

# Strategic Use of Immunosuppressants and Anti-TNF in Inflammatory Bowel Disease

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## Key Words

Crohn's disease · Ulcerative colitis · Immunosuppressants · Anti-TNF therapy

## Abstract

Controlled trials and meta-analyses have shown that immunosuppressants are effective in steroid-dependent Crohn's disease (CD) and, although less well demonstrated, ulcerative colitis (UC). It has also been demonstrated that anti-TNF are effective in steroid-dependent and steroid-refractory CD and UC. Anti-TNF can also decrease hospitalization rate and the need for surgery. This seems also to be the case for immunosuppressants. The early use of anti-TNF seems more effective than later use, and early mucosal healing is associated with decreased rate of surgery. On the contrary, early use of purine analogues does not seem to improve outcome in CD. Anti-TNF therapies have been shown superior to immunosuppressants and combination therapy superior to anti-TNF monotherapy in inducing steroid-free remission and mucosal healing. The main strategic questions which remain at this stage include: When to start immunosuppressants or anti-TNF? Is there still a place for immunosuppressant monotherapy? How to optimize anti-TNF? Is it possible to stop an-

ti-TNF? The main justification of immunosuppressant monotherapy is the low cost of this treatment and the possibility of achieving a very stable and long-standing remission in a subset of patients. According to this and provided there is no rapid need for more effective therapy, this treatment could be tried in any inflammatory bowel disease patient not correctly maintained after a course of steroids and 5-aminosalicylic acid. However, the failure to respond to this treatment should be recognized early and a step up to anti-TNF considered. An anti-TNF treatment should be considered early in patients at risk of rapid evolution towards tissue damage and complications. The benefit/risk of the immunosuppressant + anti-TNF combination therapy should be assessed on a case-by-case basis. Anti-TNF treatment should always be fully optimized by adapting dosage and potentially adding an immunosuppressant before considering treatment failure. Treatment de-escalation should only be considered when a long-standing stable remission has been achieved both clinically and biologically. The cost sparing and theoretical decrease in complication risk should be put in perspective with the risk of relapse and disease progression.

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## Introduction

Anti-TNF monoclonal antibodies are effective for the treatment of moderate to severe Crohn's disease (CD) [1–3] and ulcerative colitis (UC) [4, 5]. Meta-analyses and randomized controlled trials have also shown efficacy of purine analogues and methotrexate for the treatment of CD [6, 7]. The efficacy of purine analogues for UC is less well established, although a recent meta-analysis also suggests its superiority over placebo [8]. The efficacy of methotrexate in UC has not been adequately studied yet.

CD is now considered a progressive disease characterized by tissue damage accumulation leading to surgical resections and disability [9]. Anti-TNF and to a lesser extent immunosuppressants are able to heal the mucosa and to prevent surgical resection [10, 11]. This ability, which had not been demonstrated for steroids or mesalazine, makes these drugs the cornerstones of maintenance treatment of CD aiming at achieving sustained and deep remission. Nevertheless, natural history of CD is very heterogeneous and, according to population-based data, up to half of the patients may have a benign course of the disease and may thus not justify the use of immunosuppressants or anti-TNF antibodies [12].

Evidence for a progressive nature of UC is less striking, particularly because penetrating and stricturing lesions are not occurring, and because surgery is seen as a unique step that may to some extent cure the patient. Nevertheless, the risk of colorectal cancer due to chronic uncontrolled mucosal inflammation [13] and the mucosal fibrosis leading to colonic and rectal loss of compliance are examples of long-term tissue damage in this disease [14]. Mesalazine and steroids are more effective in UC than in CD, particularly to achieve mucosal healing [15, 16]. Therefore, immunosuppressants and anti-TNF are really reserved here for patients not adequately responding to these drugs.

Both in CD and UC, immunosuppressants and anti-TNF may induce significant side effects, sometimes severe, including infections and neoplasia [17, 18]. For this reason, as well as due to the cost of anti-TNF treatments, the benefit/risk and the benefit/cost of these treatments should be rigorously and regularly assessed during the disease course.

The most important questions that are still pending for the strategic use of immunosuppressants and anti-TNF in inflammatory bowel disease (IBD) include the following: when to start these drugs? Should one use them as monotherapy or combination therapy? Is it possible to stop these treatments?

## When to Start Immunosuppressants or Anti-TNF in IBD?

Post-hoc analyses of several clinical trials with anti-TNF in CD have shown a higher efficacy to induce remission or mucosal healing when the treatment was started earlier in the disease [19, 20]. However, this has not been demonstrated in UC yet. The situation is more difficult to interpret for immunosuppressants. The ability of these drugs to change natural history and particularly to decrease the need for surgical resection in CD has been assessed in different studies with controversial results [21–23]. One reason for these controversial results may be the timing of the introduction of immunosuppressants, a therapy started too late being unable to impact on this surgical rate. Nevertheless, a recent GETAID study specifically evaluating the question of early introduction of azathioprine in CD patients with a high theoretical risk of developing disabling disease did not show early introduction to be superior to later more classical introduction of the drug [24].

According to these data, the optimal timing of immunosuppressant or anti-TNF therapy may thus be difficult to determine. We propose to schematically split IBD into three big categories depending on their natural history: the benign disease which may represent in population-based studies up to half of the patients [12], the directly severe disease which may represent one fifth of the patients and the secondarily severe diseases which represent the last third of the patients. In the first category of patients, there is no need for immunosuppressant or anti-TNF therapy and the benefit/risk and benefit/cost ratios would be unfavorable. In the second category, there is an intuition that there would be no advantage to wait before starting intensive therapy, while in the last third, the need for such treatment may presently be difficult to establish at the diagnosis or very early in the disease, and it is the disease evolution that will dictate the optimal strategy. The second group of patients is probably the most easy to identify as it corresponds to early severe presentation of the disease, including, in CD: extensive location, problematic location such as the rectum, abdominal and complex perianal fistulizing lesions, multiple deep ulcers, and in UC: extensive severe colitis not rapidly controlled by mesalazine and/or oral steroid treatments. The first group of benign disease may be defined by localized and superficial lesions, usually in older patients [25]. The third group is composed of patients who do not meet the criteria for the two other groups. In our opinion, this group should be closely monitored and the treatment gradually adapted before the tissue damage develops.

## Should One Use Immunosuppressants and Anti-TNF as Monotherapy or Combination Therapy?

Several studies in rheumatic diseases and IBD have shown that a cotreatment with an immunosuppressant when using anti-TNF improved the pharmacokinetics of the anti-TNF and decreased the formation of anti-drug antibodies that may lead to allergic reaction and treatment failure [26, 27]. In CD, the SONIC trial has shown the superiority of anti-TNF therapy (monotherapy or combination therapy) over a treatment with purine analogues both for achieving steroid-free remission and mucosal healing [28]. Furthermore, the data coming from long-term treatment with purine analogues and anti-TNF do not seem to indicate a better safety with immunosuppressants, particularly with purine analogues, as compared to anti-TNF. Hence, the main advantage of immunosuppressants may be their low cost. Another argument may be the good stability of the remission obtained with this type of drug, although this has never been adequately assessed and particularly compared with the one obtained under anti-TNF. For these reasons, one may consider there is still indication for immunosuppressant monotherapy. This is even more the case in UC where the SUCCESS trial has not shown such a clear superiority of anti-TNF monotherapy over azathioprine monotherapy. The best candidate for immunosuppressant monotherapy may be the steroid-dependent patient with moderate disease severity. One of the most consistent results of immunosuppressant therapy in IBD has been steroid sparing and weaning.

An even more controversial question is the one of the use of anti-TNF monotherapy. As highlighted above, in UC, this option does not seem to be strikingly superior to purine analogue monotherapy and should thus not be generally prescribed. In immunosuppressant-naïve CD patients, the SONIC trial has shown a clear superiority of anti-TNF monotherapy over immunosuppressant monotherapy, but also of immunosuppressant and anti-TNF combination therapy over anti-TNF monotherapy [28]. Therefore, when an anti-TNF is prescribed early in the disease because of the initial severity of presentation, as defined in the previous paragraph, or steroid refractoriness, a combination therapy should probably be preferred to give the patient the highest chance of rapid disease control and limited tissue damage. This choice may be more debatable when an anti-TNF is prescribed in less severe patients either due to immunosuppressant intolerance or due to patient or physician preference not taking cost into account. The advantage of a combination therapy in pa-

tients having failed an immunosuppressant is less well established. Post hoc analyses of individual trials with adalimumab or even infliximab have not shown a clear superiority of combination over monotherapy [1, 2]. Nevertheless, retrospective analyses of cohorts of patients treated in referral centers have shown both for infliximab and adalimumab, a significant increase in treatment failure rate as well as an increase in the requirement for the use of higher dosage of anti-TNF in monotherapy [29, 30]. With adalimumab, this benefit on treatment failure rate was only significant for the first 6 months of therapy, while the reduction of the dosage of anti-TNF remained beyond 6 months. With infliximab, the IMID trial had already shown that the benefit of continuing immunosuppressants together with infliximab beyond 6 months of combination therapy was weak on clinical outcome, although trough levels of infliximab remained higher and level of C-reactive protein (CRP) lower in patients continuing their immunosuppressants [31]. Overall, it seems that the benefit of a combination therapy may work through both synergistic effects and improved pharmacokinetics in immunosuppressant-naïve patients, while it may be mainly through improved pharmacokinetics in patients in whom immunosuppressant therapy has failed. Recently, the report of a small series of CD patients improving their clinical situation together with an increase of trough levels and a disappearance of anti-drug antibodies following the addition of an immunosuppressant to an anti-TNF monotherapy suggested the possibility of a more flexible use of these combination therapies depending on patients' clinical evolution [32].

### Is It Ever Possible to Stop Immunosuppressants or Anti-TNF?

Anti-TNF has now been used in clinical trials and routine practice for more than 15 years and immunosuppressants for more than 30 years. They have been associated with long-term benefit including sustained clinical remission, mucosal healing, healing of fistulas, decreased amount of hospitalizations, decreased amount of surgeries, increased quality of life and ability to work and perform daily activities. This has been associated with a reasonably good safety profile and globally a favorable benefit/risk ratio. The most striking risks are rare opportunistic infections, and lymphomas [17, 18].

Despite this favorable benefit/risk ratio, reasons exist to contemplate anti-TNF or immunosuppressant withdrawal in IBD patients. The main reasons are the fear of

side effects, mild intolerance and wish of pregnancy. For anti-TNF, another important reason is the cost of therapy: anti-TNF have been shown to be potentially cost-effective for the treatment of IBD, but sensitivity analyses highlighted the fact that this cost-effectiveness was influenced by treatment duration and that treating beyond 4 years may not be cost-effective at classically admitted thresholds [3–34]. Overall, the decision to stop or continue an anti-TNF therapy is thus a trade-off integrating all the above-mentioned considerations. However, paramount in this trade-off is the risk of disease progression and the risk of relapse upon treatment withdrawal as well as the possibility to retreat these relapsing patients.

A few data are available on this topic in UC. An Italian study showed that one third, one half and two thirds of patients relapsed after 1, 2 and 3 years of azathioprine withdrawal [35]. The colectomy rate after azathioprine withdrawal was 10%; risk factors for colectomy included absence of mesalazine treatment and short duration of azathioprine treatment. Only preliminary data from Hungary are available for anti-TNF [36]. They suggest a relapse rate similar to the one described after azathioprine withdrawal. No predictor could be identified, and particularly mucosal healing at the time of withdrawal was not associated with a lower risk of relapse.

The data available on treatment withdrawal in CD are also limited. We may separately consider perianal fistulizing disease and luminal disease. For perianal disease, no prospective specific study of anti-TNF or immunosuppressant withdrawal has been performed, but retrospective analysis from experienced centers has suggested a high incidence of relapse [37]. Along the same line, long-term assessment of perianal CD continuously treated with anti-TNF showed persisting inflammatory fistulous tracks in a large proportion of them [4–38]. For luminal CD, two prospective studies by the GETAID specifically focused on the risk of relapse after infliximab and azathioprine discontinuation in patients being in stable remission without steroids [39, 5–40]. The study on azathioprine withdrawal was placebo controlled and revealed a relapse rate of 20% over 18 months as compared to 10% when continuing azathioprine. Long-term follow-up of these patients revealed that up to two thirds of the patients relapsed over the next 5 years [41]. Predictors of sustained remission included high hemoglobin level, low CRP and low white cell count. Retreatment with azathioprine was rapidly effective in almost all the patients. The study of anti-TNF withdrawal focused on patients treated by a combination therapy with infliximab and an immunosuppressant for at least one year [40]. This study re-

vealed a relapse rate over one year approaching 50%. Discontinuing anti-TNF is thus not a globally advisable strategy, as the relapse rate in such kind of patients continuing their anti-TNF is probably below 10% per year. Nevertheless, this study also showed that patients could be stratified according to their risk of relapse and that a subgroup of patients representing 25% of the whole cohort experienced a more acceptable risk, around 10% per year. The factors associated with a low risk of relapse and that may help to select patients for such de-escalation strategy included mucosal healing, normalized CRP, low fecal calprotectin and high hemoglobin levels. Another important aspect of this study was that relapsing patients could be effectively and safely retreated by resuming infliximab scheduled treatment. Around 90% of them were in remission 2–4 months after resuming infliximab, and none of them developed infusion reaction or anti-infliximab antibodies. This remission was also sustained over time and the secondary loss of response was around 6%/year with a median follow-up of 2 years.

Overall, the preliminary results available indicate that there is a need for prospective studies assessing anti-TNF and immunosuppressant de-escalation strategies in IBD. The majority of patients seem to relapse over time and one cannot exclude disease progression in CD and a risk of colectomy in UC. Therefore, currently, in routine practice, such treatment withdrawal should be carefully discussed with the patients and only contemplated in patients in long-standing stable and deep remission, extensively weighing and explaining to the patients potential benefits and risks of such withdrawal. Future studies should also determine if disease monitoring with biomarkers, endoscopy and/or cross-sectional imaging may allow to promptly re-treat the patients, avoiding the consequences of the relapse.

## Conclusion

Immunosuppressants and anti-TNF are the cornerstones of the treatment of moderate to severe CD and of UC failing steroids and mesalazine. Their introduction in the disease course should be tailored to the individual risk of disease progression, but should be early enough to avoid significant tissue damage. Today, the most effective treatment for both CD and UC seems to be a combination therapy with immunosuppressants and anti-TNF, although this may be debated in patients with immunosuppressant failure and particularly beyond 6 months of combination therapy. Immunosuppressant or anti-TNF

withdrawal is generally associated with a high risk of relapse. Nevertheless, in patients having achieved a state of long-standing and deep remission and in whom the risk of disease progression is considered to be low, this withdrawal may be discussed with the patient putting in perspective benefits, cost and risks.

## Disclosure Statement



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