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Alimentary Tract

Efficacy of tumour necrosis factor antagonists in stricturing Crohn's disease: A tertiary center real-life experience



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ABSTRACT

Background: Stenosis is the most common complication of Crohn's disease (CD). Long-term outcome of patients receiving tumour necrosis factor (TNF) antagonists for such disease complication is poorly understood

Methods: 51 CD patients (from July 2006 to November 2015) who had a diagnosis of small bowel or colonic stenosis, diagnosed by colonoscopy and/or MRI enterography, and were treated with TNF antagonists (adalimumab or infliximab) were enrolled.

The primary outcome was to assess the rate of success of TNF antagonists on avoiding abdominal surgery for stricturing CD patients.

Results: 20 patients (39.2%) underwent surgery during the follow-up period. The overall incidence of abdominal surgery was 1.8 per 100 person-months at risk, while the median time to surgery was 37.9 months. The univariable and multivariable Cox's proportional hazards analysis of baseline parameters indicated that disease location (colonic vs ileal, HR: 28.2, 95% CI: 2.45-324, p=0.007; ileocolonic vs ileal, HR: 3.38, 95% CI: 1.09-10.5, p=0.035), prestenotic dilatation (per 1-mm increase, HR: 1.08, 95% CI: 1.01–1.15, p=0.022) and the existence of non-perianal fistula (HR: 9.77, 95% CI: 2.99–31.9, p<0.001) are independent risk factors for abdominal surgery.

Conclusions: In stricturing CD, anti-TNFs are effective in up to about two-thirds of the patients.

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1. Introduction

Stenosis is a very common complication of Crohn's disease (CD). The risk of the development of this complication increases over time. It has been estimated a mean time of 13 years from diagnosis to occurrence of stenosis [1]. However, at the diagnosis, 19–38% of CD patients can have already developed a stricturing or penetrating complication [2]. This risk is over 50% after 10 years of the diagnosis [2]. Patients with stricturing CD often require abdominal surgery [3,4] and a percentage over 50% of them will have a recurrence after 10 years [5–7]. Mucosal inflammation through the release of molecular mediators and growth factors, stimulates the recruitment and proliferation of smooth muscle cells, stellate cells and myofibroblasts [8]. The mesenchymal cell expansion and the wall thickening and luminal stenosis [8,9]. Understanding whether the stenosis is mostly inflammatory or mostly fibrotic could be crucial in deciding the therapeutic strategy. In fact, an inflammatory stenosis could benefit from a medical treatment, while a fibrotic stenosis will require a surgical approach. However, the current diagnostic methods are not able to differentiate between the two conditions with any certainty [10-13]. A recent study, using Magnetic Resonance Imaging (MRI), found that the percentage of gain of enhancement correlated with the presence of severe fibrosis [14]. If this finding will be confirmed, it will be certainly of help in the management of stricturing CD. However, inflammation and fibrosis often coexist in the same stenotic lesion with varying degrees of intensity [5]. Furthermore, the concept of reversibility of intestinal fibrosis is making inroads. This is in accordance with what is observed in other organs, including liver fibrosis [15], where the removal of the triggering causes has been seen to be able to reduce the degree of fibrosis [16–19].

collagen production affect all the layers of the bowel wall, leading to

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There is little evidence on the efficacy of infliximab in stricturing CD. There are just three studies, two retrospective and one prospective, with small sample sizes [20–22]. The preliminary results of the study CREOLE (DOP034 at ECCO 2015) on the efficacy of adalimumab in CD patients with symptomatic stricture are very promising, showing a rate of success of 60% at 6 months.

The aim of this study was to evaluate the effectiveness of tumour necrosis factor (TNF) antagonists (infliximab, adalimumab) on avoiding surgery in stricturing CD patients in a real life setting.

2. Methods

2.1. Patient population

This was a retrospective, single-center, cohort study. CD patients with a diagnosis of small bowel or colonic stenosis between July 2006 and November 2015, followed up in a referral Inflammatory Bowel Disease center of Italy (IBD Center, Humanitas Research Hospital-Milan), were retrospectively reviewed. Subjects were enrolled in the study if they had any intestinal stenosis diagnosed by colonoscopy and/or MRI enterography irrespectively of clinical symptoms, and were treated with anti-TNF (adalimumab or infliximab). Data collected from the hospital inflammatory bowel disease unit case records included detailed information on the diagnosis of CD and the clinical history of the patients (location and duration of the disease, penetrating and/or perianal disease, smoking status, abdominal surgery history). Treatment history was reviewed. The type, dose and duration of anti-TNFs and associated treatment, in particular use of steroids and/or immunosuppressants, were collected. Before treatment with anti-TNFs, the baseline Harvey-Bradshaw Index (HBI) was recorded [23]. Two investigators (MA, GF), in a blinded fashion, reviewed the endoscopic recordings and calculated for each patient the Simple Endoscopic Score for Crohn's Disease (SES-CD) [24]. One radiologist (CB), blinded to endoscopy reading and to history of the patients, reviewed all the MRI and data about stenosis characteristics including location, prestenotic dilatation (mm) and associated fistulae, was collected. Two investigators (MA, GF) calculated the baseline Lèmann score [25]. After treatment with anti-TNFs, data was recorded about the response to anti-TNFs, the clinical course and a need for surgery.

2.2. Definitions

Intestinal stenosis diagnosed by MRI enterography was defined as a stricture of the small bowel or the colon with prestenotic dilatation; stenosis diagnosed by ileocolonoscopy was a stricture non passable by endoscopy [25].

2.3. End-points

The primary outcome was to assess the rate of success of TNF antagonists on avoiding abdominal surgery for stricturing CD patients.

2.4. Statistical methods

Descriptive statistics of the baseline data are presented as means \pm SD, medians and interquartile ranges (IQR), or as percentages when appropriate. In order to gain an insight into the variables that are independently associated with a patient's likelihood of experiencing surgery for stricturing CD, time-to-event (survival) methods for censored observations were used because of the varying length of follow-up. Time to event was defined as the time from the date of anti-TNF treatment initiation until the date of event (i.e. abdominal surgery), or censoring at the time of discontinuation of the same anti-TNF for reasons different from surgery, or at

the end of the follow-up period. Kaplan-Meier estimates were used to draw the cumulative incidence curves, compared by log-rank tests, as well as by univariable and multivariable Cox's proportional hazards (PH) models of relevant prognostic factors. We followed a standard approach for model selection. In the univariable Cox's PH analysis, a criterion of P less than or equal to 0.10 was used to identify candidate predictors. Then, we fitted multivariable models and used backwards selection procedure to eliminate those variables not significant in the multivariable framework. We used a criterion of P less than or equal to 0.05 for determining which ones to eliminate. The hazards ratios or relative hazards (HR) derived from the Cox's PH models are presented together with their 95% confidence intervals (CI) and the respective p-values. A ratio higher than unity implies a higher probability of event (i.e. abdominal surgery) compared to the reference group. P-values less than 0.05 were considered to be statistically significant. All statistical tests are two-sided. Stata software was used for all statistical analyses (Stata Corp., College Station, TX, USA).

3. Results

Data from 51 eligible CD patients (27 men), followed-up between July 2006 and November 2015, were retrospectively collected and analyzed. 24 stenosis were diagnosed by ileocolonoscopy in 43 patients and 46 by MRI enterography in 50 patients, 49 ileal stenosis, 2 colonic. There were 7 anastomotic strictures, no differences were observed between anastomotic and non-anastomotic strictures. Patients' age ranged from 20.1 to 72.3 years (median, 38.0) and duration of disease from 0.25 to 37 years (median, 4.4). Thirty-two patients (62.8%) were given adalimumab subcutaneously at the dose of 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week; 19 (37.2%) received infliximab 5 mg/kg intravenously at weeks 0, 2, 6 and then every 8 weeks. Six patients out of 44 (14%) received concomitant steroids and 8 patients out of 44 (18%) received concomitant immunosuppressants. A total of 1117 person-months of observation time was analyzed (mean, 21.9 months per patient; median, 15.6 months).

The baseline characteristics and clinical data of the study population are presented in Table 1.

3.1. Risk of abdominal surgery

All patients were followed-up by endoscopy and/or MRI according to current local guidelines. Based on MRI enterography findings alone, 15% of the stenosis resolved during the follow-up. However, there was an increase of 4% of the stenosis, based only diagnosed by ileocolonoscopy only.

In the entire study cohort, 20 patients (39.2%) underwent surgery during the follow-up period. The overall incidence of abdominal surgery was 1.8 per 100 person-months at risk, while the median time to surgery was 37.9 months (IQR: 20.6–51.7 months) (Fig. 1).

Among patients receiving infliximab, 8 surgeries for stricturing CD were reported (42.1%). The incidence was 1.6 per 100 person-months, while the median time to surgery was 49.2 months. Among patients receiving adalimumab treatment, 12 surgeries were reported (37.5%) with a corresponding incidence of 1.9 per 100 person-months, and a median time to surgery of 34.8 months. Kaplan–Meier analysis did not show any different cumulative probability of surgery in patients receiving infliximab compared to those receiving adalimumab (Fig. 2; log-rank p = 0.63).

The univariable and multivariable Cox's proportional hazards analysis of baseline parameters indicated that disease location (colonic vs ileal, HR: 28.2, 95% CI: 2.45-324, p = 0.007; ileocolonic vs ileal, HR: 3.38, 95% CI: 1.09-10.5, p = 0.035), pre-stenotic dilatation

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