ulcerative proctitis. *Am J Gastroenterol* 2000; **95**: 1749-1754 [PMID: 10925979 DOI: 10.1111/j.1572-0241.2000.02185.x]

30 **Marteau P**, Crand J, Foucault M, Rambaud JC. Use of mesalazine slow release suppositories 1 g three times per week to maintain remission of ulcerative proctitis: A randomised double blind placebo controlled multicentre study. *Gut* 1998; **42**: 195-199 [PMID: 9536943 DOI: 10.1136/gut.42.2.195]

31 **d'Albasio G**, Paoluzi P, Campieri M, Bianchi Porro G, Pera A, Prantera C, Sturniolo GC, Miglioli M. Maintenance treatment of ulcerative proctitis with mesalazine suppositories: A double-blind placebo-controlled trial. The Italian IBD Study Group. *Am J Gastroenterol* 1998; **93**: 799-803 [PMID: 9625131 DOI: 10.1111/j.1572-0241.1998.228\_a.x]

32 **Biddle WL**, Greenberger NJ, Swan JT, McPhee MS, Miner PB Jr. 5-Aminosalicylic acid enemas: Effective agent in maintaining remission in left-sided ulcerative colitis. *Gastroenterology* 1988; **94**: 1075-1079 [PMID: 3278942 DOI: 10.1016/0016-5085(88)90569-0]

33 **Feuerstein JD**, Isaacs KL, Schneider Y, Siddique SM, Falck-Ytter Y, Singh S; AGA Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology* 2020; **158**: 1450-1461 [PMID: 31945371 DOI: 10.1053/j.gastro.2020.01.006]

34 **Ungaro RC**, Limketkai BN, Jensen CB, Yzet C, Allin KH, Agrawal M, Ullman T, Burisch J, Jess T, Colombel JF. Stopping Mesalamine Therapy in Patients With Crohn's Disease Starting Biologic Therapy Does Not Increase Risk of Adverse Outcomes. *Clin Gastroenterol Hepatol* 2020; **18**: 1152-1160.e1 [PMID: 31419574 DOI: 10.1016/j.cgh.2019.08.012]

35 **Singh S**, Proudfoot JA, Dulai PS, Jairath V, Fumery M, Xu R, Feagan BG, Sandborn WJ. No Benefit of Concomitant 5-Aminosalicylates in Patients With Ulcerative Colitis Escalated to Biologic Therapy: Pooled Analysis of Individual Participant Data From Clinical Trials. *Am J Gastroenterol* 2018; **113**: 1197-1205 [PMID: 29925913 DOI: 10.1038/s41395-018-0144-2]

36 **Ma C**, Kotze PG, Almutairdi A, Jairath V, Panaccione R. Concomitant Use of Aminosalicylates Is Not Associated With Improved Outcomes in Patients With Ulcerative Colitis Escalated to Vedolizumab. *Clin Gastroenterol Hepatol* 2019; **17**: 2374-2376.e2 [PMID: 30528845 DOI: 10.1016/j.cgh.2018.11.062]

37 **Beaugerie L**, Brousse N, Bouvier AM, Colombel JF, Lémann M, Cosnes J, Hébuterne X, Cortot A, Bouhnik Y, Gendre JP, Simon T, Maynadié M, Hermine O, Faivre J, Carrat F; CESAME Study Group. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: A prospective observational cohort study. *Lancet* 2009; **374**: 1617-1625 [PMID: 19837455 DOI: 10.1016/S0140-6736(09)61302-7]

38 **Peyrin-Biroulet L**, Khosrotehrani K, Carrat F, Bouvier AM, Chevaux JB, Simon T, Carbonnel F, Colombel JF, Dupas JL, Godeberge P, Hugot JP, Lémann M, Nahon S, Sabaté JM, Tucat G, Beaugerie L; Cesame Study Group. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology* 2011; **141**: 1621-28.e1-5 [PMID: 21708105 DOI: 10.1053/j.gastro.2011.06.050]

39 **Lopez A**, Mounier M, Bouvier AM, Carrat F, Maynadié M, Beaugerie L, Peyrin-Biroulet L; CESAME Study Group. Increased risk of acute myeloid leukemias and myelodysplastic syndromes in patients who received thiopurine treatment for inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2014; **12**: 1324-1329 [PMID: 24582568 DOI: 10.1016/j.cgh.2014.02.026]

40 **Torres J**, Boyapati RK, Kennedy NA, Louis E, Colombel JF, Satsangi J. Systematic Review of Effects of Withdrawal of Immunomodulators or Biologic Agents From Patients With Inflammatory Bowel Disease. *Gastroenterology* 2015; **149**: 1716-1730 [PMID: 26381892 DOI: 10.1053/j.gastro.2015.08.055]

41 **Bouhnik Y**, Lémann M, Mary JY, Scemama G, Taï R, Matuchansky C, Modigliani R, Rambaud JC. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Lancet* 1996; **347**: 215-219 [PMID: 8551879 DOI: 10.1016/s0140-6736(96)90402-x]

42 **French H**, Mark Dalzell A, Srinivasan R, El-Matary W. Relapse rate following azathioprine withdrawal in maintaining remission for Crohn's disease: A meta-analysis. *Dig Dis Sci* 2011; **56**: 1929-1936 [PMID: 21476031 DOI: 10.1007/s10620-011-1671-5]

43 **Hawthorne AB**, Logan RF, Hawkey CJ, Foster PN, Axon AT, Swarbrick ET, Scott BB, Lennard-Jones JE. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. *BMJ* 1992; **305**: 20-22 [PMID: 1638191 DOI: 10.1136/bmj.305.6844.20]

44 **Cassinotti A**, Actis GC, Duca P, Massari A, Colombo E, Gai E, Annese V, D'Albasio G, Manes G, Travis S, Porro GB, Ardizzone S. Maintenance treatment with azathioprine in ulcerative colitis: Outcome and predictive factors after drug withdrawal. *Am J Gastroenterol* 2009; **104**: 2760-2767 [PMID: 19623172 DOI: 10.1038/ajg.2009.410]

45 **Kirchgesner J**, Beaugerie L, Carrat F, Sokol H, Cosnes J, Schwarzinger M; BERENICE Study Group. Impact on Life Expectancy of Withdrawing Thiopurines in Patients with Crohn's Disease in Sustained Clinical Remission: A Lifetime Risk-Benefit Analysis. *PLoS One* 2016; **11**: e0157191 [PMID: 27271176 DOI: 10.1371/journal.pone.0157191]

46 **Dohos D**, Hanák L, Szakács Z, Kiss S, Párniczky A, Erőss B, Pázmány P, Hegyi P, Sarlós P. Systematic review with meta-analysis: The effects of immunomodulator or biological withdrawal from mono- or combination therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2021; **53**: 220-233 [PMID: 33249621 DOI: 10.1111/apt.16182]

47 **Van Assche G**, Magdelaine-Beuzelin C, D'Haens G, Baert F, Noman M, Vermeire S, Ternant D, Watier H, Paintaud G, Rutgeerts P. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: A randomized trial. *Gastroenterology* 2008; **134**: 1861-1868 [PMID: 18440315 DOI: 10.1053/j.gastro.2008.03.004]

48 **Vermeire S**, Noman M, Van Assche G, Baert F, D'Haens G, Rutgeerts P. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. *Gut* 2007; **56**: 1226-1231 [PMID: 17229796 DOI: 10.1136/gut.2006.099978]

49 **Kennedy NA**, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GJ, Thomas A, Nice R, Perry MH, Bouri S, Chanchlani N, Heerasing NM, Hendy P, Lin S, Gaya DR, Cummings JRF, Selinger CP, Lees CW, Hart AL, Parkes M, Sebastian S, Mansfield JC, Irving PM, Lindsay J, Russell RK, McDonald TJ, McGovern D, Goodhand JR, Ahmad T; UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: A prospective, multicentre, cohort study. *Lancet Gastroenterol Hepatol* 2019; **4**: 341-353 [PMID: 30824404 DOI: 10.1016/S2468-1253(19)30012-3]

50 **Chalhoub JM**, Rimmani HH, Gumaste VV, Sharara AI. Systematic Review and Meta-analysis: Adalimumab Monotherapy Versus Combination Therapy with Immunomodulators for Induction and Maintenance of Remission and Response in Patients with Crohn's Disease. *Inflamm Bowel Dis* 2017; **23**: 1316-1327 [PMID: 28719541 DOI: 10.1097/MIB.0000000000001203]

51 **Chapman TP**, Gomes CF, Louis E, Colombel JF, Satsangi J. De-escalation of immunomodulator and biological therapy in inflammatory bowel disease. *Lancet Gastroenterol Hepatol* 2020; **5**: 63-79 [PMID: 31818473 DOI: 10.1016/S2468-1253(19)30186-4]

52 **Louis E**, Mary JY, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, Dupas JL, Pillant H, Picon L, Veyrac M, Flamant M, Savoye G, Jian R, Devos M, Porcher R, Paintaud G, Piver E, Colombel JF, Lemann M; Groupe D'etudes Thérapeutiques Des Affections Inflammatoires Digestives. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 2012; **142**: 63-70.e5; quiz e31 [PMID: 21945953 DOI: 10.1053/j.gastro.2011.09.034]

53 **Reenaers C**, Mary JY, Nachury M, Bouhnik Y, Laharie D, Allez M, Fumery M, Amiot A, Savoye G, Altwegg R, Devos M, Malamut G, Bourreille A, Flourie B, Marteau P, Vuitton L, Coffin B, Viennot S, Lambert J, Colombel JF, Louis E; Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif. Outcomes 7 Years After Infliximab Withdrawal for Patients With Crohn's Disease in Sustained Remission. *Clin Gastroenterol Hepatol* 2018; **16**: 234-243.e2 [PMID: 28993262 DOI: 10.1016/j.cgh.2017.09.061]

54 **Gisbert JP**, Marín AC, Chaparro M. Systematic review: Factors associated with relapse of inflammatory bowel disease after discontinuation of anti-TNF therapy. *Aliment Pharmacol Ther* 2015; **42**: 391-405 [PMID: 26075832 DOI: 10.1111/apt.13276]

55 **Casanova MJ**, Chaparro M, Nantes Ó, Benítez JM, Rojas-Feria M, Castro-Poceiro J, Huguet JM, Martín-Cardona A, Aicart-Ramos M, Tosca J, Martín-Rodríguez MDM, González-Muñoza C, Mañosa M, Leo-Carnerero E, Lamuela-Calvo LJ, Pérez-Martínez I, Bujanda L, Hinojosa J, Pajares R, Argüelles-Arias F, Pérez-Calle JL, Rodríguez-González GE, Guardiola J, Barreiro-de Acosta M, Gisbert JP; EVODIS Study Group\*. Clinical outcome after anti-tumour necrosis factor therapy discontinuation in 1000 patients with inflammatory bowel disease: The EVODIS long-term study. *Aliment Pharmacol Ther* 2021; **53**: 1277-1288 [PMID: 33962482 DOI: 10.1111/apt.16361]

56 **Martin A**, Nachury M, Peyrin-Biroulet L, Bouhnik Y, Nancey S, Bourrier A, Serrero M, Fumery M, Buisson A, Laharie D, Gilletta C, Filippi J, Allez M, Bouguen G, Roblin X, Altwegg R, Dib N, Pineton de Chambrun G, Savoye G, Carbonnel F, Viennot S, Amiot A; GETAID-Vedo-STOP Study Group. Maintenance of Remission Among Patients With Inflammatory Bowel Disease After Vedolizumab Discontinuation: A Multicentre Cohort Study. *J Crohns Colitis* 2020; **14**: 896-903 [PMID: 31930285 DOI: 10.1093/ecco-jcc/jjaa005]

57 **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**: 2657-2669 [PMID: 37214561 DOI: 10.12998/wjcc.v11.i12.2657]

58 **Panés J**, Vermeire S, Dubinsky MC, Loftus EV, Lawendy N, Wang W, Salese L, Su C, Modesto I, Guo X, Colombel JF. Efficacy and Safety of Tofacitinib Re-treatment for Ulcerative Colitis After Treatment Interruption: Results from the OCTAVE Clinical Trials. *J Crohns Colitis* 2021; **15**: 1852-1863 [PMID: 33884415 DOI: 10.1093/ecco-jcc/jjab065]

59 **Cassinotti A**, Corona A, Duca P, Nebuloni M, Maconi G, Fociani P, Ardizzone S. Noninvasive Monitoring After Azathioprine Withdrawal in Patients With Inflammatory Bowel Disease in Deep Remission. *Clin Gastroenterol Hepatol* 2021; **19**: 2293-2301.e1 [PMID: 34139332 DOI: 10.1016/j.cgh.2021.06.014]

60 **Molander P**, Färkkilä M, Ristimäki A, Salminen K, Kemppainen H, Blomster T, Koskela R, Jussila A, Rautiainen H, Nissinen M, Haapamäki J, Arkkila P, Nieminen U, Kuisma J, Punkkinen J, Kolho KL, Mustonen H, Sipponen T. Does fecal calprotectin predict short-term relapse after stopping TNFα-blocking agents in inflammatory bowel disease patients in deep remission? *J Crohns Colitis* 2015; **9**: 33-40 [PMID: 25052347 DOI: 10.1016/j.crohns.2014.06.012]

61 **Buisson A**, Mak WY, Andersen MJ, Lei D, Kahn SA, Pekow J, Cohen RD, Zmeter N, Pereira B, Rubin DT. Faecal Calprotectin Is a Very Reliable Tool to Predict and Monitor the Risk of Relapse After Therapeutic De-escalation in Patients With Inflammatory Bowel Diseases. *J Crohns Colitis* 2019; **13**: 1012-1024 [PMID: 30726887 DOI: 10.1093/ecco-jcc/jjz023]

62 **Pauwels RWM**, van der Woude CJ, Nieboer D, Steyerberg EW, Casanova MJ, Gisbert JP, Kennedy NA, Lees CW, Louis E, Molnár T, Szántó K, Leo E, Bots S, Downey R, Lukas M, Lin WC, Amiot A, Lu C, Roblin X, Farkas K, Seidelin JB, Duijvestein M, D'Haens GR, de Vries AC; CEASE Study Group. Prediction of Relapse After Anti-Tumor Necrosis Factor Cessation in Crohn's Disease: Individual Participant Data Meta-analysis of 1317 Patients From 14 Studies. *Clin Gastroenterol Hepatol* 2022; **20**: 1671-1686.e16 [PMID: 33933376 DOI: 10.1016/j.cgh.2021.03.037]

63 **Kumric M**, Zivkovic PM, Ticinovic Kurir T, Vrdoljak J, Vilovic M, Martinovic D, Bratanic A, Lizatovic IK, Bozic J. Role of B-Cell Activating Factor (BAFF) in Inflammatory Bowel Disease. *Diagnostics (Basel)* 2021; **12** [PMID: 35054212 DOI: 10.3390/diagnostics12010045]

64 **Dolinger MT**, Kayal M. Intestinal ultrasound as a non-invasive tool to monitor inflammatory bowel disease activity and guide clinical decision making. *World J Gastroenterol* 2023; **29**: 2272-2282 [PMID: 37124889 DOI: 10.3748/wjg.v29.i15.2272]

65 **Gubatan J**, Levitte S, Patel A, Balabanis T, Wei MT, Sinha SR. Artificial intelligence applications in inflammatory bowel disease: Emerging technologies and future directions. *World J Gastroenterol* 2021; **27**: 1920-1935 [PMID: 34007130 DOI: 10.3748/wjg.v27.i17.1920]

66 **Da Rio L**, Spadaccini M, Parigi TL, Gabbiadini R, Dal Buono A, Busacca A, Maselli R, Fugazza A, Colombo M, Carrara S, Franchellucci G, Alfarone L, Facciorusso A, Hassan C, Repici A, Armuzzi A. Artificial intelligence and inflammatory bowel disease: Where are we going? *World J Gastroenterol* 2023; **29**: 508-520 [PMID: 36688019 DOI: 10.3748/wjg.v29.i3.508]

**Footnotes**

**Conflict-of-interest statement:** Authors declare no conflict of interests for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

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

**Peer-review model:** Single blind

**Peer-review started:** December 31, 2023

**First decision:** January 9, 2024

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** Croatia

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Beales I, United Kingdom; Caviglia RD, Italy **S-Editor:** Zhang L **L-Editor:** A **P-Editor:**

**Figure Legends**

****

**Figure 1 Possible predictive factors of disease relapse after withdrawal of therapy in inflammatory bowel disease patients.** CD: Crohn’s disease; CRP: C-reactive protein; TNF: Tumor necrosis factor; UC: Ulcerative colitis.

**Table 1 Treatment goals in patients with inflammatory bowel disease**

|  |  |  |
| --- | --- | --- |
|  | **Short/intermediate-term goals** | **Long-term goals** |
| Clinical | Clinical response | Clinical remission; In children, the return of normal development is a long-term goal |
| Endoscopic |  | Endoscopic healing; Histological healing is not a defined goal of treatment in CD or UC |
| Laboratory | Normalization of CRP, ESR and fecal calprotectin |  |
| Quality of life | Absence of disability and normalization of health-related quality of life |

CD: Crohn’s disease; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; UC: Ulcerative colitis.