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Is there a role of magnetic resonance imaging in deciding to stop anti-tumor necrosis factor treatment in ileal Crohn's disease?

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ABSTRACT

Purpose: This study was performed to assess the ability of magnetic resonance enterography to predict the evolution of patients in whom anti-tumor necrosis factor-α therapy was suspended.
Methods: A prospective study of patients with ileal Crohn's disease was performed.
Results: Twenty-nine patients were included. Patients who later relapsed showed higher magnetic resonance scores than those who did not relapse (4.2 vs. 2.5, respectively; $p < 0.02$). The area under the receiving-operating characteristics curve was 0.755 when discriminating patients who relapsed.
Conclusions: Magnetic resonance enterography should be taken into account when deciding the withdrawal of anti-tumor necrosis factor-α in patients with Crohn's disease.

1. Introduction

Crohn's disease is characterized by chronic transmural inflammation of the gastrointestinal tract that typically evolves over time into a progressive disease and bowel damage [1]. Tumor necrosis factor-α (TNF-α), a cytokine produced by activated macrophages, plays a critical role in development of the inflammatory cascade in CD. Anti-TNF-α therapies such as infliximab or adalimumab are used to induce a clinical response and remission in patients with CD because treatments with these agents result in mucosal healing in a significant proportion of patients. These drugs have significantly altered the management of CD, especially for patients with active disease who do not respond or are intolerant to conventional therapies [2,3]. However, in addition to their high cost, they are not free of side effects including infection, hypersensitivity, and an increased risk of developing lymphoma, especially when they are used as a part of combination therapies [4]. Therefore, CD treatment in recent years has focused on the time point at which these treatments can be discontinued with a minimal risk of relapse.

For patients in prolonged remission, the decision to suspend treatment is usually based on clinical and endoscopic factors. In patients with ileal CD, however, endoscopy can be difficult and some laboratory tests such as fecal calprotectin may be less reliable than in colonic CD. No comprehensive studies have evaluated the role of imaging findings as possible predictors of recurrence when stopping treatment with anti-TNF-α agents. Some international consensuses, such as the European Crohn's and Colitis Organization-European Society of Gastrointestinal and Abdominal Radiology [5], consider that imaging methods, particularly magnetic resonance enterography (MRE), are useful for general monitoring of patients undergoing treatment for CD. However, other expert panels that have specifically analyzed the withdrawal of anti-TNF agents, such as the Second European Panel on the Appropriateness of Crohn's disease Therapy [6], consider that the suitability of imaging tests for this purpose is not clear.

The goal of the present study was to determine the ability of baseline MRE findings to predict the evolution of patients in whom anti-TNF-α therapy was suspended; the technique as a whole and its different parameters were separately analyzed.

2. Materials and methods

2.1. Study population

This observational prospective study was carried out from 2012 to 2015 and included patients who had been diagnosed with ileal CD in our center in whom anti-TNF-α therapy (infliximab or adalimumab) was suspended. It was conducted following the recommendations of the Declaration of Helsinki, and approved by the local ethics committee. Written informed consent was obtained from all patients. The patients had a well-established diagnosis of ileal CD based on a complete evaluation (at least an ileocolonoscopic study and a radiological study of the small intestine). They had been treated with anti-TNF-α drugs for at least 1 year. The clinical characteristics of the patients are shown in

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Table 1
Patients' characteristics.

	Total patients (n = 29)	No relapse	Relapse
Women, n (%)	16 (55.2)	7 (43.8)	9 (56.2)
Men, n (%)	13 (44.8)	7 (53.9)	6 (46.1)
Smokers, n (%)	6 (20.7)	2 (33.3)	4 (66.6)
Age at diagnosis (years), median (range)	29.2 (12–52)	29.8 (16–52)	27.3 (12–44)
Age at withdrawal (years), median (range)	36.6 (16–64)	40.6 (16–67)	32.7 (20–58)
Time under anti-TNF (months), median (range)	43.5 (12–72)	39.8 (24–72)	46.9 (12–60)
Infliximab, n (%)	9 (31)	4 (44.4)	5 (55.6)
Adalimumab, n (%)	20 (69)	10 (50)	10 (50)
Montreal classification			
A1L1B2	4 (21)	0 (0)	4 (100)
A1L3B1	1 (3.4)	0 (0)	1 (100)
A1L1B1	3 (15.8)	2 (66.6)	1 (33.3)
A2L1B1	1 (3.4)	1 (100)	0 (0)
A2L1B2	9 (47.4)	3 (33.3)	6 (66.6)
A2L1B2-3	3 (15.8)	2 (66.6)	1 (33.3)
A2L1B3	1 (3.4)	0 (0)	1 (100)
A2L3B2	3 (15.8)	1 (33.3)	2 (66.6)
A2L4B1-2p	1 (3.4)	0 (0)	1 (100)
A3L1B2	2 (6.8)	2 (100)	0 (0)
A3L1B2p	1 (3.4)	1 (100)	0 (0)

Table 1. Treatment was discontinued after a period of sustained deep clinical, endoscopic and analytical remission, which was defined as clinical remission (Harvey–Bradshaw index ≤ 3), endoscopic mucosal healing (simple endoscopic score for Crohn's disease of <2), and C-reactive protein concentration of <5 mg/L + calprotectin concentration of <150 mg/g for at least 3 months before treatment withdrawal.

After anti-TNF-α withdrawal, all patients were treated with immunosuppressants [azathioprine (n = 18), mercaptopurine (n = 6), or methotrexate (n = 5)] and underwent clinical follow-up every 3 months until treatment cessation (or shorter if relapse was suspected).

2.2. MRE studies

Patients underwent MRE before drug withdrawal (mean, 29 days; range, 18–82 days) without any change in clinical situation since then. The studies were conducted after patients had fasted and received 1.5 L of polyethylene glycol solution and 20–40 mg of intravenous hyoscine bromide (Buscapina®, Boehringer Ingelheim, Germany). The MRE machine contained a multichannel-body coil covering the xiphoid process to the pubis (Philips Intera 1.0; Best, the Netherlands). The technical characteristics of the MRE studies are shown in Appendix A. All sequences were acquired during breath-hold except axial single-shot T2 spectral presaturation inversion recovery turbo spin-echo, which was respiratory-triggered. Dynamic scans were performed before and at 70 and 120 s after administration of gadolinium at 0.1 mmol/kg of body weight; acquisition at 70 s was used for calculation of relative enhancement.

2.3. MRE interpretation

The degree of ileal CD activity was evaluated with a per-patient MRE score used in our hospital. This score quantifies the degree of activity within a range of 0 to 12 (Appendix B), and allows to classify the disease as inactive, mild, or moderate-severe [7]. The MRE score is based on the following parameters: bowel wall thickness, postgadolinium relative enhancement, grade of motility reduction, percentage of stenosis of the affected intestinal segment, presence/absence of bowel wall edema, presence/absence of mucosal alterations (ulcers, pseudopolyps), presence/absence of lymph nodes enlargement, presence/absence of fistulas, and presence/absence of inflammatory masses. Data were also collected on other parameters not included in the score that could be related to the disease activity: length of the affected ileum, postgadolinium layered enhancement pattern (enhancement of both mucosal and serosal bowel wall layers), and mesenteric hypervascularization (comb sign). The data were evaluated at the time of MRE by a senior abdominal radiologist with 9 years of experience in MRE; the radiologist was blind to the patient's clinical situation. To avoid possible scoring, the imaging studies were simultaneously evaluated using another activity score for CD in MRE, the magnetic resonance index of activity (MaRIA) [8].

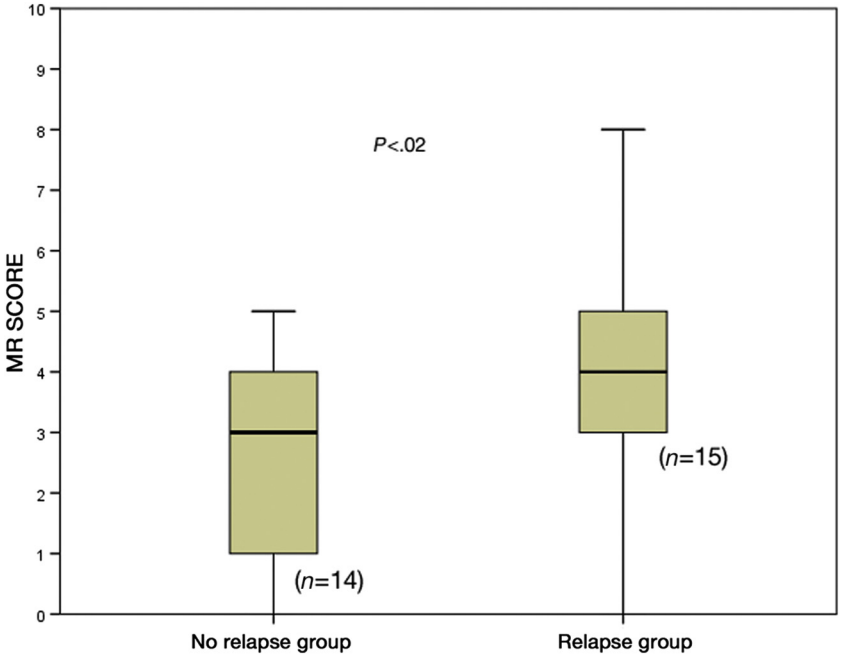

Fig. 1. No relapse and relapse group scores. Mean MR scores according to the presence or absence of relapse.