Stopping Anti-TNF in CD Remitters: Cons

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Keywords

Infliximab · Adalimumab · Crohn's disease · De-escalation · Inflammatory bowel disease

Abstract

Crohn's disease may cause a life-long disease burden in many aspects due to its progressive nature. A large proportion of refractory patients have been benefiting from scheduled maintenance anti-TNF treatment; therefore, strategy to stop anti-TNF agents in Crohn's disease is not widely conducted. There have been observational studies demonstrating that approximately half of the patients relapse within a year after discontinuation. Several factors have been suggested as potential predictors for relapse; however, a consensus has not been reached so far. Although most relapse can be rescued by the re-treatment with the same anti-TNF agent, a proportion of patients may result in progressive bowel damage and the need for surgery. Therefore, an attempt to stop anti-TNF is not recommended without careful discussion, even if they are in long-term remission.

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Published by S. Karger AG, Basel

Introduction

Crohn's disease (CD) is a type of chronic inflammatory bowel disease. It affects the digestive tract and can cause abdominal pain, diarrhea, fatigue, weight loss, and malnutrition. It may also lead to complications outside the gastrointestinal tract such as arthritis, skin lesions, and uveitis [1]. Therefore, many patients have been suffering from the life-long disease burden; however, the emergence of biologics, namely, the first anti-TNF agent infliximab (IFX), has dramatically changed the clinical course of patients with CD [2]. Anti-TNF agents have been shown to be effective in inducing and maintaining remission [3–5], reducing hospitalizations/surgeries [6], preventing postsurgical relapse [7], and treating extraintestinal manifestations [8]. It has also been shown that the long-term maintenance is more efficacious than episodic treatment [9]. Thus, a significant proportion of patients have been benefiting from the long-term maintenance treatment with anti-TNF agents. Nevertheless, one of the most frequent questions from patients with CD who have been in long-term remission on anti-TNF agent is whether they can stop it because of their safety concerns, treatment fatigue, and/or financial burden. In general, I do not recommend them to stop it on purpose, and the reasons why stopping anti-TNF is not widely accepted will be discussed in this review.

Natural History

CD is a chronic condition that may affect any part of the entire digestive system. During the last decade, the progressive nature of disease has been increasingly highlighted. Ongoing inflammatory activity may lead to the accumulation of bowel damage, which results in a significant patient burden. Bowel damage includes strictures, fistula, and abscess, which may be irreversible and often require surgery [10]. Indeed, over half of the patients with CD will have structural bowel damage (strictures/fistulae identified by imaging) within 10 years from diagnosis [11, 12], and most of these patients will undergo surgery.

Although the current surgery rate is reported to decrease owing to the breakthroughs of the medical treatment including the emergence of anti-TNF agents, nearly 20% of patients still require surgery within 5 years after diagnosis [13]. It has been also considered that CD rarely burns out over a long period of time, and its inflammatory activity persists [14, 15]. Overall, the progressive and chronic nature of CD should be carefully taken into account when considering the discontinuation of anti-TNF (or any other ongoing effective treatment) even if the patient is in long-term remission.

Increase of Relapse in Patients Who Stopped Anti-TNF: Observational Studies

Approximately 20% of patients per year still lose response even if continuing the treatment [16, 17]. However, relapse rates following discontinuation of anti-TNF agents reported in clinical studies are higher and increase over time [18–30] (approximately between 30 and 50%/year, Table 1). Louis et al. [22] performed a prospective study of 115 patients with CD who were on the combination therapy with IFX and an immunomodulator (IM) for >1 year and had been in corticosteroid-free remission for >6 months (STORI study), demonstrating that 44% of patients relapsed within 1 year. These results suggest that discontinuation of anti-TNF is likely to result in relapse in 20–30% of patients per year based on the difference in relapse rates between patients who continued and discontinued therapy.

A vast majority of patients seem to relapse in the long-term, although such data are available from only a limited number of studies. A Danish retrospective observational study reported a low rate of remission (12%) at 10 years after the withdrawal of IFX [21]. In the long-term follow-

up analysis of the STORI study [31], only 21% did not require restarting IFX during a median follow-up of 7 years.

Importantly, most studies defined relapse by the symptoms or clinical need for re-introduction of anti-TNF agents; however, recent evidence strongly indicates endoscopic, probably structural, damage precedes the emergence of clinical symptoms [32]. Therefore, there is a concern that irreversible bowel damage could be accumulated by the time of clinical relapse after stopping anti-TNF agents. It is of note that 18.5% of patients had a major complication within 7 years in the long-term data from the STORI trial [31], which may not be low enough considering the status of sustained remission when IFX was stopped. Other studies also demonstrated that some cases had required surgery for the relapse following discontinuation (Table 1). Ben-Horin et al. [33] also reported 2 cases who had developed abscesses and required surgery after stopping anti-TNF agents.

Risk Factors of Relapse after Discontinuation

One of the factors reported to be associated with the risk of relapse after stopping anti-TNF is concomitant use of IM. STORI enrolled patients who were on combination therapy with IMs. A large retrospective, observational study by Casanova et al. [30] found concomitant IM therapy was significantly protective against relapse (HR = 0.67; $p = 0.003$). This makes sense because the efficacy of IMs in maintaining remission of CD has been confirmed [34], and thus we could expect them to exert their efficacy after stopping anti-TNF agents from the combination therapy. However, why do not we consider stopping IMs rather than anti-TNF agents? It has been reported that stopping IM from the combination therapy with anti-TNF agents may not increase the risk of relapse especially if IM is stopped after a certain period of time [35–37]. In addition, safety concern is more apparent regarding the long-term use of thiopurines [38, 39]. Therefore, it seems more clinically relevant to stop IMs rather than anti-TNF agents.

Low serum drug level has been also reported to be associated with a lower likelihood of relapse. Lower trough level during remission may indicate the less contribution of anti-TNF agents to the maintenance of remission, justifying its withdrawal. However, a low trough level has been also reported to be associated with the presence of endoscopically active disease in many studies [40–42]; therefore, it may not be a sole predictor for the successful discontinuation. Confirming the complete endoscopic

Table 1. Outcomes after discontinuation of anti-TNF agents in the previous studies

Author	Study design	N	Relapse rates	Patients requiring surgery after relapse**
Domènech et al. [18]	Retrospective	23	31% at 12 months	2
Wynands et al. [19]	Retrospective	11	72% at 12 months	
Waugh et al. [20]	Retrospective	48	50% at 477 days*	
Steenholdt et al. [21]	Retrospective	53	50% at 680 days*	
Louis et al. [22]	Prospective	115	44% at 12 months	14***
Molnár et al. [23]	Retrospective	121	45% at 12 months	
Chauvin et al. [24]	Prospective	38	44	3
Dart et al. [25]	Retrospective	9	33% at 12 months	
Molander et al. [26]	Prospective	17	29% at 13 months*	4
Brooks et al. [27]	Prospective	86	36% at 12 months	
Bortlik et al. [28]	Prospective	61	41% at 12 months	2
Kennedy et al. [29]	Retrospective	146	36% at 12 months	
Casanova et al. [30]	Retrospective	731	22% at 12 months	4

* Mean observation period. ** Note that numbers of cases described in the manuscript alone are shown. It is possible that there were (1) patients who required surgery but not mentioned in the manuscript and/or (2) patients required surgery after the study period. *** Reported in the follow-up study published separately [22].

remission, probably as well as histological remission, may be necessary in such cases when considering the discontinuation of anti-TNF agents.

A recent meta-analysis with individual participant data attempted to develop a prediction model using clinical, biochemical, and endoscopic factors [43]. However, its prediction of relapse rates within a year ranges between 22 and 42% in low- and high-risk patients, which may not be sufficient to assure the successful discontinuation and make a critical decision. Taken together, there is no solid consensus on the predictors for successful discontinuation of anti-TNF agents in CD.

Re-Treatment for Relapse after Stopping Anti-TNF Agents

In general, the efficacy of re-treatment with the same anti-TNF agents for relapse after withdrawal is as high as 80% [22, 24–29, 44, 45]; however, it is still not 100%. There are a few possible explanations for the reduced efficacy of re-treatment. One is a potential development of anti-drug antibodies, which is known to be more frequent when the agent is used episodically [9]. The second possible reason could be because the structural bowel damage such as strictures, fistulas, and abscesses might subclinically progress after discontinuation until the clinical relapse becomes evident. Finally, it is also possible that

the present relapse may require treatment options other than anti-TNF agents, although there are only a few other out-of-class options at present for the refractory CD that include anti-integrins and anti-interleukin 12/23.

Potential Strategies to Avoid and Monitor Relapse

For the response described above, a decision on stopping anti-TNF should not be made without careful discussion with patients. It may be more reasonable to stop IM but continue anti-TNF rather than vice versa if the reason for considering the de-escalation from the combination therapy is safety.

Close monitoring is absolutely necessary due to the high possibility of relapse. The risk of relapse following discontinuation seems greatest especially in the initial period (6–12 months) [46]. However, there is no clear evidence that recommends how the monitoring should be performed. In general, a combination of symptoms, biomarkers (e.g., C-reactive protein/fecal calprotectin), and/or endoscopy/imaging is recommended [46]. A few studies demonstrated the possible usefulness of consecutive measurements of biomarkers (C-reactive protein and fecal calprotectin) in predicting the clinical relapse [30–32]; however, it is unclear if such monitoring strategy is sufficient to avoid bowel damage and/or future surgery during the interval after stopping anti-TNF until clinical relapse.

Conclusions

Stopping anti-TNF agents may not be routinely recommended in CD patients and should be carefully discussed on a case-by-case basis taking a high risk of clinical relapse and progressive nature of disease into account. It may not be clinically relevant to easily try it because it may result in progressive bowel damage that may increase the risk of future surgery, especially in high-risk patients.

Conflict of Interest Statement

Taku Kobayashi has served as a speaker, a consultant, or an advisory board member for AbbVie, Ajinomoto Pharma, Astellas, Alfresa Pharma, Celltrion, Covidien, EA Pharma, Eisai, Eli Lilly,

Ferring Pharmaceuticals, Gilead Sciences, Janssen Pharmaceutical, JIMRO, Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Nippon Kayaku, Pfizer, Takeda Pharmaceutical, Thermo Scientific, and Zeria Pharmaceutical and has received research funding from AbbVie, Alfresa Pharma, EA Pharma, Kyorin Pharmaceutical, Mochida Pharmaceutical, Nippon Kayaku, Otsuka Holdings, Sekisui Medical, Thermo Fisher Scientific, and Zeria.

Funding Sources

There is no funding source regarding this manuscript.

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