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Stopping Anti-TNF in Crohn's Disease Remitters: Pros and Cons: The Pros

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Keywords
Crohn's disease · Anti-TNF · Treatment withdrawal · Disease complications · Disease outcome

Abstract
Background: There is no cure for Crohn's disease (CD). Available treatments and treatment strategies, particularly anti-TNF, allow healing intestinal lesions and maintaining steroid-free remission in a subset of patients. Having in mind the remitting/relapsing nature of the disease, patients and health care providers often ask themselves whether the treatment could be withdrawn. Several studies have demonstrated a risk of relapse of CD after anti-TNF withdrawal, which varies from 20 to 50% at 1 year and from 50 to 80% beyond 5 years. These numbers clearly highlight that stopping therapy should not be a systematically proposed strategy in those remitting patients. ***Summary:*** Nobody would argue for anti-TNF withdrawal in patients with a high risk of short-term relapse. Nevertheless, they also indicate that a minority of patients may not relapse over midterm and that those who have relapsed may have benefited from a drug-free period before being again treated for a new cycle of treatment. The most relevant question is thus whether in those patients with a low to medium risk of disease relapse, treatment withdrawal could be contemplated. In this specific setting, there may be pros and cons for anti-TNF withdrawal. Among the pros are the potential side effects and toxicity of anti-TNF, the risk of loss of response over time, the patient preference allowing the patient to regain control of one's health and investing in it, also improving adherence, the absence of a negative impact on disease evolution of a transient anti-TNF withdrawal, and finally the cost. ***Key Messages:*** Although anti-TNF withdrawal in patients with sustained clinical remission is associated with a high risk of relapse, this risk seems to be much lower in a subgroup of patients, particularly in endoscopic and biologic remission. Stopping anti-TNF in this subgroup of patients may be associated with a favorable benefit/risk ratio.

Introduction

Crohn's disease (CD) is classically considered as a remitting/relapsing disease, with alternating phases of remission and active disease [1]. This concept has been most recently challenged by the focus on intestinal healing which has become a realistic target for CD treatment [2]. Meanwhile, it has been understood through clinical trials and real-life studies that reaching intestinal healing in CD without any treatment is probably very rare, put-

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Table 1. Main factors associated with a lower risk of relapse [6]

Demographic characteristics	Nonsmoking Older age Female gender
Clinical characteristics	No perianal disease Isolated ileal or colonic location No previous antimetabolite failure No recent steroid use First anti-TNF No previous anti-TNF dose intensification No previous surgical resection
Biomarkers	Normal CRP Low fecal calprotectin High hemoglobin Low white blood cells Low/undetectable infliximab trough
Medical imaging	Absence of endoscopic activity

ting in question this concept of remitting/relapsing disease and replacing it by one of the chronic diseases much more like hypertension and diabetes, and making the fluctuation of clinical symptoms the top of the iceberg. In the past, the only situation which was accepted as potentially not requiring further therapy and corresponding to a real state of remission was the one of surgically induced remission with a normal or almost normal 6–12-month endoscopy, indicating, as demonstrated by Rutgeerts and his team >30 years ago, a low risk of mid-long-term clinical relapse (around 10–20% over 8 years) [3]. A similar situation can now be encountered in a substantial number of patients after achieving sustained steroid-free remission under biological therapy, particularly anti-TNF [4]. Previous studies have clearly indicated that patients with remaining objective signs of disease activity, including elevated biomarkers of inflammation and intestinal ulcers at endoscopy, were at high risk of short-term relapse [5, 6]. However, the fate of patients achieving a normalization of biomarkers and endoscopic healing is more uncertain. The characterization of this subgroup of patients and the study of their intestinal homeostasis, microflora, and immune status, to seek factors associated with long-term treatment-free remission are important current research questions. Beyond the persistence of signs of ongoing inflammation, recent proteomic data suggest that persisting disturbances of intestinal homeostasis and immune defense may explain the risk of longer term relapse [7]. The main factors associated with a low risk of relapse after anti-TNF withdrawal are summarized in Table 1. The ability to identify a subpopulation of patients with not only short-term but also longer term low risk of relapse would bring a simple response to the above-mentioned question: treatment withdrawal would only be attempted in this subgroup of patients. If one excludes the patients with persisting objective signs of inflammation, the risk of mid-long-term relapse (up to 8 years) is around 50–60% [8], leaving us with 40–50% of potentially good candidate for treatment withdrawal. Waiting for the discovery and confirmation of biomarkers predicting a low risk of long-term relapse, we have to live with this intermediate risk and analyze the pros and cons to contemplate treatment withdrawal.

The arguments in favor of an attempt of treatment withdrawal are the ones which indicate any kind of benefit for the patient or the society without jeopardizing disease control and without putting the patient at risk of long-term outcome worsening. Those include a reduced risk of side effects, a hypothetical reduced risk of loss of response to the ongoing anti-TNF, a better integration of patients' preferences and priorities, an improved adherence to the proposed disease management, an investment of the patient in his/her own health, and finally lowering of the cost.

Decreasing the Risk of Side Effects

Although anti-TNF may be considered generally as safe therapies, some important and rarely potentially lethal side effects have been described. In particular, the risk of tuberculosis and of severe or opportunistic infection has been clearly demonstrated and quantified [9]. While this risk of infection can be dramatically decreased or even prevented by individual risk assessment, vaccination, monitoring, and other general and specific preventive measures, this is much more difficult with the risk of neoplasia. An increased risk has been essentially suggested for lymphoma, melanoma, and nonmelanoma skin cancer [10, 11]. Melanoma and nonmelanoma skin cancer can benefit from preventive measures (mainly sun protection) and regular screening, while prevention and early diagnosis of lymphoma remains difficult. Beside these most worrisome side effects, there also exist a wide range of less severe side effects, including lupus-like syndrome and autoimmunity, potentially affecting several organs [9]. These sides effects remain rare, most often reversible when stopping therapy and do not re-present, thus posing a strong argument for treatment withdrawal. Other even less severe but potentially more impactful side effects are the skin disorders. Several skin disorders have been associated with anti-TNF, ranging from a dry skin

to eczematiform and psoriasiform lesions [12]. These manifestations can affect up to 20% of the patients and are usually sufficiently controlled by topical therapies [13]. Nevertheless, they may alter the patient's quality of life and become an argument for treatment withdrawal if the risk of relapse is low.

Loss of Response under Anti-TNF

The secondary loss of response with adalimumab has been estimated up to 20% per year [14] and may even be higher with infliximab [15]. This loss of response is usually attributed to 2 main mechanisms: pharmacodynamics and pharmacokinetics. Pharmacodynamic loss of response is thought to be due to a change in the immune-inflammatory pathways, driving intestinal lesions and extraintestinal manifestations. Although sufficient data are currently not available in this field, some patients with anti-TNF failure seem to have developed a more IL-23-dependent pathway of inflammation [16]. One could speculate that it is the "pressure" maintained on TNF-mediated immune-inflammation that may favor this escape mechanism and that relieving it by at least transient anti-TNF withdrawal may allow maintaining the potential efficacy of anti-TNF later on when needed. This is pure hypothesis but certainly worth exploring. Pharmacokinetic loss of response is mainly due to the development of antidrug antibodies which contribute to both neutralizations of the active drug and acceleration of its elimination. Here, also, if a continuous sufficient drug level may help to prevent the development of these antidrug antibodies, a repeatedly very low or undetectable drug level alternating with high drug levels immediately following injections and infusions may contribute to immunogenicity [17]. These repeatedly low drug levels may be favored by loss of adherence to treatment and extending the interval between infusions or injections in patients with long-term sustained remission.

Patients' Priorities and Preferences

Patients' priorities and preferences are important to know and take into account, not only because this is one of the primary aim of medicine but also because it has a strong impact on adherence to therapy and even disease management [18]. The priority for patients with IBD is clearly the control of their symptoms, including abdominal pain and diarrhea, but after this, safety also represents an important aspect [19]. Typically, when patient's condition is improving, the safety aspect may become dominant. However, we have to acknowledge that patients' priorities and views are very heterogeneous, some privileging the control of symptoms almost at all cost, while other ones would be more ready to live with some disease activity but would have, as the main priority, avoidance of any severe adverse event [20]. In a recent survey, the BIOCYCLE consortium could demonstrate that a majority of IBD patients would accept a relapse risk up to 20% and a percentage of time spent with active disease up to 5% to be able to de-escalate therapy and stop either antimetabolite or anti-TNF [21]. These results taught us 2 important things: first, we should not stop therapy in a subgroup of patients in which the risks of relapse and active disease are above these thresholds, implying that we need good predictors to be able to restrict treatment cessation in a low risk group; second, we should integrate patient's views in our decision, and in some patients, this will preclude any attempt of treatment arrest.

Along the same line, the involvement of patients in their own care through education and empowerment represents a clear need in chronic disease management. Withdrawing a drug may be a good occasion to emphasize the role the patient can play in his own disease management. IBD is a disease which is clearly associated with environmental and behavioral factors, and genetics only explains a small part of the etiology [1]. Patients can strongly act on these nongenetic factors, for example, through improved coping with stress, healthier and more appropriate alimentation, and reinforced physical activity. Although this may be taken care of even with ongoing effective drugs, it is sometimes easier to sensitize the patients to the importance of these aspects when withdrawing a drug [22].

Lowering of the Cost

Lowering of the cost is always important, although it may be differentially appreciated, depending on the type of the health system. When the weight of the cost is put on the patient himself either directly or indirectly through private insurances, it may represent a major point of discussion and sometimes an argument to withdraw therapy. When the weight is put on a public entity, it becomes obviously less prominent for individual patients but poses important questions regarding priorities in this public entity's budget management. Cost-benefit calculation is always difficult because it implies to set cost thresholds considered as acceptable for the benefits obtained, usually measured in Qualys, and representing years with a high quality of life. Obviously, these thresholds may vary depending on cultural and economic differences. Under these perspectives, anti-TNF has usually been considered as cost-effective over the short to medium term but not

necessarily over the long term [23, 24]. More specifically, using a Markov model based on the concept of cycles of biologic treatment, the BIOCYCLE consortium could demonstrate that, at a standard cost of anti-TNF, a continuous treatment would not be considered as cost-effective as cycles of treatment where the drug is transiently withdrawn when achieving sustained steroid-free remission and resumed in case of clinical relapse [25]. However, due to the cost of relapse management and, in a minority of cases of complications, when lowering the cost of anti-TNF like it has become feasible with biosimilars, continuous anti-TNF treatment may remain cost-effective [25].

Conclusion

The standard of care is continuous anti-TNF treatment in patients who tolerate it well and still benefit from the drug. However, in a subset of patients with a lower risk of relapse and accepting this low risk, anti-TNF withdrawal may offer the opportunity of prolonged treatment-free remission, also allowing cost sparing and favoring the full involvement of the patient in his/her disease management, particularly by adopting healthier behavior.

Conflict of Interest Statement

E.L. has received fees for research grant from Takeda and Pfizer; received educational grant from Abbvie, Takeda, and Janssen; received speaker fees from Abbvie, Ferring, MSD, Falk, Takeda, Hospira, Janssen, Pfizer, and Celgene; is present in the advisory board of Abbvie, Ferring, MSD, Takeda, Celgene, Hospira, and Janssen; and is a consultant in Abbvie.

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Author Contribution

E.L. conceived, wrote, and prepared the manuscript.

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