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# Are we on our way to change our mode of thinking and treating inflammatory bowel disease patients?

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**Title:** Outcome after discontinuation of TNF-α-blocking therapy in patients with inflammatory bowel disease in deep remission

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## Summary

In the last 15 years or so anti-tumor necrosis factor (TNF) treatment has gained popularity, and concepts such striving for endoscopic remission and biomarkers remission ("deep remission") are becoming upfront issues. Anti-TNF treatment is given for years and safety and economic issues are raised as well. The questions when to stop anti-TNF therapy and how to deal with the patient relapses are other hot topics.

Molander *et al* [1] prospectively assessed the relapse rate of inflammatory bowel disease (IBD) and tried to find predictive factors for relapse after discontinuing maintenance therapy with anti-TNF-α agents in patients in "deep remission" for one year (i.e. no clinical symptoms, endoscopic remission, and fecal calprotectin <100 μg/g). In the relapsers, the authors evaluated the response to retreatment with anti-TNF-α agents, initially given at the same dose, and the documented side effects. This was a prospective multicenter study carried out in 9 Gastroenterology units in Finland. Patients had received anti-TNF-α agents as maintenance therapy for a minimum of one year. Inclusion criteria were innovative in the present study: clinical, endoscopic and laboratory remission, as well as, at least 6 months of steroid-free remission were mandatory. Thus, patients who relapsed after anti-TNF cessation belonged to a very strict subgroup, i.e. those in deep remission for 12 months. Relapse after discontinuation occurred at a median of 6 (range 2.5-15) months, but, more importantly, at a median of 13 months after therapy discontinuation, 67% of patients remained in clinical remission and 85% of them were in endoscopic remission, as well. Furthermore, the response to retreatment with anti-TNF-α during the relapse seemed to be effective and well tolerated. All but one patient with relapse achieved clinical remission or response, and 75% of the patients achieved endoscopic remission at the median follow-up period of 12 months, with no important hypersensitivity reactions occurring. No specific predictive factor, such as gender, age at diagnosis, disease duration, localization or behavior, smoking, previous surgery or duration of the anti-TNF-α were associated with the relapse when univariate analysis was applied.

## Opinion

This important study has some drawbacks: 1) it consisted of small, mixed groups of patients: Crohn's disease (CD), ulcerative colitis (UC), and undefined IBD, making the population heterogeneous; 2) The number of patients was too small for significant differences to be found in relapse rate between CD and UC, or to find predictive factors for relapse; 3) there was no standard approach for maintenance treatment (mono versus dual therapy); 4) the median time of follow up after retreatment of relapsers with anti-TNF-α was only 12 months; 5) no information about TNF-α levels or drug antibodies was given. But one should not be harsh with the authors and may say that some of these drawbacks are in fact "real-life" phenomena.

After more than 15 years of biological treatment in CD, the question when to start and when and in whom to stop anti-TNF-α treatment remains unclear. To balance pros and cons it is important to: 1) predict our patients' future at the onset of anti-TNF therapy; 2) decide how aggressive we should be in inducing remission: should we aim for deep remission in everyone?; 3) consider when we should stop anti-TNF in patients who enter remission; 4) establish which the predictive factors of relapse are upon cessation of treatment; and 5) ascertain regaining remission in patients who relapse.

The STORI trial addresses some of these questions. In the STORI trial when anti-TNF was stopped after a median

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follow-up period of 28 months, relapse rate at the 1st year was 43.9% [2]. In this study patients were treated for at least one year with scheduled infliximab and an antimetabolite and were in steroid-free remission for at least 6 months. There are at least two major differences between these studies. In the STORI trial 34% of the patients had ulcers and 52% had calprotectin levels higher than 50 μg/g at anti-TNF-α cessation (i.e. no endoscopic remission or normal calprotectin were required). This questions mucosal healing as a predictor of relapse in patients receiving anti-TNF-α. Based on multivariate analysis, risk factors for relapse in the STORI trial included male sex, absence of surgical resection, leukocyte counts $>6.0 \times 10^9$/L, hemoglobin level ≤14.5 g/L, C-reactive protein ≥5.0 mg/L, and fecal calprotectin ≥300 μg/g [2]. Endoscopic activity was not included in the predictive factors model of relapse. In another study by Farkas *et al* [3], biological therapy had to be restarted in 78% of patients who achieved complete mucosal healing in CD and in 100% of patients with UC. Neither clinical remission nor mucosal healing were associated with the time to restarting the biological therapy [3]. Thus, the issue of achieving mucosal healing as a must to stop anti-TNF-α remains unsolved or at least of questionable importance. Nevertheless, signs of persistent inflammation or a previous severe disease seem to gain more and more weight in predicting relapse in CD. In another study, Molnar *et al* [4] reported relapse rates comparable with those of the STORI one year after anti-TNF was stopped. Dose intensification and previous biological therapy were found to predict relapse after anti-TNF treatment cessation. Sustained clinical remission for nearly 7 years was observed in 35% of CD patients after stopping infliximab, without any factor predicting this persistent response [5], similar to the commented study [1].

Few studies exist in UC as well. Steenholdt *et al* [6] reported a remission rate of 75% in UC patients 1 year after discontinuation of infliximab, and 40% of the patients were still in remission at the end of 4.5 years of follow up. Farkas *et al* [7] followed 51 UC patients in whom infliximab was discontinued when clinical remission was achieved after 1 year of infliximab therapy. Thirty-five percent relapsed and needed to be retreated within 1 year. Logistic regression analysis revealed that previous biological therapy was the only factor associated with the need of restarting infliximab.

Another very important message arising from the present study by Molander *et al* [1] is the fact that retreatment with anti-TNF-α therapy is well-tolerated and effective. This seems to be transversal to most of the studies [1,2], however when the biologics are restarted after a drug holiday the risk of immunization, hypersensitivity reactions, or loss of effect should be taken in consideration [8,9]. In the STORI study most of the patients were given corticosteroid pre-infusion prophylaxis and were under immunomodulator therapy, which could explain the absence of serious adverse reactions or loss of response. Moreover, in the rheumatology setting, similar results in terms of hypersensivity and efficacy were reported [10]. In the commented study, no adverse events occurred on re-starting anti-TNF treatment, even though some patients were on monotherapy [1].

An important question is when do we stop biologic therapy in IBD patients in remission? Up to date most studies suggested a minimum of 1 year was necessary to consider anti-TNF a drugs cessation [1-5]. A multidisciplinary European expert panel proposed treatment-stopping rules for patients in clinical and/or endoscopic remission, with normal C-reactive protein and fecal calprotectin levels (i.e. "deep remission"). Withdrawing anti-TNF mono-therapy was judged appropriate after 2 years in case of clinical and endoscopic remission, or after 4 years of clinical remission alone. In case of combined therapy, anti-TNF withdrawal, while continuing the immunomodulator, was considered appropriate after 2 years of clinical remission [11]. Nevertheless, the data to support these conclusions is scarce or lacking.

In summary, assuming that these data are reproducible and longer follow up after retreatment has good results, one may need to change the mode of treating IBD patients, doing ileo-colonoscopies in cases of UC and L3 CD or capsule endoscopy in patients with small bowel disease in order to see and seek endoscopic remission as well as biomarker remission. Then one may weigh the risks and benefits of discontinuation after at least 1 year of such remission in patients who are also steroid free for at least 6 months, and permit stopping anti-TNF-α. If needed, treatment can restart at the same dose, maybe for another year or more until another deep remission is achieved and then stopped again. However until now we do not have enough evidence to support/advocating treatment cycles with biologics, as a consequence of stopping strategy. New and more data are needed: 1) drug and drug antibodies levels might possibly guide treatment cessation; 2) serial measurements of fecal calprotectin before stopping; 3) cross-sectional imaging support, or capsule endoscopy; 4) long-term follow up after anti-TNF-α cessation; 5) more physiological knowledge on the intermittent burden in the gut. So, are we there? No, but perhaps we are getting close.

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