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*TOPIC HIGHLIGHT*

**Emiko Mizoguchi, MD, PhD,** *Series Editor*

# Are we giving biologics too much time? When should we stopping treatment?

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## Abstract

The optimal duration of biological treatment, particularly anti-TNF, in inflammatory bowel disease (IBD) is a very important question both for patients and physicians. There is no published evidence to clearly and definitely answer this question. However data on natural history of IBD, long term safety of biologics, immunosuppressors (IS) cessation and some preliminary studies on biologics cessation may help us to discuss this topic. The decision to stop a biological treatment is currently based on a compromise between the benefits and risks associated with the prolongation of this treatment. IBD, more particularly CD, are characterized by the development of complications and the need for recurrent hospitalizations and surgeries in approximately 2/3 of cases. In these patients potentially in need of biological treatments, it is probable that, as it has been demonstrated for IS, the longer a stable remission has be achieved under treatment, the lower the risk of relapse is after treatment cessation. Further prospective studies should now aim at disclosing patient characteristics associated with a low risk of relapse to implement this strategy.



**Key words:** Inflammatory bowel disease; Immunosuppressors; Biological treatment

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## INTRODUCTION

The question of treatment duration in IBD is certainly a very important one and is one of the greatest preoccupations of patients. When starting a new treatment in IBD, one of the first questions of the patients is usually: "when will I be able to stop this treatment"? While the question is very important, we actually have very little data to give a clear answer, because the controlled data we have with pivotal trials usually give us efficacy data for remission and response induction and for remission and response maintenance over a one year period[1-3].

However we have most often indirect elements to help us and discuss this point of optimal duration of biological treatment in IBD: these elements are the natural history of the disease, the available data with immunosuppressive drugs, the long term safety of biologics, and a few investigator-initiated studies having started to address this question. Beyond that, the cessation of a biological treatment in IBD must be decided on a case-by-case basis and adapted strategies must be proposed.

## NATURAL HISTORY OF IBD

IBD are chronic relapsing diseases. There is probably a difference between UC and CD, the latter being more often a chronic active disease. In CD, population-based and cohort studies have showed that a small half of the patients have little evolutive disease with low prevalence of relapses, hospitalizations, or complications[4-7]. These patients probably do not need biologics and if a biological treatment has been used, an arrest must certainly be discussed as soon as the flare has been controlled. The other patients will develop complications including strictures and internal or perianal fistulas over the course of the disease[8,9]. These will lead to hospitalizations and surgeries and will considerably interfere with patients every day life and long term projects. For these patients a sustained control of the disease process is strongly warranted and an effective treatment can only be stopped if reasonable evidence shows absence of activity of

this process. There is probably a difference between early disease and long-lasting disease, the reversal and control of the disease process being more difficult and unstable in the latter situation. Long-lasting disease are indeed characterized by anatomical damages including mucosal and submucosal architectural changes, fibrosis, strictures and complex fistulas that will favour clinical relapse and that will render an asymptomatic remission more difficult to achieve. Furthermore, immunological status of the patients may change over the course of the disease[10]. In parallel, immunisation against luminal material may increase, enhancing the potential reactivation of the immune process [11,12]. As a correlate, a stable remission will usually be more difficult to obtain in long-lasting diseases[13] and these diseases will usually be more treatment-dependent. This certainly represents an argument for earlier treatment with biologics in CD. These patients being treated earlier with biologics and in whom a more complete reversal of the immune process and the tissue lesions can be achieved are also probably better candidates for treatment cessation.

The problem of ulcerative colitis is a little bit different. There is usually less tissue damage in UC, the disease affecting only the mucosa. Strictures and fistulas are unusual and the biggest long term complication is cancer development. This risk of cancer is linked to several factors, including disease extent and chronic uncontrolled inflammation. In UC, flares can be separated by long period of full remission with both endoscopic and histological normalisation of the mucosa. Therefore, apart from patients with chronic active disease and incomplete mucosal healing, biological treatment cessation could be attempted when the flare has been controlled and a mucosal healing has been achieved.

## AVAILABLE DATA WITH IMMUNOSUPPRESSIVE DRUGS

Little data exist on immunosuppressive drug cessation in CD. In an observational GETAID study of relapse after azathioprine cessation in CD, it was shown that the longer the duration of remission under azatioprine, the lowest the risk of relapse was[14]. Particularly, the risk of relapse seemed particularly low after 4 years of sustained remission. The same group then embarked a placebo-controlled trial of azathioprine prolonged treatment beyond 42 mo of sustained remission[15]. This trial showed that the strategy of treatment cessation was not equivalent to treatment prolongation. Particularly, 18-mo relapse rate were around 20% in the cessation group as compared to 10% in the prolongation group. This study indicates that even in patients in stable remission, the cessation of an immunosuppressive drug is associated with an increased risk of relapse. The risk of relapse in the cessation group remains however reasonably low and one could consider it on a case-by-case basis after discussion with the patients. No such data are available with methotrexate in CD or more generally in ulcerative colitis.

## LONG TERM SAFETY OF BIOLOGICS

While short and mid term safety and tolerance of biologics is usually very good, the fear of long term complication is generally the reason why both patients and physicians would like to stop the drug when the disease has been completely stabilized. This fear is based on the mechanism of action of these drugs. For IBD, we currently only have anti-TNF treatments. These drugs block the tumor necrosis factor alpha which is a pivotal cytokine in some anti-microbial and anti-tumoral physiological processes. Indeed, the best documented side-effects are the increased risk of tuberculosis[16] and of other infections, mainly with intra-cellular pathogens (mycobacteria, lysteria, histoplasmosis…), as well as a probable slight increase in the risk of lymphoma[17]. The active and systematic search for latent tuberculosis has already significantly decreased the incidence of active tuberculosis under anti-TNF treatment. Furthermore, a recent meeting of the European Crohn and Colitis Organisation on infections and biologics has proposed a series of guidelines, including vaccination against herpes zoster, hepatitis B, influenza and streptococcus pneumoniae as well as avoiding some aliments potentially containing germs as lysteria (i.e. unpasteurized milk or insufficiently cooked meat). These guidelines, not yet published, should also in a near future help and diminish fatal complications linked to biologics. Another measure that gains more and more support is the avoidance of long term combined treatment with immunosuppressors. While there is currently very little evidence for a cumulative benefit of these drugs[1,2], combined therapies were associated in a retrospective study with a very significant increase in the risk of opportunistic infections with a relative risk of 12 when two treatments were combined[18]. Furthermore in a recently reported pediatric series of nearly universally fatal hepato-splenic T cell lymphoma in infliximab treated patients, all the patients affected had been treated with combined therapy with thiopurines[19]. All together, these measures should lower the risk profile associated with biologics and allow the physician to prescribe them for enough time to achieve stable and durable remission of the disease.

## AVAILABLE STUDIES ON BIOLOGICAL TREATMENT CESSATION IN IBD

Early data with infliximab in CD were only short term induction data[20]. Only one single infusion was used at that time and it is striking to note the some patients had a very prolonged clinical response or even remission after such isolated infusion[21]. These data already suggested that prolonged treatment was probably not necessary in all the treated patients. Since then however, it has become clear that such one-shot treatment was not a good option for the majority of patients because the median time to relapse was 10 wk and because re-

use of infliximab more than 4 mo after a single infusion was associated with high risk of allergic reaction. More recently the "bridge" study of the GETAID explored the idea of a 3-dose infliximab induction given in parallel with immunosuppressor that would then maintain the remission[22]. The results of this study were rather disappointing. While the short term effect of infliximab was very strong, the maintenance effect with immunosuppressor was globally rather weak. After one year, the overall sustained remission rate in these patients was low and actually close to the one of patients receiving a placebo induction. Only in the patients who were immunosuppressor-naïve at the time of infliximab induction, the benefit was more consistent with a reasonable 40% remission rate after one year. This study clearly shows that in patients who have failed under immunosuppressors, a longer period of anti-TNF treatment is necessary to obtain a durable remission and allow treatment cessation. This has been explored in a recent GETAID study, not yet fully completed. In this cohort study, over 100 patients with a stable remission on combined immunosuppressor-infliximab therapy for more than one year had their infliximab stopped, while pursuing immunosuppressor treatment. An interim analysis indicates that after one year more than half of the patients are still in sustained remission. A multivariate analysis of predictive factors for such sustained remission should allow to better identify the subgroup of patients in whom such strategy may be proposed.

## PRACTICAL CONSIDERATION FOR STOPPING BIOLOGIC TREATMENT IN IBD

Usually, a biological treatment is started in patients who do no longer respond to conventional therapies. In patients responding to the treatment, it is certainly not wise to contemplate a treatment cessation as long as a complete clinical remission has not been achieved. In patients who have been in clinical remission for a sufficient period of time, it is probably useful to assess biological as well as endoscopic signs of disease activity. In several models and clinical situations, C-reactive protein (CRP) serum concentration has been associated with the risk of relapse[23]. More sophisticated serum or stool markers have also been proposed, but their added value as compared to CRP has not been clearly demonstrated[24-26]. A stable value of CRP within normal range should therefore also be obtained before biologics cessation. Correlation between clinical indexes of activity or biological markers of inflammation and mucosal healing is not very strong[27]. Mucosal healing under anti-TNF treatment has been associated with a decrease in relapse rate, hospitalisation and surgeries[28]. A third condition for biologics cessation is thus the existence of a mucosal healing in patients with ileo-colonic disease accessible to endoscopic control. For patients with proximal small bowel disease, there is not universally accepted exploration to assess the control of inflammation at the tissue level. However, entero-MRI could be a good candidate[29]. An absence of mucosal lesion (not always easy to detect), and of contrast enhancement of the bowel wall or the mesenterium could be interpreted as tissue healing.

## CONCLUSIONS

Globally, the decision to stop or carry on with biological treatment in IBD is based on an estimated benefit-risk ratio. The patient must certainly be informed at the highest levels on both advantages and risks linked to any therapeutic strategy that is proposed. In patients with unstable chronic active disease, stopping an effective treatment will put the patients at risk of worsening and complications development and should probably not be attempted. However in patients stabilized for a reasonably long period of time, a careful assessment of the clinical, biological and endoscopic situation may help to take a thoughtful decision in collaboration with the patient himself.

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