

## Withdrawal of anti-tumour necrosis factor $\alpha$ therapy in inflammatory bowel disease

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representing a true challenge for patients, clinicians and health care systems. Consequently, a crucial question is raised namely if therapy can be stopped once remission is achieved and if so, how and in whom. Additionally, in a real-life clinical setting, discontinuation may also be considered for other reasons such as the patient's preference, pregnancy, social reasons as moving to countries or continents with less access, or different local policy or reimbursement. In contrast to initiation of anti-TNF $\alpha$  therapy guidelines regarding stopping of this treatment are missing. As a result, the decision of discontinuation is still a challenging aspect in the use of anti-TNF $\alpha$  therapy. Currently this is typically based on an estimated, case-by-case, benefit-risk ratio. This editorial is intended to provide an overview of recent data on this topic and shed light on the proposed drug withdrawal strategies.

**Key words:** Inflammatory bowel disease; Anti-tumour necrosis factor  $\alpha$  therapy; Withdrawal; Remission; Infliximab

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**Core tip:** Anti-tumour necrosis factor  $\alpha$  (anti-TNF $\alpha$ ) therapy is an established treatment in inflammatory bowel disease. Although guidelines exist on initiation of anti-TNF $\alpha$  therapy in inflammatory bowel diseases, information on if, when, how and in whom therapy can be stopped is limited. This is nevertheless an important topic taking under consideration the cost and the possible adverse events associated with biological agents as well as the desire of patients to discontinue medication especially after a long maintained remission. Moreover, although drug discontinuation for reasons other than loss of response is very usual in real-life clinical practice, the optimal withdrawal strategy is still debated.

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### Abstract

Anti-tumour necrosis factor  $\alpha$  (anti-TNF $\alpha$ ) therapy is an established treatment in inflammatory bowel disease. However, this treatment is associated with high costs and the possibility of severe adverse events

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## INTRODUCTION

Anti-tumor necrosis factor  $\alpha$  (anti-TNF $\alpha$ ) therapy has greatly improved the management of patients with inflammatory bowel diseases (IBD) namely Crohn's disease (CD) and ulcerative colitis (UC)<sup>[1]</sup>. However, this treatment is associated with high costs and the possibility of severe adverse events such as opportunistic infections or risk for lymphoma. These aspects represent a true challenge not only for patients and clinicians but also for health care systems<sup>[2]</sup>. Consequently, a crucial question is raised: can therapy be stopped once remission is achieved and if so, when, how and in whom? Additionally, in a real-life clinical setting, discontinuation may also be considered for other reasons such as the patient's own preference, pregnancy, moving to places with less access to biological agents, local policy or different reimbursement systems<sup>[2]</sup>.

Nowadays, as supporting data is lacking, there are no stopping rules for anti-TNF $\alpha$  therapy in IBD. There is even less information regarding prognostic factors that could predict relapse or sustained remission after anti-TNF $\alpha$  therapy discontinuation. The only provided evidence regarding CD comes from the landmark STORI trial<sup>[3]</sup> and a few retrospective observational<sup>[4-8]</sup> or small prospective studies<sup>[9-12]</sup>, while for UC there are even less data available<sup>[7,9,13]</sup> (Table 1). As a result, the decision of discontinuation is currently made on the basis of an individual judgement of benefits versus risks and cost-effectiveness<sup>[14-18]</sup>.

Another important issue when considering cessation of anti-TNF $\alpha$  therapy is whether the drug can safely be restarted when needed and whether efficacy will be similar. Possible lower response rates after re-initiation of biological therapy, limited alternative treatment options and/or immunogenicity concerns are all factors which constitute to the fear of stopping treatment<sup>[18,19]</sup>.

## WITHDRAWAL OF ANTI-TNF $\alpha$ THERAPY IN INFLAMMATORY BOWEL DISEASE. IS IT FEASIBLE?

Current guidelines suggest that anti-TNF $\alpha$  therapy should be started early in the course of the IBD to maximize its efficacy before irreversible bowel damage has occurred<sup>[20]</sup>. On the other hand, there are no rules and/or recommendations with respect to stopping, although it is often empirically proposed not to routinely stop anti-TNF $\alpha$  agents in IBD patients who respond, and especially in patients with disabling features of disease and/or at high-risk for relapse<sup>[14-18]</sup>. However, recent data indicate that a

proportion of patients, in clinical remission can stop anti-TNF $\alpha$  therapy without a major impact on disease control even for a relatively long time period, while on immunomodulators (IMM) (Table 1). The pivotal STORI trial showed that it was possible to identify a subgroup of patients with only a 10% relapse risk 24 mo post-discontinuation<sup>[3]</sup>.

Nevertheless, the results of the various studies may not always be comparable as the type of IBD (CD vs UC), of anti-TNF $\alpha$  therapy (infliximab vs adalimumab), the study design (prospective vs retrospective observational), the studied outcome (clinical vs endoscopic), the duration of remission before stopping anti-TNF $\alpha$  agents and the phenotypic and clinical characteristics of the patients often differ, as were the definition of relapse and the (median) follow up time after anti-TNF $\alpha$  cessation<sup>[21]</sup>. Moreover, CD patients are very heterogeneous in terms of disease type (luminal or fistulising), location (ileal, ileo-colonic or colonic) and behaviour (inflammatory, stricturing, or penetrating) and the consequences of relapse may widely vary, while establishment of complete mucosal healing and clinical remission is much more straightforward in UC than in CD.

One argument in favour of discontinuation of anti-TNF $\alpha$  therapy is the fact that all studies show that anti-TNF $\alpha$  therapy can be restarted without risking loss of response or adverse events in a large proportion of patients (Table 1). In a recent study by Baert *et al*<sup>[22]</sup> re-starting of infliximab therapy reintroduced response in 84.5% of patients at week 14, 70% at 1 year, and in 61% of patients at more than 4 years. Re-introduction of anti-TNF $\alpha$  therapy therefore seems possibly independent of the drug holiday<sup>[22]</sup>, although Laharie *et al*<sup>[23]</sup> showed that retreatment with IFX in CD primary responders should be administered within 50 wk after induction, for better efficacy and tolerance.

Discontinuation of anti-TNF $\alpha$  therapy for clinical remission has been shown to be feasible in other autoimmune, chronic diseases such as rheumatoid arthritis<sup>[24]</sup>, Behçet's uveitis<sup>[25]</sup>, spondyloarthritis<sup>[26]</sup> and sarcoidosis<sup>[27]</sup>.

## WHEN SHOULD WE STOP?

Stopping of anti-TNF $\alpha$  therapy is more likely to succeed in terms of maintaining prolonged remission when complete clinical (CDAI < 150), endoscopic (complete mucosal healing) and serological (normal CRP) remission, were achieved prior to discontinuation<sup>[20]</sup>. However, the minimum time of remission before stopping anti-TNF $\alpha$  therapy has not been yet well defined. It is proposed that clinical remission for over than one year prior to discontinuation of anti-TNF $\alpha$  therapy is adequate<sup>[11,20]</sup> while others suggest to stop after a minimum of two years of clinical and endoscopic remission or longer if only clinical remission can be documented<sup>[28]</sup>.

**Table 1** Studies on the discontinuation of anti-tumor necrosis factor  $\alpha$  therapy in inflammatory bowel disease

IBD type	Anti-TNF $\alpha$ therapy	n	Median follow up, mo	SCR at the end of follow up, %	Clinical benefit after re-introduction of anti-TNF $\alpha$ therapy for relapse, %	Ref.
CD	IFX	115	28	55	88	[3]
CD	IFX	48	49	35	ND	[4]
CD	IFX	53	18	12	96	[7]
UC	IFX	28	29	40	71	[7]
CD	IFX or ADM	121	12	55	55	[11]
UC	IFX	51	12	65	94	[13]
CD	IFX or ADM	37	1-44 (range)	26 (1 yr)	ND	[10]
CD	IFX or ADM	17	13	71	100	[9]
UC	IFX	34	13	65	90	[9]
CD	IFX	100	120	52	ND	[6]
CD	IFX or ADM	86	17	64 (1 yr)	93	[12]
CD	IFX	92	47	28	89	[5]

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; IFX: Infliximab; ADM: Adalimumab; TNF $\alpha$ : Tumor necrosis factor  $\alpha$ ; ND: Not defined; SCR: Sustained clinical remission.

Moreover, preliminary evidence suggests that a long lasting and profound drug-free remission may be achieved in case of a short duration of disease from diagnosis to start of anti-TNF $\alpha$  therapy, probably before irreversible immunological aberrations and more intestinal tissue impairment have occurred<sup>[6,7]</sup>.

## HOW SHOULD WE STOP?

The optimal treatment following discontinuation of anti-TNF $\alpha$  therapy in IBD has not yet been clearly defined, as in all previous studies the majority of patients (67%-100%) maintained clinical remission after cessation of treatment, by a continuous administration of an IMM<sup>[2,21]</sup>. Consequently, it is unclear whether a sustained clinical remission can be achieved during a true drug-free period.

Most will agree that a close follow up is needed when anti-TNF is stopped but how to monitor these patients in the most optimal way is not clear. Monitoring of CRP and fecal calprotectin levels every 8-12 wk may be very useful for predicting early clinical relapse with endoscopic re-evaluation in case of a significant increase of these biomarkers (Figure 1)<sup>[29]</sup>. If and when endoscopic evaluation should be implemented in the follow up of patients who remain in full remission remains to be elucidated<sup>[28]</sup>.

## IN WHOM?

Another important issue, before applying a stopping strategy for anti-TNF $\alpha$  therapy, is to assess prediction of sustained remission after withdrawal of the drugs, in order to identify the ideal candidate for discontinuation of anti-TNF $\alpha$  treatment. We believe that the decision-making approach to stop anti-TNF $\alpha$  therapy is currently based on limited data (Table 2).

Although patients with (perianal) fistulising CD were excluded from many studies including the STORI trial<sup>[3]</sup> current data suggest that these patients relapse with the same rate as those with luminal disease<sup>[5,6,9,11,12]</sup>.

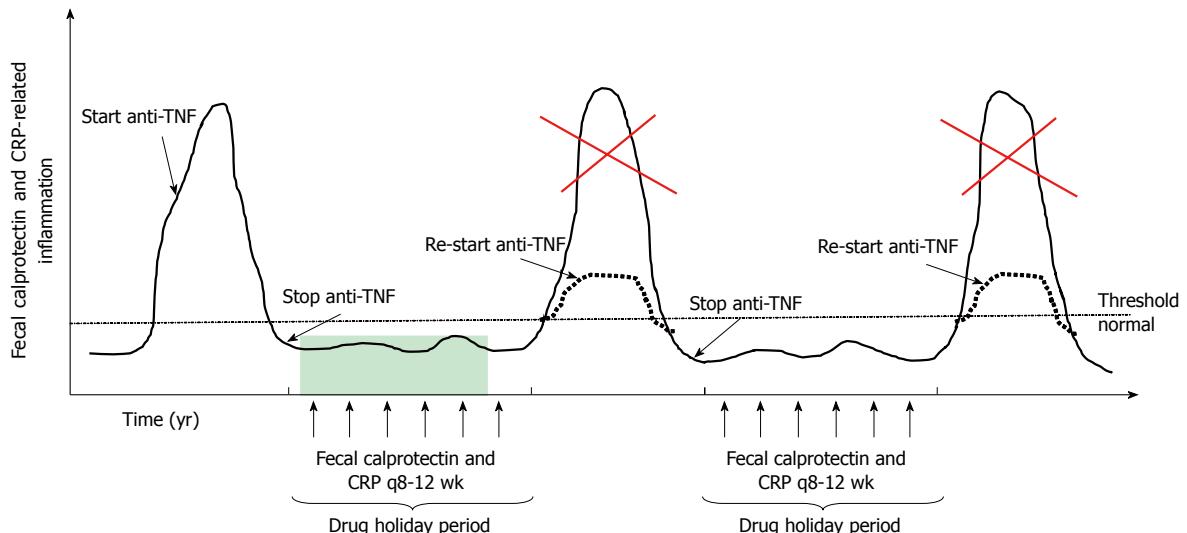
However, in previous studies infliximab discontinuation led to a higher rate of relapse in patients with perianal fistulising compared to luminal CD<sup>[23,30,31]</sup>. One possible explanation could be that in most of these studies clinical remission and relapse for the majority of patients with (perianal) fistulising CD were not evaluated by imaging techniques or this information was missing. This is very important taking into account that perianal disease is often active despite external fistulae closure. Consequently, evaluation of CD patients with stricturing and/or penetrating disease, before discontinuation of anti-TNF $\alpha$  therapy, may include also imaging techniques. Patients with internal fistulas, an intestinal stenosis or a complex perianal fistulising disease may have a poor prognosis after discontinuation of the anti-TNF $\alpha$  therapy.

Moreover although complete mucosal healing at the time of IFX discontinuation for clinical remission in CD patients was predictive for sustained clinical remission after cessation of the drug<sup>[3,6]</sup>, this was not confirmed by other studies<sup>[11,13,32]</sup>.

Finally, regarding the role of therapeutic drug monitoring on the decision making of stopping anti-TNF therapy for clinical remission preliminary evidence points out that low IFX trough levels at the time of discontinuation are predictive of sustained remission after drug cessation in CD, while the role of antibodies to IFX has not been yet clearly defined<sup>[3,6]</sup>. It seems that these patients do not need the drug anymore to maintain remission which is in agreement with the results of the TAXIT trial where 9% of the patients being in remission had undetectable trough levels and were stopped successfully without relapse<sup>[33]</sup>.

## NEW CONCEPT OF INTERMITTENT ANTI-TNF $\alpha$ THERAPY IN INFLAMMATORY BOWEL DISEASE

Tailoring of anti-TNF $\alpha$  maintenance therapy for patients achieving remission is becoming nowadays a necessity



**Figure 1** New concept of intermittent anti-tumor necrosis factor  $\alpha$  therapy in inflammatory bowel disease. Stopping anti-TNF $\alpha$  agents after achieving a deep remission may result in prolonged clinical remission. Close monitoring of these patients with fecal calprotectin and CRP measurements (arrows) will allow early re-initiation of anti-TNF $\alpha$  therapy, when inflammation is starting to rise, which may result to a sustained clinical benefit (dotted line) preventing a disease flare (red cross). These patients may be considered as treated periodically and not episodically. TNF: Tumor necrosis factor; CRP: C-reactive protein.

**Table 2** Risk factors for relapse after stopping anti-tumor necrosis factor  $\alpha$  therapy for remission (clinical or endoscopic) in inflammatory bowel disease

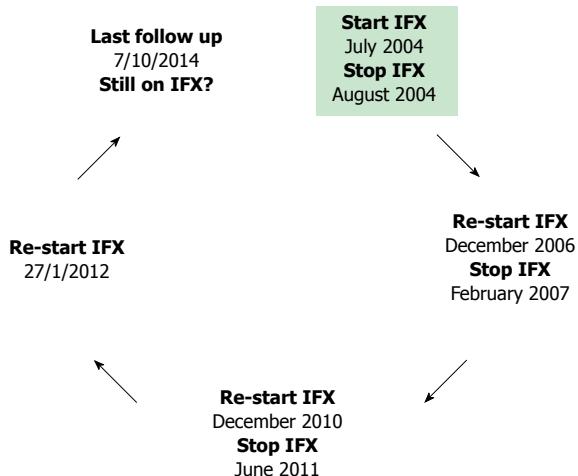
Risk factors	Ref.
Clinical or phenotypic	
Corticosteroid use between 12 and 6 mo before baseline	[3]
Male gender	[3]
Absence of previous surgical resection	[3]
Longer disease duration from diagnosis to first infliximab	[7]
Previous biological therapy	[11-13]
Dose intensification during the first year of anti-TNF $\alpha$ therapy	[11]
Age at CD diagnosis $\geq 25$ yr	[6]
Ileocolonic disease at diagnosis	[12]
Active smoking	[5]
Previous antimetabolite failure	[5]
Perianal disease	[5]
Serological <sup>1</sup>	
Hemoglobin levels $\leq 14.5$ g/dL	[3]
White blood count $> 6 \times 10^9$ /L	[3]
High sensitive CRP $\geq 5$ mg/L	[3]
Infliximab trough levels $\geq 2$ $\mu$ g/mL	[3]
Serum calprotectin $> 5675$ ng/mL	[37]
Endoscopic <sup>1</sup>	
CDEIS $> 0$	[3]
Mucosal <sup>1</sup>	
Lack of normalization of IL-17A and TNF $\alpha$ expression levels	[10]
Microbiological <sup>1</sup> (CD-associated dysbiosis)	
Low rate of <i>Faecalibacterium prausnitzii</i> in fecal samples	[38]
Low rate of <i>Bacteroides</i> in fecal samples	[38]
Fecal <sup>1</sup>	
Fecal calprotectin $\geq 300$ $\mu$ g/g	[3]
Genetic	
Fc gamma receptor III B-NA2/NA2 genotype (fistulising disease)	[39]

<sup>1</sup>At the time of anti-TNF $\alpha$  therapy discontinuation. CD: Crohn's disease; CRP: C-reactive protein; CDEIS: Crohn's Disease Endoscopic index of severity; IL: Interleukin; NA: Neutrophil antigen; TNF $\alpha$ : Tumor necrosis factor  $\alpha$ .

as safety and costs issues may hinder the long-term, sustained clinical benefit deriving from this therapy. This could be achieved either by lowering the dose of these drugs<sup>[33]</sup>, based on therapeutic drug monitoring<sup>[34]</sup> or by stopping them following the intermittent non-continuous pharmacological treatment approach<sup>[2]</sup>. Patients following the latter strategy may be considered as treated periodically rather than episodically (Figure 1)<sup>[35]</sup>. A paradigm of this therapeutic pharmacological approach from real-life clinical practice is described in Figure 2. We believe that prediction of sustained clinical remission after discontinuation of anti-TNF $\alpha$  therapy along with the close monitoring of these patients so as to avoid an upcoming disease flare by early re-introduction of these drugs may be a first step for optimizing maintenance anti-TNF $\alpha$  treatment in patients achieving remission.

## CONCLUSION

Intentional cessation of anti-TNF $\alpha$  treatment will become a more prevalent practice in the future not only for safety and cost reasons but probably also due to newly available non TNF $\alpha$  neutralizing pharmaceutical therapeutics options, although with the introduction of biosimilars, costs will probably become less important. Anti-TNF $\alpha$  withdrawal strategy to achieve disease control based on an on-demand use of anti-TNF $\alpha$  therapy (when relapse is suspected after discontinuation of the drugs) and a continuous treatment with IMM, could be an option to reduce chronic exposure to biologics, at least to a highly selected IBD population.



**Figure 2 Successful intermittent infliximab therapy in a patient with ulcerative colitis: A paradigm from real-life clinical practice.** This is an example of a UC patient (male, age at diagnosis 33 years) with pancolitis, treated in our center, who received successfully intermittent infliximab (IFX) therapy (black arrows represent time periods of clinical remission). He has been treated with IFX for relapse, after discontinuation of the drug on his own preference while in clinical remission continuing on azathioprine. At the last time of follow up he was still in clinical and biochemical (normal CRP) remission under IFX maintenance monotherapy. This patient has never developed antibodies to IFX despite receiving interrupted therapy, while the last available (25/2/2014) trough concentrations of IFX were 8.09  $\mu$ g/mL (q5).

Nevertheless, in order to elucidate whether discontinuation of anti-TNF $\alpha$  therapy for remission will become a routine strategy in the future for the long-term management of IBD patients and to define the optimal withdrawal strategy more studies are needed. One of them would definitely be the SPARE study from the Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives group, a Phase IV, prospective, open-label, randomized controlled trial comparing infliximab antimetabolites combination therapy to anti-metabolites monotherapy and infliximab monotherapy in CD patients in sustained steroid-free remission on combination therapy (ClinicalTrials.gov Identifier: NCT02177071)<sup>[36]</sup>. The main goal of this study is to demonstrate that infliximab scheduled maintenance with or without antimetabolites is superior to antimetabolites alone to maintain sustained steroid-free remission over 2 years, while the latter is non inferior with regards to the mean time spent in remission over the same duration<sup>[36]</sup>.

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