World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i16.4773

World J Gastroenterol 2015 April 28; 21(16): 4773-4778
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Withdrawal of anti-tumour necrosis factor α therapy in inflammatory bowel disease

Konstantinos Papamichael, Severine Vermeire

Konstantinos Papamichael, Severine Vermeire, Department of Clinical and Experimental Medicine, Translational Research Center for Gastrointestinal Disorders, 3000 Leuven, Belgium

Author contributions: Papamichael K wrote the manuscript; Vermeire S critically revised the manuscript; all authors approved the final version of the article.

Conflict-of-interest: Papamichael K has received a consultancy fee from MSD Hellas; and Vermeire S has received research funding from UCB Pharma, Abbvie and UCB Pharma, lecture fees from Abbott, Abbvie, MSD, Ferring Pharmaceuticals and UCB Pharma and consultancy fees from Pfizer, Ferring Pharmaceuticals, Shire Pharmaceuticals Group, MSD, and AstraZeneca Pharmaceuticals.

Correspondence to: Konstantinos Papamichael, MD, PhD, FEBGH, Department of Clinical and Experimental Medicine, Translational Research Center for Gastrointestinal Disorders, Herestraat 49, 3000 Leuven,
Belgium. konstantinos.papamichail@kuleuven.be
Telephone: +32-16-377557
Fax: +32-16-344419

Received: November 18, 2014
Peer-review started: November 19, 2014
First decision: December 11, 2014
Revised: January 7, 2015
Accepted: February 11, 2015
Article in press: February 11, 2015
Published online: April 28, 2015

Abstract

Anti-tumour necrosis factor α (anti-TNFα) therapy is an established treatment in inflammatory bowel disease. However, this treatment is associated with high costs and the possibility of severe adverse events 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-TNFα 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-TNFα 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 α therapy; Withdrawal; Remission; Infliximab

Core tip: Anti-tumour necrosis factor α (anti-TNFα) therapy is an established treatment in inflammatory bowel disease. Although guidelines exist on initiation of anti-TNFα 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.

Papamichael K, Vermeire S. Withdrawal of anti-tumour necrosis factor α therapy in inflammatory bowel disease. *World J*

Gastroenterol 2015; 21(16): 4773-4778 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i16/4773.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i16.4773

INTRODUCTION

Anti-tumor necrosis factor α (anti-TNFα) therapy has greatly improved the management of patients with inflammatory bowel diseases (IBD) namely Crohn's disease (CD) and ulcerative colitis (UC)[1]. 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[2]. 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[2].

Nowadays, as supporting data is lacking, there are no stopping rules for anti-TNFα therapy in IBD. There is even less information regarding prognostic factors that could predict relapse or sustained remission after anti-TNFα therapy discontinuation. The only provided evidence regarding CD comes from the landmark STORI trial[3] and a few retrospective observational[4-8] or small prospective studies[9-12], while for UC there are even less data available[7,9,13] (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[14-18].

Another important issue when considering cessation of anti-TNFα 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[18,19].

WITHDRAWAL OF ANTI-TNFα THERAPY IN INFLAMMATORY BOWEL DISEASE. IS IT FEASIBLE?

Current guidelines suggest that anti-TNFα therapy should be started early in the course of the IBD to maximize its efficacy before irreversible bowel damage has occurred[20]. 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-TNFα agents in IBD patients who respond, and especially in patients with disabling features of disease and/or at high-risk for relapse[14-18]. However, recent data indicate that a proportion of patients, in clinical remission can stop anti-TNFα 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[3].

Nevertheless, the results of the various studies may not always be comparable as the type of IBD (CD *vs* UC), of anti-TNFα therapy (infliximab *vs* adalimumab), the study design (prospective *vs* retrospective observational), the studied outcome (clinical *vs* endoscopic), the duration of remission before stopping anti-TNFα 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-TNFα cessation[21]. 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-TNFα therapy is the fact that all studies show that anti-TNFα 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*[22] re-starting of infliximab therapy re-introduced 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-TNFα therapy therefore seems possibly independent of the drug holiday[22], although Laharie *et al*[23] 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-TNFα therapy for clinical remission has been shown to be feasible in other autoimmune, chronic diseases such as rheumatoid arthritis[24], Behçet's uveitis[25], spondyloarthritis[26] and sarcoidosis[27].

WHEN SHOULD WE STOP?

Stopping of anti-TNFα 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[20]. However, the minimum time of remission before stopping anti-TNFα therapy has not been yet well defined. It is proposed that clinical remission for over than one year prior to discontinuation of anti-TNFα therapy is adequate[11,20] 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[28].

Table 1 Studies on the discontinuation of anti-tumor necrosis factor α therapy in inflammatory bowel disease

IBD type	Anti-TNFα therapy	*n*	Median follow up, mo	SCR at the end of follow up, %	Clinical benefit after re-introduction of anti-TNFα 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; TNFα: Tumor necrosis factor α; 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-TNFα therapy, probably before irreversible immunological aberrations and more intestinal tissue impairment have occurred[6,7].

HOW SHOULD WE STOP?

The optimal treatment following discontinuation of anti-TNFα 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[2,21]. 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)[29]. If and when endoscopic evaluation should be implemented in the follow up of patients who remain in full remission remains to be elucidated[28].

IN WHOM?

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

Although patients with (perianal) fistulising CD were excluded from many studies including the STORI trial[3] current data suggest that these patients relapse with the same rate as those with luminal disease[5,6,9,11,12]. However, in previous studies infliximab discontinuation led to a higher rate of relapse in patients with perianal fistulising compared to luminal CD[23,30,31]. 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-TNFα 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-TNFα 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[3,6], this was not confirmed by other studies[11,13,32].

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[3,6]. 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[33].

NEW CONCEPT OF INTERMITTENT ANTI-TNFα THERAPY IN INFLAMMATORY BOWEL DISEASE

Tailoring of anti-TNFα maintenance therapy for patients achieving remission is becoming nowadays a necessity

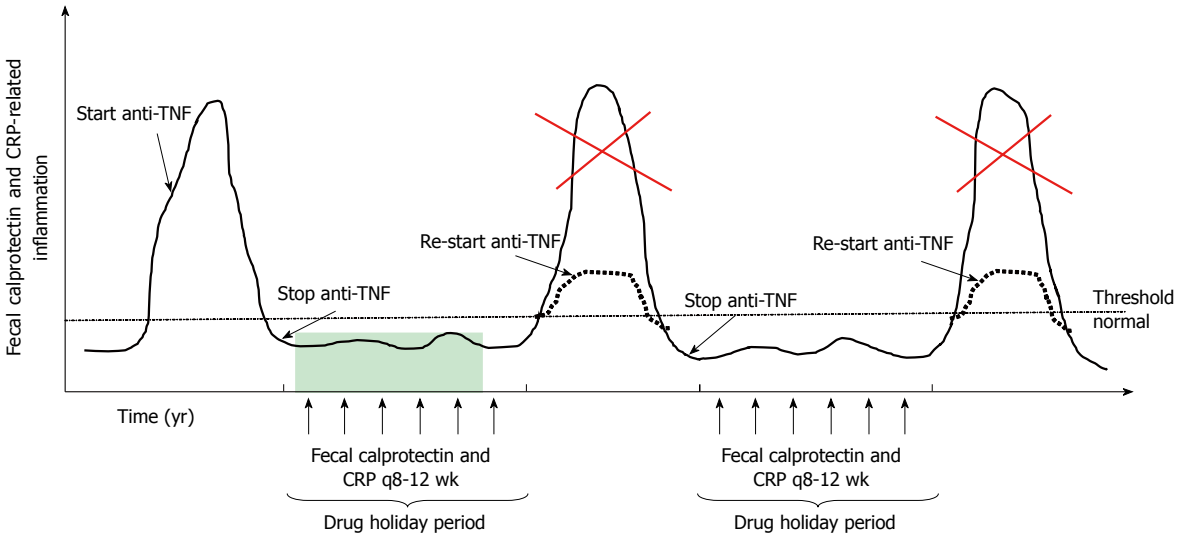

Figure 1 New concept of intermittent anti-tumor necrosis factor α therapy in inflammatory bowel disease. Stopping anti-TNFα agents after achieving a deep remission may result in prolonged clinical remission. Close monitoring of these patients with fecal calprotectin and CRP measurements (arrows) will allow early re-initiation of anti-TNFα 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 α 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-TNFα therapy	[11]
Age at CD diagnosis ⩾ 25 yr	[6]
Ileocolonic disease at diagnosis	[12]
Active smoking	[5]
Previous antimetabolite failure	[5]
Perianal disease	[5]
Serological[1]	
Hemoglobin levels ⩽ 14.5 g/dL	[3]
White blood count > 6 × 10^9/L	[3]
High sensitive CRP ⩾ 5 mg/L	[3]
Infliximab trough levels ⩾ 2 μg/mL	[3]
Serum calprotectin > 5675 ng/mL	[37]
Endoscopic[1]	
CDEIS > 0	[3]
Mucosal[1]	
Lack of normalization of IL-17A and TNFα expression levels	[10]
Microbiological[1] (CD-associated dysbiosis)	
Low rate of Faecalibacterium prausnitzii in fecal samples	[38]
Low rate of Bacteroides in fecal samples	[38]
Fecal[1]	
Fecal calprotectin ⩾ 300 μg/g	[3]
Genetic	
Fc gamma receptor ⅢB-NA2/NA2 genotype (fistulising disease)	[39]

[1]At the time of anti-TNFα therapy discontinuation. CD: Crohn's disease; CRP: C-reactive protein; CDEIS: Crohn's Disease Endoscopic index of severity; IL: Interleukin; NA: Neutrophil antigen; TNFα: Tumor necrosis factor α.

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[33], based on therapeutic drug monitoring[34] or by stopping them following the intermittent non-continuous pharmacological treatment approach[2]. Patients following the latter strategy may be considered as treated periodically rather than episodically (Figure 1)[35]. 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-TNFα 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-TNFα treatment in patients achieving remission.

CONCLUSION

Intentional cessation of anti-TNFα 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 TNFα neutralizing pharmaceutical therapeutics options, although with the introduction of biosimilars, costs will probably become less important. Anti-TNFα withdrawal strategy to achieve disease control based on an on-demand use of anti-TNFα 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.

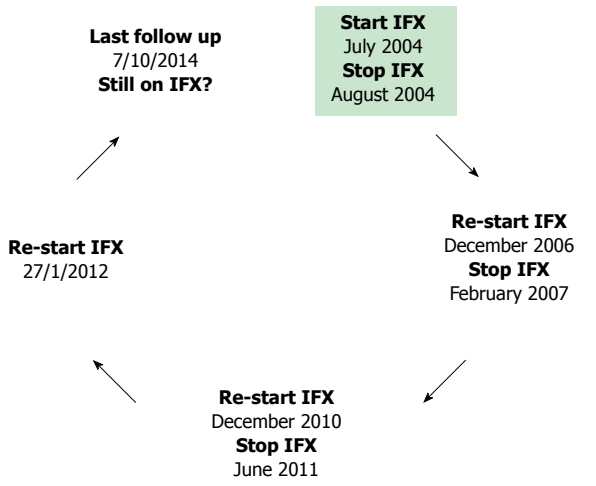

Figure 2 Successful intermittent infliximab therapy in a patient with ulcerative colitis: A paradigm from real-life clinical practice. This is an example of a UC patient (male, age at diagnosis 33 years) with pancolitis, treated in our center, who received successfully intermittent infliximab (IFX) therapy (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 μg/mL (q5).

Nevertheless, in order to elucidate whether discontinuation of anti-TNFα 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)[36]. 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[36].

ACKNOWLEDGMENTS

Papamichael K received a fellowship grant from the Hellenic Gastroenterology Society and the European Crohn's and Colitis Organization; Vermeire S is a Senior Clinical Investigator of the Research Foundation-Flanders, Belgium.

REFERENCES

1 **Billiet T**, Rutgeerts P, Ferrante M, Van Assche G, Vermeire S. Targeting TNF-α for the treatment of inflammatory bowel disease. *Expert Opin Biol Ther* 2014; **14**: 75-101 [PMID: 24206084 DOI: 10.1517/14712598.2014.858695]

2 **Sorrentino D**, Nash P, Viladomiu M, Hontecillas R, Bassaganya-Riera J. Stopping anti-TNF agents in patients with Crohn's disease in remission: is it a feasible long-term strategy? *Inflamm Bowel Dis* 2014; **20**: 757-766 [PMID: 24572206 DOI: 10.1097/01.MIB.0000442680.47427.bf]

3 **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. 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]

4 **Waugh AW**, Garg S, Matic K, Gramlich L, Wong C, Sadowski DC, Millan M, Bailey R, Todoruk D, Cherry R, Teshima CW, Dieleman L, Fedorak RN. Maintenance of clinical benefit in Crohn's disease patients after discontinuation of infliximab: long-term follow-up of a single centre cohort. *Aliment Pharmacol Ther* 2010; **32**: 1129-1134 [PMID: 20807218 DOI: 10.1111/j.1365-2036.2010.04446.x]

5 **Chauvin A**, Le Thuaut A, Belhassan M, Le Baleur Y, Mesli F, Bastuji-Garin S, Delchier JC, Amiot A. Infliximab as a bridge to remission maintained by antimetabolite therapy in Crohn's disease: A retrospective study. *Dig Liver Dis* 2014; **46**: 695-700 [PMID: 24893686 DOI: 10.1016/j.dld.2014.04.012]

6 **Papamichael K**, Vande Casteele N, Gils A, Tops S, Hauenstein S, Singh S, Princen F, Van Assche G, Rutgeerts P, Vermeire S, Ferrante M. Long-Term Outcome of Patients With Crohn's Disease Who Discontinued Infliximab Therapy Upon Clinical Remission. *Clin Gastroenterol Hepatol* 2014; Epub ahead of print [PMID: 25478919 DOI: 10.1016/j.cgh.2014.11.026]

7 **Steenholdt C**, Molazahi A, Ainsworth MA, Brynskov J, Østergaard Thomsen O, Seidelin JB. Outcome after discontinuation of infliximab in patients with inflammatory bowel disease in clinical remission: an observational Danish single center study. *Scand J Gastroenterol* 2012; **47**: 518-527 [PMID: 22375898 DOI: 10.3109/00365521.2012.660541]

8 **Lu C**, Waugh A, Bailey RJ, Cherry R, Dieleman LA, Gramlich L, Matic K, Millan M, Kroeker KI, Sadowski D, Teshima CW, Todoruk D, Wong C, Wong K, Fedorak RN. Crohn's disease genotypes of patients in remission vs relapses after infliximab discontinuation. *World J Gastroenterol* 2012; **18**: 5058-5064 [PMID: 23049214 DOI: 10.3748/wjg.v18.i36.5058]

9 **Molander P**, Färkkilä M, 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. Outcome after discontinuation of TNFα-blocking therapy in patients with inflammatory bowel disease in deep remission. *Inflamm Bowel Dis* 2014; **20**: 1021-1028 [PMID: 24798636 DOI: 10.1097/MIB.0000000000000052]

10 **Rismo R**, Olsen T, Cui G, Paulssen EJ, Christiansen I, Johnsen K, Florholmen J, Goll R. Normalization of mucosal cytokine gene expression levels predicts long-term remission after discontinuation of anti-TNF therapy in Crohn's disease. *Scand J Gastroenterol* 2013; **48**: 311-319 [PMID: 23302000 DOI: 10.3109/00365521.2012.758773]

11 **Molnár T**, Lakatos PL, Farkas K, Nagy F, Szepes Z, Miheller P, Horváth G, Papp M, Palatka K, Nyári T, Bálint A, Lőrinczy K, Wittmann T. Predictors of relapse in patients with Crohn's disease in remission after 1 year of biological therapy. *Aliment Pharmacol Ther* 2013; **37**: 225-233 [PMID: 23181359 DOI: 10.1111/apt.12160]

12 **Brooks AJ**, Sebastian S, Cross SS, Robinson K, Warren L, Wright A, Marsh AM, Tsai H, Majeed F, McAlindon ME, Preston C, Hamlin PJ, Lobo AJ. Outcome of elective withdrawal of anti-tumour necrosis factor-α therapy in patients with Crohn's disease in established remission. *J Crohns Colitis* 2014; Epub ahead of print [PMID: 25311864 DOI: 10.1016/j.crohns.2014.09.007]

13 **Farkas K**, Lakatos PL, Nagy F, Szepes Z, Miheller P, Papp M, Palatka K, Bálint A, Bor R, Wittmann T, Molnár T. Predictors of

relapse in patients with ulcerative colitis in remission after one-year of infliximab therapy. *Scand J Gastroenterol* 2013; **48**: 1394-1398 [PMID: 24131338 DOI: 10.3109/00365521.2013.845906]
14 **Louis E**, Belaiche J, Reenaers C. Are we giving biologics too much time? When should we stop treatment? *World J Gastroenterol* 2008; **14**: 5528-5531 [PMID: 18810771]
15 **Peyrin-Biroulet L**, Danese S. Stopping infliximab in Crohn's disease: still an ongoing STORI. *Inflamm Bowel Dis* 2012; **18**: 2201-2202 [PMID: 23236615]
16 **Kamm MA**, Ng SC, De Cruz P, Allen P, Hanauer SB. Practical application of anti-TNF therapy for luminal Crohn's disease. *Inflamm Bowel Dis* 2011; **17**: 2366-2391 [PMID: 21337669 DOI: 10.1002/ibd.21655]
17 **Hashash JG**, Regueiro MD. The great debate: stopping immunomodulators and biologics in Crohn's disease patients in remission. *Expert Rev Gastroenterol Hepatol* 2013; **7**: 501-503 [PMID: 23984997 DOI: 10.1586/17474124.2013.814933]
18 **Clarke K**, Regueiro M. Stopping immunomodulators and biologics in inflammatory bowel disease patients in remission. *Inflamm Bowel Dis* 2012; **18**: 174-179 [PMID: 21674731 DOI: 10.1002/ibd.21792]
19 **Nanda KS**, Cheifetz AS, Moss AC. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. *Am J Gastroenterol* 2013; **108**: 40-47; quiz 48 [PMID: 23147525 DOI: 10.1038/ajg.2012.363]
20 **D'Haens GR**, Panaccione R, Higgins PD, Vermeire S, Gassull M, Chowers Y, Hanauer SB, Herfarth H, Hommes DW, Kamm M, Löfberg R, Quary A, Sands B, Sood A, Watermeyer G, Lashner B, Lémann M, Plevy S, Reinisch W, Schreiber S, Siegel C, Targan S, Watanabe M, Feagan B, Sandborn WJ, Colombel JF, Travis S. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? *Am J Gastroenterol* 2011; **106**: 199-212; quiz 213 [PMID: 21045814 DOI: 10.1038/ajg.2010.392]
21 **Pariente B**, Laharie D. Review article: why, when and how to de-escalate therapy in inflammatory bowel diseases. *Aliment Pharmacol Ther* 2014; **40**: 338-353 [PMID: 24957164 DOI: 10.1111/apt.12838]
22 **Baert F**, Drobne D, Gils A, Vande Casteele N, Hauenstein S, Singh S, Lockton S, Rutgeerts P, Vermeire S. Early trough levels and antibodies to infliximab predict safety and success of reinitiation of infliximab therapy. *Clin Gastroenterol Hepatol* 2014; **12**: 1474-81. e2; quiz e91 [PMID: 24486408 DOI: 10.1016/j.cgh.2014.01.033]
23 **Laharie D**, Chanteloup E, Chabrun E, Subtil C, Kowo M, El Hanafi K, DE Lédinghen V. The tolerance and efficacy of a postponed retreatment with infliximab in Crohn's disease primary responders. *Aliment Pharmacol Ther* 2009; **29**: 1240-1248 [PMID: 19416134 DOI: 10.1111/j.1365-2036.2009.03997.x]
24 **Tanaka Y**, Hirata S. Is it possible to withdraw biologics from therapy in rheumatoid arthritis? *Clin Ther* 2013; **35**: 2028-2035 [PMID: 24290736 DOI: 10.1016/j.clinthera.2013.10.008]
25 **Kawaguchi T**, Kawazoe Y, Kamoi K, Miyanaga M, Takase H, Sugita S, Mochizuki M. Clinical course of patients with Behçet's uveitis following discontinuation of infliximab therapy. *Jpn J Ophthalmol* 2014; **58**: 75-80 [PMID: 24129677 DOI: 10.1007/s10384-013-0283-3]
26 **Olivieri I**, D'Angelo S, Padula A, Leccese P, Nigro A, Palazzi C. Can we reduce the dosage of biologics in spondyloarthritis? *Autoimmun Rev* 2013; **12**: 691-693 [PMID: 22940233 DOI: 10.1016/j.autrev.2012.08.013]
27 **Vorselaars AD**, Verwoerd A, van Moorsel CH, Keijsers RG, Rijkers GT, Grutters JC. Prediction of relapse after discontinuation of infliximab therapy in severe sarcoidosis. *Eur Respir J* 2014; **43**: 602-609 [PMID: 23988768 DOI: 10.1183/09031936.00055213]
28 **Pittet V**, Froehlich F, Maillard MH, Mottet C, Gonvers JJ, Felley C, Vader JP, Burnand B, Michetti P, Schoepfer A. When do we dare to stop biological or immunomodulatory therapy for Crohn's disease? Results of a multidisciplinary European expert panel. *J Crohns Colitis* 2013; **7**: 820-826 [PMID: 23664620 DOI: 10.1016/j.crohns.2013.04.013]
29 **De Suray N**, Salleron J, Vernier-Massouille G. Close monitoring of CRP and fecal calprotectin is able to predict clinical relapse in patients with Crohn's disease in remission after infliximab withdrawal. A subanalysis of the STORI study. *Gastroenterology* 2012; **142**: S-149
30 **Molnár T**, Farkas K, Miheller P, Nyári T, Szepes Z, Herszényi L, Müzes G, Nagy F, Tulassay Z, Wittmann T. Is the efficacy of successful infliximab induction therapy maintained for one year lasting without retreatment in different behavior types of Crohn's disease? *J Crohns Colitis* 2008; **2**: 322-326 [PMID: 21172231 DOI: 10.1016/j.crohns.2008.07.003]
31 **Domènech E**, Hinojosa J, Nos P, Garcia-Planella E, Cabré E, Bernal I, Gassull MA. Clinical evolution of luminal and perianal Crohn's disease after inducing remission with infliximab: how long should patients be treated? *Aliment Pharmacol Ther* 2005; **22**: 1107-1113 [PMID: 16305724]
32 **Dai C**, Liu WX, Jiang M, Sun MJ. Mucosal healing did not predict sustained clinical remission in patients with IBD after discontinuation of one-year infliximab therapy. *PLoS One* 2014; **9**: e110797 [PMID: 25330148 DOI: 10.1371/journal.pone.0110797]
33 **Sorrentino D**, Paviotti A, Terrosu G, Avellini C, Geraci M, Zarifi D. Low-dose maintenance therapy with infliximab prevents postsurgical recurrence of Crohn's disease. *Clin Gastroenterol Hepatol* 2010; **8**: 591-599.e1; quiz e78-79 [PMID: 20139033 DOI: 10.1016/j.cgh.2010.01.016]
34 **Vande Casteele N**, Gils A, Ballet V, Compernolle G, Peeters M, Van Steen K, Simoens S, Ferrante M, Van Assche G, Vermeire S, Rutgeerts P. Randomised controlled trial of drug level versus clinically based dosing of infliximab maintenance therapy in IBD: Final results of the TAXIT study. *UEG J* 2013; **1**: A1
35 **Ben-Horin S**, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. *Autoimmun Rev* 2014; **13**: 24-30 [PMID: 23792214 DOI: 10.1016/j.autrev.2013.06.002]
36 **Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives**. A proSpective Randomized Controlled Trial comParing infliximAb-antimetabolites Combination Therapy to Anti-metabolites monotheRapy and Infliximab monothErapy in Crohn's Disease Patients in Sustained Steroid-free Remission on Combination Therapy (SPARE). Last Updated Date June 26, 2014. Available from: URL: https://clinicaltrials.gov/ct2/show/record/NCT02177071?term=spare&rank=3
37 **Meuwis MA**, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, Piver E, Seidel L, Colombel JF, Louis E. Serum calprotectin as a biomarker for Crohn's disease. *J Crohns Colitis* 2013; **7**: e678-e683 [PMID: 23845231 DOI: 10.1016/j.crohns.2013.06.008]
38 **Rajca S**, Grondin V, Louis E, 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, Paintaud G, Piver E, Allez M, Mary JY, Sokol H, Colombel JF, Seksik P. Alterations in the intestinal microbiome (dysbiosis) as a predictor of relapse after infliximab withdrawal in Crohn's disease. *Inflamm Bowel Dis* 2014; **20**: 978-986 [PMID: 24788220 DOI: 10.1097/MIB.0000000000000036]
39 **Papamichail K**, Arias M, Ferrante M, Ballet V, Claes K, Wollants WJ, Van Assche G, Rutgeerts PJ, Vermeire S. Fc gamma receptor mutations for prediction of sustained clinical remission after infliximab discontinuation in Crohn's disease patients. *UEG J* 2014; **2**: A374

P- Reviewer: Ahluwalia NK, Mendall MA, Negreanu L, Trifan A
S- Editor: Ma YJ **L- Editor**: A **E- Editor**: Zhang DN