Chapter 10
Cessation of Biologics: Can It Be Done?

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Introduction

The inflammatory bowel diseases (IBD) which comprise Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory conditions of the gastrointestinal tract characterized by a relapsing and remitting course which may lead to progressive bowel damage [1, 2]. Historically, treatment of IBD comprised corticosteroids, 5-ASA agents, and immunomodulators including thiopurines and methotrexate. As a result of the limited therapeutic efficacy of these agents, up to 80% of patients with CD and 30% with UC require bowel resection to treat medically refractory disease or to attend to associated complications including strictures, fistulae, and abscesses [3, 4]. The use of biologic therapies, in particular anti-TNF-α agents, has resulted in a significant paradigm shift in the management of IBD with the ability to achieve deep remission [5, 6]. Mucosal healing is associated with lower rates of hospitalization, surgery, postoperative recurrence, colorectal cancer, and improved colectomy-free survival and quality of life [7–11]. Despite the overall favorable safety and efficacy profile, patients on anti-TNF-α therapies may lose response and may have an increased risk of infection and malignancy, and the therapy is expensive. The question therefore arises as to whether withdrawal of biologic therapy

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may be a viable option. The concept of withdrawal of IBD therapies is not new. Prior to the introduction of anti-TNF-α therapies, the withdrawal of azathioprine had been studied and was well demonstrated to be associated with high relapse rate, ranging from 11 to 77% at 1 year [12]. This book chapter will aim to address who, when, and how withdrawal of biologic could be considered. For the purpose of this book chapter, we will focus on anti-TNF-α therapies which are the most widely used biologics as data on withdrawal of other newer biologics (including the anti-integrins, IL-12/23 inhibitors, etc.) are limited at this juncture.

The Case for Continuing Anti-TNF-α Therapy

Anti-TNF-α agents target tumor necrosis factor-α which is a key mediator of inflammation. Targan et al. published the first randomized double-blind placebo-controlled trial comparing a single dose of cA2 (infliximab) to placebo in CD in 1997 with impressive results at week 4 (clinical response 81% versus 17%, clinical remission 33% versus 4%, all comparisons, $p < 0.05$) [13]. This was followed by the ACCENT trial in individuals with CD and the ACT trial in patients with UC which demonstrated the efficacy of induction and maintenance of anti-TNF-α therapy with infliximab [14, 15]. Systematic reviews and network meta-analyses have reported comparable clinical efficacy for all anti-TNF-α agents [16, 17]. Efficacy can be further improved by combining therapy with an immunomodulator and introducing therapy in the early stages of disease [5, 6, 18–20].

Existing data indicates that both gastroenterologists and patients generally prefer to continue anti-TNF-α therapy as long as it is effective and well tolerated, citing concerns of the risk of relapse and lower response with subsequent reintroduction of an anti-TNF-α agent [21, 22]. It has been well documented that episodic anti-TNF-α treatment results in an increased risk of immunogenicity, secondary loss of response, and infusion reactions, and elective switching between anti-TNF-α agents should be avoided due to loss of efficacy [23–25].

The Case for Discontinuing Anti-TNF-α Therapy

The reasons for requesting cessation of therapy should be discussed at length with the patient given that there may be differing concerns by the patient and physician underlying the request. Switching an anti-TNF-α therapy to an alternative biologic therapy may be a reasonable alternative to complete discontinuation of therapy in select circumstances, e.g., intolerance to a class of therapy. Despite the above, there may be specific situations in which the risks of ongoing therapy may outweigh the benefits. The following topics plus the management of IBD during pregnancy are covered in detail in other chapters of the book, but a short summary is provided here.

Infusion Reactions Anti-TNF-α therapies are generally well tolerated with only a small proportion (4%) of patients experiencing infusion or local injection reactions which can be managed by changes to the injection/infusion technique; pretreating with antihistamines, acetaminophen, or corticosteroids; or a switch to an alternate therapy [26, 27]. Acute serum sickness is uncommon (1–3% of patients) but may necessitate cessation of existing therapy [27, 28].

Risk of Infection The TREAT registry followed a large cohort of 6273 individuals with IBD and reported the risk of serious infection for anti-TNF-α therapy being higher (HR 1.43; 95% CI 1.11–1.84) than that seen with immunomodulators (HR 1.23; 95% CI 0.96–1.57) but lower than with corticosteroids (HR 1.57; 95% CI 1.17–2.10) [29]. Mycobacterial, fungal, bacterial, and viral infections have all be reported with anti-TNF-α therapies, but these may be prevented by screening for these infections and providing appropriate prophylaxis or vaccination [30, 31]. In the setting of other recurrent or severe infections, a switch to a gut-specific antibody with lesser systemic adverse effects (such as vedolizumab) could be considered.

Risk of Malignancy No significant increased risk of malignancy was identified in the TREAT registry nor in two separate systemic reviews [32–34]. A number of studies, albeit underpowered, suggest that anti-TNF-α therapies may be safe in the setting of active or recent malignancy [35]. However, an in-depth discussion with the treating oncologist should always be undertaken before deciding to continue or cease anti-TNF-α therapy.

Elderly with IBD The management of the elderly with IBD should take into account altered pharmacokinetics, polypharmacy, age-related changes to the immune system, and comorbid illness, which may increase the risk of infections, malignancy, morbidity, and mortality [36].

Health Economic Concerns While anti-TNF-α therapies have significantly decreased the rates of hospitalization and surgery, the increasing use of these agents has replaced hospitalization and surgery as the main driver of total medical costs [37, 38]. In United States, it was estimated that the annual medication cost per CD patient was $18,637 [39]. The emergence of subsequent entry biologics may result in decreased costs but requires specific study.

The Risk of Discontinuing Anti-TNF-α Therapy

Situations may arise in which patients, physicians, or health jurisdictions request elective cessation of anti-TNF-α therapy based on personal preference or health economic concerns. In these scenarios, it is important to determine how and in whom this is best performed. The overall risk of IBD relapse following withdrawal of anti-TNF-α therapies was reported as 44% (95% CI 37–51, follow-up range 6–125 months) in a meta-analysis of 27 studies by Gisbert et al., with approximately one third of patients in remission relapsing 1 year after discontinuation [40]. Summaries of studies on withdrawal of anti-TNF-α therapies can be found in Table 10.1.

Table 10.1 Studies on the withdrawal of anti-TNF-α therapies

	Authors	Number of participants (*n*)	Study design	Relapse rate	Significant predictors of relapse	Predictors evaluated but not found to be significant	Recapture rate
CD	Brooks et al. [52]	86	Prospective observational	4.7% (3 months)	Ileocolonic disease	Age, gender, disease behavior, previous surgical resection, immunosuppression at start of anti-TNF-α treatment, disease duration, dose escalation of anti-TNF-α agent, concomitant IMM, raised CRP	93%
				18.6% (6 months)	Previous anti-TNF-α treatment		
			(88% concomitant IMM)	36% (1 year)	Raised fecal calprotectin		
	Domenech et al. [42]	23	Prospective observational (69% with concomitant IMM)	31% (1 year)	Perianal disease	Gender, smoking status, previous treatment with IFX, concomitant IMM, location, development of infusion acute reactions	–
				66% (1 year) for perianal disease			
	Louis et al. (STORI) [41]	115	Prospective observational (100% with concomitant IMM)	43.9% (1 year)	Male, absence of surgical resection, elevated leucocyte count >6.0 × 10^9/L, hemoglobin ≤ 145 g/L	Age, smoking status, location, previous resection, disease duration, treatment duration	88%
				15% (1 year) for those with ≤2 predictors of relapse	C-reactive protein ≥5.0 mg/L		
					Fecal calprotectin ≥ 300 μg/g		
	Reenaers et al. (long-term follow-up of STORI trial) [77]	102/115 (long-term outcome)	Prospective observational (100% with concomitant IMM)	85% (median 8 years)	Upper GI involvement	Not reported (only abstract is available)	40%
					Elevated leucocyte count > 6.0 × 10^9/L		

Molnar et al. [43]	121	Prospective observational (85% with concomitant IMM)	45% (1 year)	Previous biologic therapy Dose intensification of biologic therapy	Gender, concurrent steroid use at biologic initiation, high CRP, smoking status	50%
Annunziata et al. [78]	16	Retrospective (% on IMM not available)	62.5% (5 years)	Absence of normalized intestinal wall thickness	–	–
Ampuero et al. [44]	75	Retrospective (100% concomitant IMM)	30.9% (1 year)	CRP > 5 mg/L Younger age at diagnosis	Gender, smoking status, location, duration of treatment	100%
Molnar et al. [53]	50	Retrospective (86% concomitant IMM)	56% (1 year)	Fistula Smoking status	Location of disease	–
Papamichael et al. [66]	100	Retrospective (84% with concomitant IMM)	48% (10 years)	Age at diagnosis <25 (multivariate analysis)	Disease location, behavior (perianal), fistulizing disease, type of infliximab therapy (episodic or scheduled), number of infliximab infusions, CRP, previous ileocolonic resection, smoking at initiation of infliximab, IMM or type of IMM after infliximab cessation, positive ATIs during infliximab therapy or at the time of infliximab cessation	–

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Table 10.1 (continued)

	Authors	Number of participants (*n*)	Study design	Relapse rate	Significant predictors of relapse	Predictors evaluated but not found to be significant	Recapture rate
	Ramos et al. [79]	25	Retrospective (% of IMM not reported)	16% (1.6 ± 1 year)	Not reported	Not reported	–
	Waugh et al. [54]	48	Retrospective (67% concomitant IMM)	50% (1.3 year) 35% remained well with no relapse at 7 years follow-up	Nil identified	Age, gender, disease location, duration from diagnosis to the start of infliximab therapy, concomitant IMM, number of infliximab doses	–
UC	Farkas et al. [80]	51	Prospective observational (100% concomitant IMM)	35% (0.3 year)	Previous biological therapy	Gender, smoking status, appendicectomy, disease extent, extraintestinal manifestation, concomitant IMM, previous surgery, dose intensification	94%
	Munoz Villafranca et al. [81]	19	Prospective observational (57.8% with concomitant IMM)	25% (1–2 years)	Not reported	Not reported	–
	Fiorino et al. [82]	193	Retrospective (65.3% with concomitant IMM)	47.7% (median follow-up of 2 years)	Infliximab discontinuation Absence of concomitant thiopurines	Age, disease extension, disease severity, previous therapies, smoking status	77%

CD/UC	Bortlik et al. [83]	CD: 61 UC: 17	Prospective observational (77% of CD and 59% of UC with concomitant IMM)	CD: 18% (0.5 year), 41% (1 year), 49% (2 years) UC: 23% (0.6 year), 23% (1 year), 36% (2 years)	Non-colonic location for CD, previous anti-TNF-α treatment, previous surgery	Type of anti-TNF-α agent, smoking status, disease behavior, corticosteroid therapy within 1 year before biologics withdrawal, concomitant IMM, CRP level, fecal calprotectin, anti-TNF-α trough levels at the time of anti-TNF-α withdrawal	82%
	Dai et al. [49]	CD: 109 UC: 107	Prospective observational (31% concomitant IMM)	CD: 21% (1 year) UC: 14% (1 year)	Nil	Clinical remission, mucosal healing, gender, disease duration, smoking status, history of appendicectomy, location, behavior, extraintestinal manifestations, previous surgery, previous biological therapy, CRP level, effect of induction therapy	CD: 78.3% UC: 66.7%
	Hlavaty et al. [84]	CD:17 UC: 5	Prospective observational (36% with concomitant IMM for cohorts in clinical remission) (64% with concomitant IMM for cohorts in deep remission)	Cohorts with deep remission, 18% (0.5 year), 27% (1 year) Cohorts with clinical remission, 18% (0.5 year), 27% (1 year)	Male	Type of IBD, age, disease duration, CD location, behavior, smoking status, previous surgery, type and duration of anti-TNF-α agent, concomitant azathioprine, fecal calprotectin, CRP, hemoglobin	100%

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Table 10.1 (continued)

Authors	Number of participants (*n*)	Study design	Relapse rate	Significant predictors of relapse	Predictors evaluated but not found to be significant	Recapture rate
Molander et al. [67]	CD,17; UC, 30	Prospective observational (83% with concomitant IMM)	CD: 29% (1.1 year)	Nil identified	Age, gender, duration of disease, location, disease activity at discontinuation	100% (CD)
	IBDU: 5		UC: 35% (1.1 year)			90% (UC)
Armuzzi et al. [55]	CD: 65	Retrospective (% of with concomitant IMM not reported)	CD: 49% [median 1.1(0.3–6.2) years]	Absence of mucosal healing	Not reported	–
	UC: 31		UC: 41% [median 1.3(0.3–2.5) years]	High CRP		
Casanova et al. [60]	CD: 717 UC: 338	Retrospective (71% with concomitant IMM)	24% (1 year)	Adalimumab (rather than infliximab)	Not available	75%
			38% (2 years)			
			46% (3 years)	Elective discontinuation of anti-TNF-α therapy		
			56% (5 years)	Discontinuation of anti-TNF-α due to adverse events		
				Younger age at discontinuation		
				No maintenance IMM		

	Caviglia et al. [85]	CD: 29	Retrospective (100% CD and 33% UC with concomitant IMM)	CD: 69% [median 1.3 (0.4–2.5) years]	Not reported	Not reported	–
		UC: 9		UC: 56% [median 0.5 (0.3–1.3) years]			
	Ciria et al. [86]	CD:24	Retrospective (% of concomitant IMM not reported)	35% (median follow-up 1.7 years)	Absence of mucosal healing	Type of IBD	–
		UC: 10					
	Farkas et al. [87]	CD:41	Retrospective (85% CD and 73% UC with concomitant IMM)	CD: 78% (0.4 year)	Nil identified	Clinical remission	81% (CD)
		UC:22		UC: 59% (0.6 years)		Mucosal healing	54% (UC)
	Luppino et al. [88]	CD: 21 UC: 10	Retrospective (100% with concomitant IMM)	42% (median time to relapse 1.5 years)	Longer disease duration	Not available	80%
	Marino et al. [89]	CD: 8 UC: 2	Retrospective (20% with concomitant IMM)	CD: 75% (mean 1.2 (SD ± 0.7) years]	Not available	Not available	100%
				UC: 0% (mean 1.7 years)			

(continued)

Table 10.1 (continued)

Authors	Number of participants (*n*)	Study design	Relapse rate	Significant predictors of relapse	Predictors evaluated but not found to be significant	Recapture rate
Steenholdt et al. [57]	CD: 53 UC: 28	Retrospective 86% concomitant IMM (CD and UC)	CD: 39% (1 year), 88% (10 years)	CD: longer disease duration	Not available	96% (CD)
			UC: 25% (1 year), 60% (4.5 years)			71% (UC)
Gisbert et al. [40]	27 studies	Systematic review, Meta-analysis	CD: 38% (0.5 year), 40% (1 year), 49% (>2.1 years)	Younger age	–	80%
				Smoking status		
				Longer disease duration		
			UC: 28% (1 year)	Fistulizing perianal CD		
				Low hemoglobin		
				High C-reactive protein		
				High fecal calprotectin		
				Absence of mucosal healing		

	Kennedy et al. [45]	146 CD, 20 UC; 11 cohort totaling 746 patients (meta-analysis)	Retrospective observational	*Observational*	CD: younger age at diagnosis (<22 years old) Elevated white cell count > 5.25×10^9/L Elevated fecal calprotectin (> 50μg/g)	Continued immunomodulator	88% (CD)
				CD: 36% (1 year)		Mucosal healing	76% (UC/IBDU)
				56% (2 year)			
				UC/IBDU: 42% (1 year)	UC: no predictive factor identified		
				47% (2 years)			
				Meta-analysis			
				CD: 39% (1 year)			
			Systematic review, Meta-analysis	UC/IBDU: 35% (1 year)			
	Torres et al. [12]	37 studies	Systematic review	50% (CD/UC), 2 years	Markers of active disease	–	54.7–100% (CD)
					Poor prognostic factors including complicated or relapsing disease course		67–100% (UC)

IMM Immunomodulator, *CD* Crohn's disease, *UC* ulcerative colitis

Table 10.2 Predictors of relapse following anti-TNF-α therapy withdrawal

	UC (Ref.)	CD (Ref.)
Patient factors		
Male		[41]
Young age at diagnosis		[66]
Smoking		[43, 64]
Disease factors		
Phenotypic picture		
Behavior		Fistulizing [53]
Location/extent		Perianal [42, 64]
		Ileocolonic [52]
Markers of disease activity		
Low hemoglobin		[41]
High C-reactive protein		[41, 90]
High leucocyte counts	[90]	[90]
High fecal calprotectin	[56]	[41, 52, 56]
Absence of mucosal healing	[40]	[40]
Absence of normalization of mucosal cytokine gene expression		[58]
Absence of normalization of mucosal TNF-α	[59]	
Treatment factors		
Absence of concomitant immunomodulator	[60]	[60]
Previous immunomodulator failure		[64]
Late initiation of biologic therapy		[66]
Previous biological therapy		[43, 52]
Dose intensification of biologic therapy		[43]
Anti-infliximab antibody		[91]
Previous surgical resection		[41]

Predictive Factors for Relapse

Multiple factors, both modifiable and non-modifiable, have been suggested to predict risk of relapse for IBD. These can broadly be classified into patient factors, disease factors (disease activity and disease phenotype), and treatment factors as illustrated in Table 10.2.

Patient Factors

The prospective STORI trial studied infliximab withdrawal in 115 CD patients who had been treated with combination therapy with an immunomodulator for at least 1 year with a minimum of 6 months of steroid-free remission. On multivariate analysis, males were significantly more likely to relapse than females (HR 3.5; 95% CI 1.7–7.0) [41]. This finding was however not replicated by other studies [42–44].

Younger age at diagnosis was reported by two separate meta-analyses to be an adverse prognostic factor following anti-TNF-α therapy withdrawal [40, 45]. Smoking has been reported as a risk factor for relapse in patients with CD, in keeping with existing data that it augments disease progression [46].

Disease Factors

Disease Phenotype

CD patients with a fistulizing phenotype or with perianal disease carry a high risk of relapse post-anti-TNF-α therapy withdrawal [40, 42]. For (perianal) fistulizing disease, clinical assessment of remission is often suboptimal, and there may be ongoing subclinical inflammation in the fistula tract despite no fistula output [47]. In a prospective cohort study, it was observed that radiological healing lagged behind clinical remission by a median of 12 months [48]. MRI imaging to document healing should be considered prior to drug withdrawal given potential disabling outcomes including fecal incontinence. Similarly, radiologic investigations should be considered for those with small bowel disease where documentation of mucosal healing may be difficult to achieve with endoscopy alone. Internal fistulizing disease and the need for surgery are markers of an aggressive phenotype [40, 49–51]. Ileocolonic CD was reported in a prospective observational study to be predictive of relapse [52]. This observation was however not replicated by other studies [41, 42, 44, 53, 54].

Disease Activity

Active disease at time of drug withdrawal has consistently been shown to predict relapse [12, 40, 41, 44, 45, 52, 55]. Both clinical assessment and biochemical markers can be useful in predicting relapse (Table 10.2). This includes the presence of a low hemoglobin or elevated leucocyte counts, C-reactive protein concentrations, or a high fecal calprotectin level with some variation in the cutoff thresholds reported by different assays and studies [41, 45, 56]. The STORI trial observed hazard ratios of 6.0 (95% CI 2.2–16.5) for hemoglobin <145 g/L, 2.4 (95% CI 1.2–4.7) for leucocyte counts >6 × 10^9/L, 3.2 (95% CI 1.6–6.4) for C-reactive protein concentrations of ≥5 mg/L, and 2.5 (95% CI 1.1–5.8) for fecal calprotectin ≥300 μg/g [41].

Mucosal healing appears to be the most important prognostic factor for durable disease remission. In the Gisbert meta-analysis of 27 studies on the effects of anti-TNF-α therapy discontinuation in IBD, there was a significantly lower rate of relapse if mucosal healing was achieved prior to anti-TNF-α therapy withdrawal. The risk of relapse in CD patients at 1 year was 26% in those with mucosal healing versus 42% in those who did not achieve mucosal healing. The corresponding risk of relapse was 33% versus 50% for those with UC at 2 years [40]. Duration of remission has also been considered. Most studies attempted anti-TNF-α therapy

withdrawal after a median of 7.5 months to 2 years of treatment. Despite this, 21–45% of patients relapsed at 1 year [41–43, 49, 52, 54, 57]. While mucosal markers of sustained remission have been proposed, they have not been as well validated [58, 59].

Overall, anti-TNF-α therapy withdrawal should only be considered in those who have achieved sustained mucosal healing, and patients should be made aware that even in this scenario, the risk of relapse is still considerable, with one third of patients relapsing at 1 year and with this proportion increasing in the long term.

Treatment Factors

In Table 10.1, data on withdrawal of anti-TNF-α therapy was listed, and importantly, many cohorts received ongoing immunomodulator therapy (Table 10.1). This is important to consider, as Casanova et al. reported preliminary data in a retrospective observational study that ongoing maintenance immunomodulator therapy reduced the risk of relapse after withdrawal of the anti-TNF-α therapy by one third (HR = 0.70; 95% CI = 0.57–0.88) [60]. Although the risk of relapse would expectedly be lower for those in whom the immunomodulator was withdrawn in comparison with those who stopped the anti-TNF-α therapy in the setting of combination therapy, this has not been directly compared. SPARE, an ongoing prospective randomized trial comparing combination therapy to immunomodulator monotherapy and infliximab monotherapy, will hopefully confirm and provide further data on this area [61].

The role of therapeutic drug monitoring in predicting successful anti-TNF-α therapy withdrawal requires further prospective evaluation and validation. Drobne et al. observed in a retrospective study that CD patients on infliximab maintenance therapy who had high infliximab drug levels, defined as >5 μg/mL in this study, versus undetectable infliximab trough levels at time of immunomodulator withdrawal had a 0% versus 86% risk of relapse following immunomodulator withdrawal at median follow-up of 29 months. The median co-therapy duration was 13 months (IQR, 8–23 months). While it is stated that immunomodulators were withdrawn in patients with a durable response (CRP <10 mg/L with a persistent improvement of IBD symptoms), the goal of mucosal healing was not deemed a prerequisite to therapy withdrawal [62]. In contrast, a study by Ben-Horin identified a subgroup of patients with undetectable trough levels of anti-TNF-α who remained in clinical remission after drug withdrawal. Importantly, 95% of these patients had endoscopic or MRE evidence of absence of active inflammation. Rather than suggesting an imminent drug failure, this may represent a subgroup of patients whose clinical status is no longer dependent on anti-TNF-α therapy or may have non-TNF-α-mediated disease. As therapeutic drug monitoring is increasingly used, identification of a subgroup of patients who will not be disadvantaged from anti-TNF-α therapy withdrawal may therefore be possible [63]. Further prospective validation is required into the role of therapeutic drug monitoring in prognosticating patients for

anti-TNF-α therapy withdrawal, and to quote Ben-Horin, "[This] illustrates[s] the need for careful and case-by-case interpretation of drug/anti-drug antibody results, as interpretation may differ substantially depending on the context of the specific clinical situation when the blood test was ordered" [63].

Those with more active disease, requiring dose intensification of anti-TNF-α therapy during a 1-year course of biological therapy, were identified as at greater risk of relapse on therapy withdrawal (OR 12.96; 95% CI = 1.39–120.5) [43]. Further, previous immunomodulatory failure and previous exposure to biologic therapy were at increased risk of relapse following anti-TNF-α therapy withdrawal [43, 52, 64].

Patients with CD of short disease duration (less than 2 years) are more likely to benefit from anti-TNF-α therapies and may also have a lower risk of relapse following anti-TNF-α therapy withdrawal [5, 41, 54, 65–67]. This likely reflects that therapy was commenced before the irreversible immunological and structural damage occurred [68]. In keeping with this, patients with a previous surgical resection are at increased risk of relapse [41].

How to Withdraw Anti-TNF-α Therapy if Necessitated

The STORI trial has suggested that withdrawal of anti-TNF-α therapy is possible with careful risk stratification. Six risk factors were identified as predictors of relapse: male gender, absence of surgical resection, leukocyte counts $>6.0 \times 10^9$/L, hemoglobin ≤145 g/L, C-reactive protein ≥5.0 mg/L, and fecal calprotectin ≥ 300 μg/g. For those with two or less risk factors, the relapse rate was 15% at 1 year [41]. Before a patient is considered for drug withdrawal, they should be in deep remission with absence of clinical, biochemical, and endoscopic disease activity. The patient should lack symptoms of rectal bleeding, abdominal pain, urgency, and increased stool frequency. Laboratory markers/fecal calprotectin/imaging should be normal although validated cutoff points especially for fecal calprotectin are lacking. On endoscopy, there should be an absence of mucosal ulceration with a SES-CD score of <3 for CD [69]. For UC, the Mayo Clinic Score remains the most commonly used with most trials defining mucosal healing as a Mayo score of 0 or 1. A recent longitudinal study suggested that a Mayo score of 0 predicted a lower risk of relapse at 6 months, in comparison with a Mayo score of 1 (9.4% versus 36.6%, $p < 0.001$) [70]. Currently, histologic remission is not considered standard of care.

The minimum duration of deep remission requires prospective validation. The EPACT-II expert panel suggested a stopping rule of 4 years for immunomodulator/anti-TNF-α agent monotherapy for luminal CD patients in clinical remission. This can be shortened to 2 years for anti-TNF-α agent monotherapy if both clinical and endoscopic remission are achieved. For CD patients on combination immunomodulator/anti-TNF-α agents, the anti-TNF-α agent was judged appropriate to be stopped after 2 years if clinical and/or endoscopic remission was achieved [71].

No recommendation was made for fistulizing CD. There is currently no recommendation on the minimal duration of remission for individuals with UC prior to consideration of anti-TNF-α therapy withdrawal. In a systematic review of 14 studies on withdrawal of anti-TNF-α therapy in UC, duration of remission before study entry (minimum 6 months) was only stated in two studies [12].

Rather than withdrawing the biologic therapy completely, there are emerging studies of the use of lower maintenance doses in an attempt to minimize drug exposure and reduce costs. A prospective study on a cohort of 12 postoperative CD patients observed that when infliximab was given at lower doses titrated to endoscopic findings, infliximab doses of 3mg/kg were adequate to achieve mucosal healing [72]. However, this was a selected cohort of patients who underwent surgically induced remission and therefore may require lower circulating drug levels related to a smaller disease burden. Another prospective study on 16 CD patients observed that infliximab intervals of 10 weeks rather than 8 weekly infusions as titrated according to fecal calprotectin were as efficacious and did not increase the risk of loss of response provided that fecal calprotectin levels are within the normal range [73]. Prospective validation of these findings will be required. Down-titration of anti-TNF-α therapies has been studied in other immune-mediated disease such as rheumatoid arthritis. Even though short-term clinical disease activity and functional outcomes are maintained, down-titration is associated with significant radiological progression which may have long-term clinical implications [74].

There are also emerging data to support titrating biologic dose using therapeutic drug monitoring. In the TAXIT trial, it was shown that titrating infliximab dose to achieve a trough level of 3–7 mcg/mL resulted in higher remission rates than those with levels of <3 mcg/mL and also saved costs by allowing dose de-escalation for those with levels >7 mcg/mL [75]. The concept of titrating infliximab according to drug level (aiming for >3 mcg/mL) versus clinical symptoms in active CD was also explored in the TAILORIX trial. While proactive trough level-based dose intensification was not superior to clinically based dose adaptation, the full results of the study are still eagerly awaited [76].

Further prospective studies are required, as disease relapse may still occur following drug withdrawal even in those who demonstrate deep remission with mucosal healing, with a sufficiently long observational follow-up. Importantly, attention should be given to identify those who relapse early and restart treatment promptly. Currently, there is insufficient evidence to recommend whether complete drug withdrawal can be achieved or if a maintenance immunomodulator is always required. Close monitoring for disease recurrence is mandatory although there are no strong recommendations on the interval of monitoring. It has been proposed that fecal calprotectin and serum C-reactive protein should be performed every 8–12 weeks, with a low threshold to reevaluate if the CRP increases beyond 5 mg/L or fecal calprotectin is ≥300 mcg/g [41, 47]. The EPACT group proposed routine ileoscopy to be done at year 1 and year 4 in the absence of clinical symptoms [71]. Imaging modalities should be tailored to disease location and phenotype.

Summary

Based on the current literature, withdrawal of anti-TNF-α therapy is possible in highly selected patients who are in deep remission with a favorable risk profile. However, withdrawal of anti-TNF-α therapy is a decision that requires detailed discussion between the physician and patient, a meticulous assessment of a patient's risk profile, and acknowledgment of the risk of long-term disease relapse. The assessment should take into account disease phenotype, disease activity, treatment history, as well as consideration of specific situations including comorbidity status, patient age, and the presence of recurrent infections, malignancy, or pregnancy. Patients with active disease, younger disease onset, smoking habits, complex fistulizing or perianal CD, and history of intestinal resection or those who were required recent anti-TNF-α therapy dose escalation are considered high risk for relapse. Individualized management, with the patient closely involved in the decision-making process with appropriate counseling of the risk of relapse, and lower re-treatment response rates should be undertaken. Close interval monitoring is strongly recommended to identify early relapse and to provide prompt re-initiation of treatment.

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