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Evaluation of Crohn's Disease Recurrence after Suspension of Immunobiological use in Patients in Sustained Remission

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Abstract

Objective To evaluate the relapse rate after discontinuation of biological therapy in patients with Crohn's disease treated at the University Hospital.

Methods This is a series of 9 cases of CD patients who used long-term immunobiologicals. Non-randomized sample, followed for 1 year, prospectively.

Results Nine patients were studied, 8 females, with an average age of 43.8 years, and non-smokers. The average time of use of the immunobiological for suspension was 6.77 years, with 66.66% of them having been in use for more than 5 years. The mean initial CDAI was 25. After 6 months of follow-up, CRP was less than 10 mg/L in 88.8% of them. Only 3 patients measured the Calprotectin, low. (10, 15 and 30 mcg/g). The ESR averaged 15.77 mm/h. In 66.6% of those studied, the 6-month colonoscopy was normal - mayo 0. In the 1-year follow-up, 3 patients underwent CT, normal. At 1-year colonoscopy of 3 patients, there was endoscopic recurrence in 2. The mean CDAI after the first year was 38.11. The mean ESR was 17.11 mm/h. The worst outcomes occurred in 2 (20%) patients, both Montreal A3L3B2, with clinical and endoscopic recurrence. The same previous immunobiological was reintroduced, with excellent clinical response.

Conclusion Individualized analysis of the course of the disease proves to be the best way for adequate clinical monitoring during its use, optimization of the therapeutic regimen, and the possibility of interruption.

Keywords
- Crohn's disease
- immunobiological
- recurrence

Introduction

Crohn's disease (CD) is a chronic inflammatory condition of unknown origin, with multifactorial causes, associated with genetic, environmental, and immunological factors.[1,2] It is characterized as an inflammatory bowel disease; however, it can affect any region of the gastrointestinal tract, from the mouth to the perianal region, assuming various distribution patterns and, consequently, different clinical presentations. Its incidence and prevalence are higher in developed countries but have been steadily increasing in developing nations, such as Brazil.[1,3]

Early diagnosis with appropriate and individualized therapy is essential for disease control and a better prognosis. The treatment's goal is to induce and maintain clinical, laboratory, and endoscopic remission, with a focus on mucosal healing in a sustained manner, free from steroids, and leading to a good quality of life.[1,4]

The main pharmacological treatment options include corticosteroids, aminosalicylates, immunosuppressants, antibiotics, and immunobiological agents. This has led to the definition of therapeutic strategies known as "step up" and "top down." The "step-up" model follows an ascending

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escalation, starting with salicylates or oral budesonide and, depending on severity, may progress to systemic corticosteroids, azathioprine, 6-mercaptopurine, or, as a last resort, biological therapy, successively, in cases that are difficult to control. The second model follows the inverted course, with the early introduction of biological therapy, followed by sustained remission, and subsequent substitution with other medications. The *top-down* approach is recommended for patients with risk factors for severe inflammation or an unfavorable disease course in an attempt to eliminate the inflammatory process as early as possible, preventing early and late complications. However, there is a stagnant use of biologics for an indefinite period, with no reduction in their use or replacement when clinical, biological, and endoscopic markers demonstrate total control with deep remission.[5–7]

Despite the prevailing belief that anti-tumor Necrosis Factor (anti-TNF) agents are cost-effective, there are many questions about their long-term benefits. However, concerns regarding potential disadvantages related to discontinuing immunobiological agents in Crohn's disease patients include the risk of relapse, the possible loss of effectiveness upon retreatment, the risk of infusion reactions, and the need for surgeries, among others. Hence, efforts are made to establish profiles that identify a higher risk of relapse after immunobiological discontinuation, providing a more secure basis for such decisions.[8,9] Studies demonstrate the importance of maintaining immunosuppressants after discontinuation, as they ensure more sustained remission.[8–10]

Considering data of lesser relevance, medication costs are relatively high, and the government provides access to two anti-TNF agents for the treatment of severe cases of Crohn's disease, as per updated clinical guidelines. Discontinuation should also be considered when specific criteria are met, according to the Ministry of Health's Ordinance No. 14, dated NOVEMBER 28, 2017.[11] Reevaluation of anti-TNF use is recommended every 12 months. The ordinance further states, "After 12 months of treatment with anti-TNF, patients who show clinical and endoscopic remission (mucosal healing/absence of ulcers) can have anti-TNF therapy discontinued and transition to maintenance treatment with azathioprine." This recommendation is based on meta-analyses of observational studies, which indicate a recurrence rate of 18% to 26% between 6 and 12 months after anti-TNF discontinuation in patients who achieved clinical and endoscopic remission, as opposed to 61% to 42% in those who only achieved clinical remission. If a recurrence occurs, restarting biologic therapy is indicated, with an 80% remission rate upon retreatment with the same immunobiological agent used previously.[12] Laboratory analysis, including complete blood count, leukogram, ESR, PCR, and fecal calprotectin, are also necessary for determining discontinuation, in addition to total abdominal tomography to rule out possible hidden complications.[13–15]

Additionally, the use of immunobiological agents, while generally safe, may carry short-term and long-term side effects, including susceptibility to severe bacterial or viral infections, as well as mycobacterial infections such as *mycobacterium tuberculosis*. There is also an association with neutropenia,[16] heart failure,[17] and potentially neoplasms.[15,18,19]

Well-executed discontinuation, based on individualization and predictive factors indicating a higher risk of relapse, can be a valuable tool for better resource allocation in patient care. This approach can reduce waiting times in infusion rooms and the acquisition of costly medications, ultimately leading to fewer complications associated with medication side effects.

Materials and Methods

Study Design, Sample, and Data Collection

This is a pilot project of a larger prospective study, framed as a series of cases of Crohn's disease patients who have been using an immunobiologic for an extended period. The study commenced in 2019 and is ongoing. A non-randomized sample was prospectively followed over a one-year period. The patients shared the same underlying pathology but were heterogeneous with respect to age, gender, disease involvement, and disease progression. Inclusion criteria were defined as follows: patients had to be in clinical and endoscopic remission for more than 2 years and have a history of regular medical check-ups. Exclusion criteria included patients with disease onset before the age of 25, those with a history of clinical management difficulties prior to remission, perianal manifestations, and prior corticosteroid dependence. Patients who agreed to participate in the study underwent quarterly in-person or online medical consultations. Laboratory tests were conducted every 3 months, and fecal calprotectin assessments were performed every 6 months. Colonoscopy was conducted at the 6-month mark and repeated at another 6-month interval during the first year. Abdominal computed tomography was performed annually. Following the discontinuation of the biological agent, all patients were maintained on azathioprine.

Initial data were collected from medical records, and the protocol was applied and filled out over the course of one year, with data collection ongoing.

Ethical Considerations

After a thorough analysis of the inclusion and exclusion criteria, patients were selected and approached in a compassionate and humane manner, providing instructions and clarification for any possible doubts. Candidates were given the option to discontinue their treatment, and the decision was entirely voluntary, following a comprehensive explanation of the issues involved at the time of signing the informed consent form. Patients were informed about confidentiality and anonymity, and they were free to withdraw their participation at any time if they wished to do so.

The research received approval from the Research Ethics Committee under registration number CAAE-16480819.9.0000.5546.

Assessment Tools

Following the primary assessment, patients were characterized using a protocol (Appendix - ►**Table 1**) that included sociodemographic information such as age, gender, and municipality of origin. Clinical characteristics, including

the onset of symptoms, year of diagnosis, clinical presentation, and initial colonoscopy findings, were also recorded.

The Crohn's Disease Activity Index (CDAI) was employed, which is a scoring system calculated by summing the products of 8 items encompassing symptoms and additional tests.

According to this system, disease activity can be classified as follows: scores between 0 and 150 are associated with the absence of disease activity, scores between 151 and 220 indicate mild activity, and scores between 221 and 450 indicate moderate to severe activity. Values exceeding 450 represent extremely severe disease.

Statistical Analysis

The variables were described using absolute and relative frequency percentages, as well as measures of variance and standard deviation.

Results

Nine patients were included in the study, with 8 being female (88.88%) and 1 male (11.11%). The average age was 43.8 years, and all were non-smokers. The mean duration of immunobiological use before discontinuation was 6.77 years, with 66.66% of them having used it for more than 5 years. According to the Montreal classification,[20,21] 55.55% were classified as A3 and 44.44% as A2. Regarding the location of disease involvement, 66.66% had L2, 22.22% had L3, and 11.11% had L1 involvement. As for the disease phenotype, 33.33% were classified as B1, 33.33% as B3p, 22.22% as B2, and 11.11% as B2p. Regarding the specific biological agent used, 7 (77.77%) primarily used Infliximab, and 2 (22.22%) used Adalimumab, with the majority (77.77%) already on combination therapy. Among the study participants, 5 (55.55%) had a history of prior surgeries, including 2 Miles procedures, 2 total colectomies, and 1 right colectomy. All patients in the study presented with abdominal pain in their initial clinical profile (100%), with 88.88% experiencing diarrhea, 44.44% having anemia, 44.44% reporting weight loss, and 11.11% having a palpable abdominal mass. The most common findings in the initial colonoscopy results were pancolitis in 55.55% of cases, proctocolitis in 33.33%, and fistulas in 11.11%. The initial CDAI[22] mean was 25, with a standard deviation of 15.

After 6 months of follow-up following discontinuation, C-Reactive Protein (CRP) levels were below 10 mg/L in 88.88% of cases, with a single case registering 48 mg/L. Only 3 patients underwent fecal calprotectin testing (10, 15, and 30 mcg/g). The mean erythrocyte sedimentation rate (ESR) was 15.77 mm/h, with a range of 7 to 38 mm/h and a standard deviation of 9.79. Hemoglobin levels in patients at 6 months of follow-up remained above 10 g/dL. In 66.66% of participants, the 6-month colonoscopy was normal - Mayo 0. Among the altered exams, there was 1 case of ileitis with erosions (i1) and 2 cases of segmental colitis (Mayo 1).[23,24]

At the 1-year follow-up, only 3 patients underwent abdominal computed tomography, with no abnormalities detected. In the 1-year colonoscopy of 5 patients, endoscopic recurrence was observed in 2 patients: 1 with proctocolitis (Mayo 2) and 1 with worsening i2 involvement, while the other 3 showed no alterations. The mean Crohn's Disease Activity Index (CDAI) after the first year was 38.11, with a range of 10 to 74 and a standard deviation of 23.21. Similarly, the mean ESR was 17.11 mm/h, with an increase observed in 5 patients, ranging from a maximum of 9 mm3 (all below 30 mm3), with a range between 6 and 27 mm/h and a standard deviation of 7.77. Only 2 patients underwent fecal calprotectin testing at 1 year, with values of 57 and 67 mcg/g.

The most adverse outcomes observed were in 2 patients (22.22%) classified as Montreal A3L3B2, both of whom experienced relapse with clinical signs of disease activity. One patient (11.11%) experienced relapse within the first year, accompanied by severe arthralgia in major joints, as well as pain and significant abdominal distension. After the first year, one more patient reactivated the disease with severe proctitis and associated shoulder and ankle arthritis. In both cases, the previously used immunobiological agent (Infliximab) was reintroduced, resulting in an excellent clinical and endoscopic response. All 9 patients continue to receive regular outpatient follow-up care. An important

Table 1 Characteristics

	N	%
Sex		
Female	8	88,88
Male	1	11,11
Age		
$\leq$ 40 years old	4	44,44
$>$ 40 years old	5	55,55
Location of Involvement (Montreal)		
L1	1	11,11
L2	6	66,66
L3	2	22,22
Phenotype (Montreal)		
B1 B2 B2p B3p	3 2 1 3	33,33 22,22 11,11 33,33
Previous Surgeries		
Milles	2	40
Total Colectomy Right Colectomy	2 1	40 20
Primary Immunobiological Agent Used		
Infliximab	7	77,77
Adalimumab	2	22,22
Initial Colonoscopy		
Pancolitis	5	55,55
Proctocolitis	3	33,33
Fistulas	1	11,11

Legend: N - Absolute frequency; % - Relative percentage frequency.
Source: Research Data.

consideration is the measurement of serum infliximab (IFX) levels in these two patients during the reinduction phase (10 and 4.5 mcg/ml). The measurement of anti-drug antibodies in the latter patient was 46.5 ng/ml.

Discussion

The topic is currently highly controversial in scientific circles. Increasingly, research is uncovering new molecules and immunobiological agents that exhibit great efficacy for various immune-mediated conditions. Understanding the immune system and the inflammatory cascade allows for more specific treatments for each clinical entity and target organ involved. Research on the immunogenicity produced by such medications is also emerging, leading to a balance of risks and benefits. The *"top-down"* strategy is described and recommended for moderate to severe cases, enabling more rational use of such medications.[5–7] Studies on the discontinuation of biological therapy are currently the exception, but there is growing interest in identifying potential patient profiles that would not be harmed in the long term.[25,26] Large research centers in Inflammatory Bowel Diseases (IBD) have already published some numbers, ranging from 20% to 40% recurrence depending on the patient profile and the concept of disease remission.[9,12] Various criteria are used in these studies, making it challenging to establish a recommendation.[9,12,25]

In this initial study, a clinical and endoscopic relapse rate of 22.22% was observed, all in female patients with a Montreal pattern of A3L3B2. These were patients who had previously achieved disease control but experienced symptoms and mucosal inflammation recurrence within a year, accompanied by manifestations of rheumatologic activity, such as arthralgia in large joints. Reintroducing the same previously used anti-TNF yielded excellent clinical results, with no need for medication change or therapeutic adjustment, and no requirement for surgical intervention or mortality. The presence of anti-drug antibodies in one patient did not warrant a medication change since it was a single measurement with low titers. In the second patient, serum IFX levels were adequate. This aligns with the literature, which demonstrates that re-treatment with anti-TNF is safe and effective.[9,12,15]

Another important point to consider is the cost-effectiveness of this approach. Although it involves high-cost medication (included in the RENAME-SUS - National List of Essential Medicine-National Health System), it would lead to significant savings for both public and private healthcare budgets, enabling better resource allocation and affirmative healthcare actions for this group of patients. It is essential to consider the social aspect of patient care, as regular follow-up is crucial to avoiding adverse outcomes. In this study, these patients had close contact with the medical team, despite the ongoing pandemic. The TAXIT study demonstrated substantial savings through dose reduction and increased dosing intervals, resulting in a 28% reduction in medication costs without changes in the proportion of patients in remission and CRP values.[27]

For the development of this study, a higher confidence level and a smaller margin of error would have been preferable for a larger sample size. In 2020, the pandemic, along with multiple emotional and logistical factors, posed significant challenges to the study and affected these patients, as well as the entire population. Although the service did not stop, fear significantly hindered access to medical appointments due to the established health and economic barriers. Another crucial aspect was the accessibility of fecal calprotectin testing due to its high cost relative to the average income of the patients served in this healthcare facility. Most colonoscopy procedures were also postponed due to the suspension of non-urgent procedures during the most critical phase of the pandemic.

Furthermore, the data aligns with studies prioritizing the individualization of suspension,[13,26] considering not only clinical analysis but also other remission criteria, including endoscopy. This replicates the safety described, providing better guidance to the medical community in such management.

Conclusion

After nearly two decades of using immunobiological agents, some questions have been answered, while others remain partially unresolved, and some adverse effects have been documented, along with cases of treatment failure. A new landscape is emerging in the management of IBD. Individualized analysis of the disease course has proven to be the best approach for appropriate clinical monitoring during its use, optimizing the therapeutic regimen and the possibility of discontinuing or continuing its use.[25] Patients with low plasma concentrations of anti-TNF exhibit a lack or loss of treatment response, which may result from the formation of anti-drug antibodies.[28]

More clinical trials and systematic reviews are needed to establish an increasingly secure profile of patients who are candidates for discontinuing immunobiological agents, with a focus on individualization and periodic follow-up of eligible patients.

Sources of Research Grants
Authors' own resources.

Research Ethics Committee Approval
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Declaration of Conflicts of Interest of All Authors
The authors declare that there are no conflicts of interest.

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