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Immunosuppression in inflammatory bowel disease: how much is too much?

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Abstract

Purpose of review—Current treatment approaches favor the early introduction of immunomodulators and/or antitumor necrosis factor (TNF) agents. There is now strong evidence showing that combination therapy appears to be more effective than monotherapy in both ulcerative colitis and Crohn's disease. However, there are concerns associated with this strategy, and eventually the following questions will emerge when discussing therapeutic options with our patients: is it safe to maintain these therapies for the long-term?; how long should we maintain therapy?; and if we decide to stop or de-escalate therapy, what strategy should we use?

Recent findings—During the past year new evidence regarding safety of long-term therapy with anti-TNF and immunomodulators, and predictors of relapse following therapy discontinuation have become available.

Summary—In this review we aim to discuss some of the safety concerns related to the use of immunosuppressive drugs used in inflammatory bowel disease, as well as the possible strategy for de-escalation or discontinuation therapy. Eventually, choosing to stop either the anti-TNF or the immunomodulator is a case-by-case decision based on the estimated risk–benefit ratio. In addition to the identified predictors of relapse after therapy discontinuation, other considerations such as long-term safety, cost, and natural history of the disease must be brought into this discussion.

Keywords

immunosuppression; long-term safety; predictors of relapse

INTRODUCTION

The current goals of therapy in inflammatory bowel disease (IBD) are evolving from symptomatic control to altering the natural history of disease by achieving deep and

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Conflicts of interest

There are no conflicts of interest.

sustained remission and by preventing disease progression and bowel damage [1⁶]. The Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) and ulcerative colitis Infliximab, Azathioprine, or Infliximab Azathioprine for Treatment of Moderate to Severe Ulcerative Colitis trials provided strong evidence that antitumor necrosis factor (anti-TNF) agents in combination with immunomodulators in patients with moderate-to-severe Crohn's disease [2] and steroid-refractory ulcerative colitis [3], is the most effective strategy. Nevertheless, immunomodulator and/or anti-TNF discontinuation or de-escalation must be considered in clinical practice for reasons such as safety concerns (especially serious infections and cancer), cost, and in special patient populations, such as pregnant women or those at higher risk for developing complications (e.g., old and young patients).

To answer the clinical question: 'immunosuppression in IBD: how much is too much?' we will first discuss the influence of dose, duration of use, and the impact of combination therapy in safety, focusing on infections and cancer. Thereafter, we will review the available evidence regarding therapy discontinuation and/or de-escalation.

Influence of dose, duration, and use of combination therapy in the risk of infections

No studies in the IBD literature address the impact of dosing of anti-TNF on the risk of infections. In the original trials of infliximab (IFX) [4,5], in which dosing ranged from 5 to 20 mg/kg, higher doses were not reported to cause more adverse effects than the 5 mg/kg dose. However, these trials were not powered to detect differences in adverse effects. Westhovens *et al.* [6] compared the rate of serious infections among 1000 rheumatoid arthritis (RA) patients randomly assigned to placebo, IFX 3 or 10 mg/kg, at weeks 0, 2, 6, and 14 in combination with methotrexate (MTX). Patients receiving the higher dose had a three-fold increased risk of serious infections at week 22 compared with placebo ($P=0.013$).

Several studies have suggested an increased risk of infections during the initial months of therapy, followed by a decline thereafter [7,8]. For example, among the first 500 Crohn's disease patients treated with IFX at the Mayo Clinic, nearly 70% of infections occurred after three or fewer infusions [7]. However, it was unclear if this declining risk reflected only a worse clinical status of the patient (malnutrition, steroid use, high inflammatory burden, etc.) when therapy was started or if it could also be due to methodological reasons (e.g., treatment dropout, deaths, etc.). Investigators from the German biologicals register in RA clarified this using different statistical models to adjust for the potential confounding variables [9]. They found that approximately two-thirds of the decreased infectious risk over time could be explained by selective switching of patients who were at increased risk of infection. Only one-third was due to clinical improvement and decrease in concomitant use of corticosteroids [9].

The impact of combination therapy on infectious risk remains a controversy among studies, reflecting both heterogeneity and methodological issues (Table 1) [2,10–14]. Lin *et al.* [15] recently performed a meta-analysis to evaluate the efficacy and safety of combination therapy compared with monotherapy. Five studies involving 1158 patients were included, including the SONIC and A Crohn's Disease Clinical Trial Evaluating Infliximab trials. In overall analysis, there were no significant differences in the frequency of infection [odds

ratio (OR)= 0.88; 95% confidence interval (CI)= 0.69– 1.11; $P= 0.27$] or severe infection (OR=0.68; 95% CI=0.37– 1.24; $P=0.21$) between combination therapy and anti-TNF monotherapy [15]. In a recent pooled analysis derived from 10 IFX-sponsored clinical trials in Crohn's disease and ulcerative colitis (Lichtenstein GR *et al.* unpublished data), important safety outcomes of long-term IFX treatment (infections, malignancy, mortality), with or without concomitant immunomodulators, were analyzed. Interestingly, in patients with ulcerative colitis, but not in Crohn's disease, independently of IFX use, immunomodulator treatment yielded a higher incidence of infections [120.07 (95% CI 110.66–130.08)/100 patient-years] compared with no immunomodulator treatment [92.47 (84.54– 100.94)/100 patient-years].

Elderly patients are a subpopulation for whom therapy's risk/benefit ratio deserves special consideration. A recent study evaluated the risk of infections in patients older than 65 treated with anti-TNF [16]. Among 3079 patients treated with anti-TNF, 3% were older than 65. Among patients more than 65 years old who received IFX or adalimumab (ADA), 11% developed serious infections, 3% developed neoplasms, and 10% died compared with 0.5%; in matched patients older than 65 not receiving anti-TNF the same outcomes were 2% and 2%. Therefore, the use of anti-TNF as monotherapy or in combination with immunomodulators should be carefully considered in older patients, as they may be at higher risk of serious infections.

Influence of dose, duration, and use of combination therapy on the risk of cancer and lymphoma

The most reassuring long-term data regarding use of anti-TNF and cancer risk come from the rheumatology field. A recent report determined the risk of malignancy with anti-TNF treatment based on prospective registries and observational studies (well representative of the usual clinical setting outside clinical trials). The analysis included more than 40 000 patients with over 150 000 patient-years exposure. Anti-TNF was not associated with increased risk of all-site malignancy (risk ratio: 0.95, 95% CI 0.85– 1.05) [17[&]]. Two studies reporting risk over time (6-year follow-up) showed a relative risk for malignancy near one, suggesting that longer duration of exposure does not significantly increase the risk [18,19].

Yet, when evaluating the safety of therapies in IBD, we must recognize that the follow-up time for anti-TNF and combination therapy is still very limited. An example of this point can be drawn from thiopurine use. Although thiopurines have been used in IBD for more than 30 years, only recently have we confirmed their association with the development of lymphoproliferative disorders [20,21] and nonmelanoma skin cancer (NMSC) [22[&],23]. Still, nothing is known in IBD about the influence of thiopurine dosing on neoplasia development. There is some evidence from the pediatric literature that higher levels of 6-thioguanines (6TGNs) may be associated with neoplastic transformation [24,25]. The Scandinavian Nordic Society of Pediatric Hematology and Oncology reported a significantly higher risk of therapy-associated acute myeloid leukemia and myelodysplastic syndrome in patients with lower thiopurine methyltransferase activity compared with control patients ($P < 0.03$), resulting in 6TGNs levels higher than the 90% percentile for all patients who developed secondary malignant neoplasms [24].

In a recent report, among 16 023 IBD patients followed for an average of 5.8 years, 43 developed lymphoma (75% of whom were neither exposed to anti-TNF nor thiopurines) [26]. In concordance with previous observations [21], current but not past use of thiopurines was associated with an increased risk of lymphoma [standardized incidence ratio (SIR): 1.4, 95% CI 1.2–1.7]. This differs from what was observed for NMSC in the Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France cohort. During 49 719 patient-years of follow-up, 32 patients were diagnosed with incident NMSC. Apart from age (hazard ratio: 1.08; 95% CI: 1.05– 1.11; $P < 0.0001$), ongoing (hazard ratio: 5.9; 95% CI: 2.1– 16.4 $P=0.0006$) and also past thiopurine exposure (hazard ratio: 3.9; 95% CI: 1.3– 12.1; $P=0.02$) were identified as risk factors for NMSC in multivariable analysis [22&]. This indicates that skin surveillance strategies need to be maintained even after stopping thiopurine therapy.

Although the impact of combination therapy on the risk of cancer remains poorly characterized, there are great concerns that its use may accelerate neoplastic development. The proportion of patients with malignancies treated with ADA monotherapy or in combination with immunomodulators has recently been determined based on the cumulative adverse event data from the CLASSIC I and II, Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance, Gauging Adalimumab Efficacy in Infliximab Nonresponders, Additional Long-Term Dosing with HUMIRA to Evaluate Sustained Remission and Efficacy in Crohn's Disease, and Extend the Safety and Efficacy of Adalimumab through Endoscopic Healing trials (Lewis JD *et al.* unpublished data). Although the SIR of malignancy with ADA alone was not elevated, the SIR of combination therapy for all malignancies (including NMSC) was higher in relation to the general population and to ADA monotherapy.

One unsolved question remains the relative contribution of anti-TNF or combination therapy to the risk of developing lymphoproliferative disorders, as most of the patients treated with anti-TNF have current or past exposure to immunomodulators. In an attempt to determine the thresholds at which the risk of lymphoma associated with combination therapy would offset its benefits, Siegel *et al.* [27&] recently published a theoretical decision model. The base-case analysis was a Crohn's disease patient, older than 35 and naive to anti-TNF and immunomodulators. Over a 1-year period, combination therapy yielded higher quality-adjusted life-years as long as lymphoma did not occur in more than 3.9% of the population (a 65-fold higher rate than what was described in the literature). Although reassuring, this decision model leaves behind the discussion of hepatosplenic T-cell lymphoma (HSTCL), a major fear in younger male patients. As of January 2011 a total of 36 patients had developed HSTCL in association with IBD treatment: 72% had Crohn's disease, 90% were younger than 35, 93.5% were men and 55.5% were on combination therapy [28]. The median time from thiopurine initiation to the development of HSTCL was similar for both monotherapy and combination therapy (6 and 5.5 years, respectively). The median number of doses of IFX was three (range, 1– 24 doses). The authors tried to provide a risk estimate for HSTCL in men under age 35 and calculated it to be 1 : 7404 for patients on thiopurine monotherapy and 1 : 3534 for patients on combination therapy. Thus, monotherapy (anti-TNF or immunomodulators) may be preferred in men younger than 35, especially for long-term treatment. However, we must consider that the full spectrum of this malignancy may

not yet be known. A recent review of the HSTCL cases in the American Food and Drug Administration data- base included four cases not previously described [29]. Of the 25 identified patients with HSTCL, 22 had IBD and three had RA. Interestingly, 16% were women, 36% were older than 35 years old, and three patients had been exposed to MTX in combination with anti-TNF, suggesting that overall immunosup- pression may be the risk factor for HSTCL rather than a class effect of thiopurines or anti-TNF.

FEASIBLE DE-ESCALATION STRATEGIES

De-escalation strategies may include: stopping the anti-TNF; stopping the immunomodulator; or reducing the dose of one or both agents. Unfortunately, there are limited clinical data to guide us in whether high dose combined immunosuppression can be safely continued for the long-term or whether an efficacious exit strategy exists.

Stopping the antitumor necrosis factor agent

Potential for sustained remission after stopping anti- TNF therapy has been seen in observational studies. Waugh *et al.* [30] reported their experience with 48 patients who discontinued anti-TNF therapy while in full clinical remission. Two-thirds of the patients were on concomitant immunomodulators, and patients had been on IFX therapy for a median duration of 15.6 months (1.0– 67.3). Although the majority relapsed off anti-TNF, 35% of patients remained in a sustained clinical remission. Unfortunately, in the multivariable analysis no predictors of sustained remission were identified.

The ‘Study of infliximab discontinuation in Crohn’s disease patients in stable Remission on com- bined therapy with Immunosuppressors’ (STORI) was a prospective multicenter cohort study to assess the risk of relapse and identify predictors of relapse following anti-TNF withdrawal in patients on com- bination therapy [31&&]. All patients were in cortico- steroid-free remission for a minimum of 6 months, while on at least 1 year of scheduled IFX combined with a stable dose of immunomodulators (azathio- prine, 6-mercaptopurine, or MTX). Among the enrolled 115 patients, there was a 43.9% (5.0%) rate of relapse over 1 year and a 52.2% (5.2%) rate of relapse over 2 years after stopping IFX. Nine factors were found to be independently associated with time to relapse: corticosteroid use between 12 and 6 months prior to enrollment (hazard ratio 3.5, 95% CI 1.1–10.7), no prior surgical resection (hazard ratio 4.0, 95% CI 1.4–11.4), male sex (hazard ratio 3.7, 95% CI 1.9–7.4), hemoglobin 14.5 g/l or less (hazard ratio 6.0, 95% CI 2.2–16.5); leukocyte count more than 6 10 /l (hazard ratio 2.4, 95% CI 1.2–4.7), Crohn’s disease endoscopic index of severity more than 0 (hazard ratio 2.3, 95% CI 1.1–4.9), C-reactive protein (CRP) at least 5 (hazard ratio 3.2, 95% CI 1.6– 6.4), IFX trough level at least 2 (hazard ratio 2.5, 95% CI 1.1–5.4) and fecal calprotectin at least 300 mg/g (hazard ratio 2.5, 95% CI 1.1–5.8). Patients with three or fewer risk factors had a 0–6% risk of relapse over 1 year. Importantly, patients in the study who relapsed off IFX were retreated successfully, as 93% achieved remission and 98% had a clinical response after two infusions. Therefore, although about half of patients will relapse after de-escalating from combi- nation therapy to immunomodulator monotherapy, there are identifiable subgroups of patients who are at low risk and nearly all patients relapsing can be restarted successfully. In practice, the subgroup of patients who may be

candidates for stopping anti-TNF therapy are those who achieve deep remission (symptom control, normalization of biomarkers and mucosal healing) [32,33] off steroids for 6 months after at least 1 year of combination therapy. Achieving deep remission may prevent progressive bowel damage and has been shown to reduce hospitalizations and surgeries early in the disease course [34]. Prior to stopping the anti-TNF, deep remission should be confirmed by ileocolonoscopy and/or small bowel imaging as well as normalization of laboratory markers of inflammation (CRP, ESR, and/or calprotectin). Similar results have been seen in RA when de-escalating the anti-TNF [35–37].

Stopping the immunomodulator

The literature yields conflicting results with respect to withdrawal of the immunomodulators in combination therapy maintenance. Van Assche *et al.* [38] performed an open-label, randomized, controlled trial of Crohn's disease patients in remission with combination therapy to answer the question of whether the immunomodulator can be discontinued. Patients in remission at least 6 months after starting combination therapy were randomized to continue or discontinue the immunomodulators. After 104 weeks of follow-up, continued combination therapy was not found to be superior to stopping the immunomodulators in the primary endpoint of requiring an infliximab dose interval adjustment or stopping therapy, nor in the secondary endpoint of mucosal healing. However, the group randomized to continue combination therapy had lower CRP levels throughout the study and higher median trough infliximab levels (2.87 vs. 1.65, $P < 0.0001$).

Oussalah *et al.* [39] performed a retrospective observational study to identify predictors of IFX failure after withdrawal of azathioprine in combination therapy for Crohn's disease. Azathioprine was withdrawn in 48 patients in clinical remission (Crohn's Disease Activity Index <150) after at least 6 months of combination therapy. Although 85% of patients were IFX failure free after 12 months, this number went down to 41% after 24 and 32 months of follow-up. Predictors of IFX monotherapy failure included use of combination therapy less than 27 months (hazard ratio 7.46, $P = 0.01$), CRP more than 5 mg/l (hazard ratio 4.79, $P = 0.008$), and platelet count more than $298 \times 10^9/l$ (HR 4.75, $P = 0.02$) at azathioprine discontinuation.

Decreasing the dose of the antitumor necrosis factor and/or immunomodulator

One of the limitations of using combination therapy earlier in the disease course is associated with the risk of overtreating some patients. Therefore, in patients who achieve remission with combination therapy, the question can be asked whether the patient can maintain clinical remission with lower doses of medication. In addition to the potential toxicity of overtreatment, rheumatologists have estimated that over 1 billion dollars is lost each year on overdosing with IFX [40]. Yet, anti-TNF step-down protocols have not been tested extensively in IBD or rheumatology. Van den Bemt *et al.* [41] performed a small uncontrolled de-escalation study in RA to assess the feasibility of IFX dose adjustment based on disease activity. Eighteen patients with low disease activity on stable IFX dose (5 mg/kg every 8 weeks) were dose reduced to 3 mg/kg every 8 weeks. Most patients (16/18) did not have an increase in disease activity despite the dose reduction. One patient required a dose increase back to 5 mg/kg to control disease activity and another stopped treatment for

a lupus-like reaction. Although promising, guiding dose reductions based on disease activity may place patients at risk for flares and development of immunogenicity if drug levels are sub-therapeutic. In a retrospective cohort from Leuven, among 158 patients treated with combination therapy, immunomodulators were discontinued in 117 after a stable clinical remission had been achieved. Of those, 26% had a disease flare necessitating IFX dose optimization and 12% lost response to IFX during a median follow-up of 29 months. Undetectable IFX trough levels at the time of immunomodulator withdrawal were found to be predictive of disease flare (hazard ratio=8.6, $P=0.003$) and of complete loss of response (hazard ratio=6.2, $P=0.027$) [42]. Therefore, new drug assays that measure anti-IFX antibodies in the presence of detectable IFX levels may become important tools to enhance our ability to optimize IFX therapy, eventually guiding dose reductions or dose interval augmentation [43].

Immunomodulator use has been associated with reduced immunogenicity and increased trough levels of the anti-TNF in combination therapy [2,44]. However, it may be possible to maintain this effect while using reduced immunomodulator doses. There is some evidence from the rheumatology literature that low-dose oral MTX (7.5 mg/wk) can prevent IFX immunogenicity, maintaining efficacy [45]. It is unknown whether low dose 6-MP or azathioprine has a similar effect. Combining therapeutic drug monitoring with disease activity monitoring may be a target for future clinical trials to step-down therapy toward the minimum effective dose and potentially reduce drug side effects.

CONCLUSION

Although the short-term and mid-term safety and tolerance of anti-TNF and combination therapy is usually good, the lack of long-term safety data is the major reason why patients and physicians may consider de-escalating therapy after achieving stable remission. De-escalating therapy should be a case-by-case decision. Factors to be considered in this decision include the risk for severe adverse effects, the presence of predictors of bad disease outcome, the perceived risk of relapse and the presence or absence of deep remission (normalization of biomarkers and mucosal healing) (Fig. 1). More prospective studies are needed to identify effective de-escalation strategies.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 407).

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KEY POINTS

- Current treatment approaches favor the early introduction of immunomodulator and/or anti-TNF in IBD.
- The long-term safety profile of anti-TNF and combination therapy is not well known.
- Therapy discontinuation can be considered in patients who have achieved a stable clinical, biological and endoscopic remission.
- Future research should focus on feasible de-escalation strategies that are able to maintain remission while decreasing risks.

FIGURE 1.

Therapy de-escalation and/or discontinuation should be an individualized decision. Predictors of relapse and poor disease outcome, as well as potential for therapy side effects need to be balanced with the presence or absence of deep remission. CRP, C reactive protein; HSTCL, hepatosplenic T-cell lymphoma.

Summary of studies looking at the risk of infections associated with the use of combination therapy

Table 1.

Author	Setting	Patient number	Major findings	Comment
Colombel <i>et al.</i> [2]	Randomized controlled trial	170 patients on azathioprine monotherapy, 169 on infliximab monotherapy, and 169 on combo therapy	45.3% patients on azathioprine, 46% patients on infliximab, and 41.9% patients on combo developed infections	Not powered enough to detect rare adverse effects
Toruner <i>et al.</i> [10]	Case-control study; end-point: development of opportunistic infections	100 patients; 2 controls per patient	Use of 2 or 3 immunomodulator drugs (steroids/immunomodulators/anti-TNF) yielded an OR of 14.5 (95% CI, 4.9–43) for opportunistic infections; Relative risk of opportunistic infections greater in IBD patients older than 50 y/o (OR, 3.0; 95% CI, 1.2–7.2)	Retrospective study; Minor opportunistic infections (e.g., oral thrush) were included; No adjustment for disease severity; Combo therapy was not associated w/increased risk of opportunistic infections
Lichtenstein <i>et al.</i> [11]	Retrospective analysis from ACT1 and 2 and ACCENT I and II	376 patients on combo vs. 631 on anti-TNF	44.1% patients on combo vs. 44.5% patients monotherapy developed infections; 3.7% on combo vs. 3.2% on monotherapy developed serious infection	Post-hoc analysis: original studies were not designed to evaluate the effect of combination therapy
Fidler <i>et al.</i> [12]	Case-control study	501 patients treated with combo therapy vs. 385 controls ever exposed to azathioprine	Concomitant treatment with methotrexate or azathioprine had no effect on the occurrence of infections; the infection risk was significantly increased when corticosteroids were given concomitantly	Retrospective study
Lichtenstein <i>et al.</i> [13]	Prospective, observational registry; time to first serious infection in relation to medications was analyzed	3401 patients received infliximab and 2872 received other therapies	Serious infection risk similar for infliximab alone (2.1, 95% CI 1.2–3.6) and infliximab and immunomodulators (2.2, 95% CI 1.3–3.7)	Adverse events based on physician reporting; Registry presented dropout rate of 20%
Marebian <i>et al.</i> [14]	Retrospective case-control study	22 310 patients with CD and 111 550 controls	Use of any 2 or more therapies (steroids/immunomodulators/anti-TNF) increased the risk for opportunistic infections: 2.06 (0.61, 7.00)	Based on retrospective analysis of claim data; Adjustment by disease severity not performed

Combo, combination therapy; infliximab and thiopurines; CD, Crohn's disease; IBD, inflammatory bowel disease; OR, odds ratio; TNF, tumor necrosis factor.