INFLAMMATORY BOWEL DISEASE

Antitumor Necrosis Factor Agents to Treat Endoscopic Postoperative Recurrence of Crohn's Disease: A Nationwide Study With Propensity-Matched Score Analysis

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INTRODUCTION: Patients with Crohn's disease experiencing endoscopic postoperative recurrence (POR) may benefit from antitumor necrosis factor (TNF) agents but scarce data on this are available. Our aim was to assess the efficacy of anti-TNF in improving mucosal lesions in patients with endoscopic POR.

METHODS: Multicenter, retrospective, study of patients with Crohn's disease who underwent therapy with anti-TNF agents for endoscopic POR (Rutgeerts score > i1). Treatment outcomes were assessed by the findings in the last ileocolonoscopy performed after anti-TNF therapy was initiated. Endoscopic improvement and remission were defined as any reduction in the baseline Rutgeerts score and by a Rutgeerts score < i2, respectively.

RESULTS: A total of 179 patients were included, 83 were treated with infliximab and 96 with adalimumab. Median time on anti-TNF therapy at the last endoscopic assessment was 31 months (interquartile range, 13–54). Endoscopic improvement was observed in 61%, including 42% who achieved endoscopic remission. Concomitant use of thiopurines and treatment with infliximab were associated with endoscopic improvement (odds ratio [OR] 2.15, 95% confidence interval [CI] 1.04–4.46; $P = 0.03$, and OR 2.34, 95% CI 1.18–4.62; $P < 0.01$, respectively) and endoscopic remission (OR 3.16, 95% CI 1.65–6.05; $P < 0.01$, and OR 2.01, 95% CI 1.05–3.88; $P = 0.04$, respectively) in the multivariable logistic regression analysis. These results were confirmed in a propensity-matched score analysis.

DISCUSSION: In patients with endoscopic POR, anti-TNF agents improve mucosal lesions in almost two-thirds of the patients. In this setting, concomitant use of thiopurines and use of infliximab seem to be more effective in improving mucosal lesions.

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Received February 21, 2020; accepted June 29, 2020; published online August 3, 2020

INTRODUCTION

Crohn's disease (CD) is a chronic condition of unknown origin which leads, in most patients, to cumulative transmural intestinal tissue damage that causes disease-related complications, including intestinal strictures and intra-abdominal penetrating complications. These complications often require a surgical approach, and, despite the current availability of new, potent anti-inflammatory biological drugs, a noteworthy proportion of patients with CD must still undergo intestinal resection (1,2). Unfortunately, surgery is not curative and 70% of patients go on to develop new intestinal lesions in the neoterminal ileum within the first year if no therapy is prescribed early after surgery (3), a process known as postoperative recurrence (POR).

Active smoking, penetrating disease behavior, perianal disease, and previous intestinal resection have been identified as risk factors for POR (4,5). Nonetheless, these factors do not afford an adequate prediction of POR nor a stratification of patients for prevention strategies, and patients may be overtreated or undertreated if a systematic policy is followed in this scenario. Therefore, the appropriateness of preventive therapies is still a matter of debate, even in patients at a high risk of POR (6). The fact that mucosal lesions (as assessed by ileocolonoscopy and called endoscopic POR) occur early after surgery and always precede the development of symptoms (clinical POR) (4), and the existence of a fine correlation between their severity and the likeliness of developing clinical POR (3), are the main arguments for advising early endoscopic monitoring in these patients, regardless of the fact that preventive therapy has been initiated (7–9). In the absence of lesions or in cases of mild mucosal lesions, some guidelines recommend a conservative attitude, together with a close monitoring with noninvasive diagnostic tools afterward (8,10). By contrast, if severe lesions are noticed in this endoscopic assessment, treatment escalation is strongly recommended (8,9).

Among the many drugs that have been tested in this clinical setting, only thiopurines and antitumor necrosis factor (TNF) agents have proven to be efficient in preventing endoscopic and clinical POR (11,12). The POCER study, a randomized clinical trial (RCT) designed to compare early vs conventional endoscopic monitoring, demonstrated that early treatment escalation in patients with severe lesions results in a better short-term outcome even if they were on preventive therapy with thiopurines or adalimumab (13). It therefore seems reasonable that anti-TNF agents should be used in patients developing endoscopic POR while on thiopurines or even in those patients who did not undergo any preventive therapy. Nevertheless, in the setting of asymptomatic patients with endoscopic POR, only one RCT comparing the usefulness of azathioprine and oral aminosalicylates 5-ASA in the prevention of clinical POR has been published to date, and no other drugs have been evaluated by the means of RCTs for the treatment of confirmed endoscopic POR (14). For anti-TNF agents, only some retrospective series and small, open studies are available, reflecting the need for further data on this issue (15–17), and the number of patients starting adalimumab therapy for endoscopic POR in the POCER study was rather small (13).

The aim of this study was to describe the use of infliximab and adalimumab for the treatment of endoscopic POR in clinical practice, to assess and compare their effectiveness, and to identify the factors associated with treatment outcomes.

METHODS

Study population

This is a retrospective, multicenter, observational study including all those patients with CD who underwent an intestinal resection with ileocolonic anastomosis and who were treated with anti-TNF agents (infliximab or adalimumab) after a diagnosis of endoscopic POR (defined by a Rutgeerts endoscopic score > i1) (3), regardless of concurrent clinical symptoms. Patients were identified from the local IBD databases of each participating center. CD diagnosis was based on the accepted criteria of the European Crohn's and Colitis Organization (18). To be included in the study, patients had to have undergone an endoscopic examination at least 6 months after starting anti-TNF therapy for POR. Exclusion criteria were the presence of transient or definitive ostomy at the time anti-TNF therapy was started, a Rutgeerts endoscopic score < i2 at the last endoscopic examination before anti-TNF treatment, anti-TNF therapy indicated for primary prevention of POR, and less than 6 months of treatment with anti-TNF therapy at the time of the last endoscopic assessment. The collected variables and the case record database (19) are detailed in the Supplemental Digital Content 1 (http://links.lww.com/CTG/A339).

The study was approved by the Ethics Committee of the coordinating center (Hospital Universitari Germans Trias i Pujol, Badalona, Catalonia, Spain).

Outcomes and definitions

Endoscopic response to treatment was assessed in those ileocolonoscopies performed during anti-TNF therapy or within the first 3 months after anti-TNF discontinuation. *Endoscopic remission* was defined as a Rutgeerts score < i2, whereas *endoscopic improvement* was defined by any reduction in the baseline Rutgeerts score. Finally, we defined *advanced endoscopic POR* as a Rutgeerts endoscopic score of i3 or i4.

We also assessed the induction of clinical remission in patients with clinical POR at the beginning of anti-TNF therapy and the development of clinical POR during anti-TNF therapy or within the 3 months after treatment discontinuation. For this purpose, and given that no clinical score has been validated to date for clinical POR and these patients may develop chronic diarrhea as a consequence of ileocolic resections (i.e., intestinal bacterial overgrowth and bile salt malabsorption), we defined *clinical POR* as the presence of 2 of the following 3 criteria: weight loss, increase in stool frequency of at least 2 bowel movements/day, and new onset of abdominal pain.

Statistical analysis

Categorical variables were expressed as frequencies and percentages. Continuous variables were described as means $\pm$ SD or as medians and interquartile range for cases with a skewed distribution. Normal distribution was assessed using normal Q-Q plots. Statistical differences between groups were assessed using the χ^2 test for categorical variables, the Student t test, or the Fisher exact test for continuous variables with normal distribution or the Kruskal-Wallis test for variables with a non-normal distribution. Univariable and multivariable logistic regression models were performed applying the backward stepwise procedure to determine which variables were independent predictors of endoscopic improvement and remission. Variables included in the multivariable analysis were those significantly associated with the end point or

with a *P* value < 0.05 in the univariable analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported.

In a secondary analysis and considering the difficulty of quantifying the association of infliximab or adalimumab with endoscopic improvement and remission in an unbiased manner, a propensity score analysis was also performed with a logistic regression model. The dependent variable was receipt treatment with infliximab, and a total of 17 covariates were selected (see Table, Supplemental Digital Content 2, http://links.lww.com/CTG/A340). According to the propensity score, patients were selected by 1:1 matching without replacement using the nearest neighbor method. A caliper width of 0.2 standardized differences was used for matching. The balance of the baseline characteristics' distribution between the 2 groups was evaluated using the absolute standardized differences. Differences were considered statistically significant at *P* < 0.05. All analyses were performed with STATA V.13.0 (College Station, TX).

RESULTS

Baseline characteristics

A total of 179 patients were included, 96 (54%) of whom were undergoing treatment with adalimumab and 83 (46%) with infliximab because of endoscopic POR as conventionally defined by a Rutgeerts endoscopic score > i1. Table 1 summarizes the baseline characteristics of the included patients, and Supplemental Digital Content 2 (see Table, http://links.lww.com/CTG/A340) details the baseline characteristics of patients in the propensity score-matched cohorts. Of note, almost two-thirds had been exposed to thiopurines and one-third to anti-TNFs before the index surgery. As expected, 76% of patients had at least one well-established risk factor for POR (active smoking, penetrating disease behavior, previous intestinal resections, or history of perianal disease) and more than one-third had more than one risk factor, active smoking at surgery being the most common one. Regarding CD treatment, 28% of the patients did not follow any preventive therapy for POR after the index surgery, 16% followed long-term mesalazine or a short course of metronidazole, whereas 56% were on thiopurines (alone or together with a 3-month course of metronidazole). All these demographic and clinical characteristics were evenly distributed between the 2 treatment groups.

The first endoscopic assessment after the index surgery was performed after a median of 16 months (IQR, 8–56); however, the index ileocolonoscopy demonstrating endoscopic POR before starting anti-TNF therapy was performed after a median of 41 months (IQR, 13–78) from surgery. Of note, 63% of the cohort had advanced endoscopic POR at the baseline endoscopy (Rutgeerts score > i2). Furthermore, 39 patients (22%) met the arbitrarily predefined criteria for clinical POR at the beginning of the anti-TNF therapy. Despite the presence of mucosal inflammatory lesions, not all patients exhibited biological evidence of disease activity; C-reactive protein measurements were available in all the patients at the time anti-TNF therapy was started, and only 31% of them showed levels >5 mg/L (Table 2).

Main features of anti-TNF therapy

Tables 2 and 3 summarize the main clinical and therapeutic characteristics at the beginning of anti-TNF therapy and during follow-up, respectively. The median interval from surgery to the beginning of anti-TNF therapy was 44 months, with more than 77% of patients starting beyond the first year after surgery. The

median time from the index ileocolonoscopy to the beginning of anti-TNF therapy was 2 months (IQR, 1–5), without differences between infliximab and adalimumab-treated patients (2 [IQR, 1–6] vs 2 [IQR, 1–5] months, respectively; *P* = 0.08). As mentioned previously, 53 patients had been exposed to anti-TNF before the index surgery; of them, 24 (45%) were further treated with the same anti-TNF for endoscopic POR, particularly among those previously exposed to infliximab (67% vs 31%; *P* = 0.01). Almost all the patients followed a conventional induction and maintenance regimen schedule for each anti-TNF drug (5 mg/kg at weeks 0, 2, 6 and every 8 weeks for infliximab and 160 mg followed by 80 mg and 40 mg every 2 weeks, for adalimumab). The use of concomitant immunosuppressants was common among both infliximab and adalimumab-treated patients.

The median time of follow-up while on anti-TNF therapy was 51 months. One-third of patients were dose escalated, almost in half of them because of a lack of endoscopic improvement or biological activity and a large proportion for the development of symptoms attributed to disease activity. Moreover, one-third discontinued the initial anti-TNF treatment, mainly because of clinical, biological, or endoscopic worsening or the development of drug-related adverse events. Once again, none of these features differed between infliximab and adalimumab-treated patients.

Treatment outcomes

During the follow-up, all the patients underwent at least one endoscopic assessment (55% one, 31% two, and 14% three or more colonoscopies). The first endoscopic assessment was performed after a median of 16 months (interquartile range [IQR], 11–31) from the initiation of anti-TNF therapy (no differences between treatment groups), whereas the last endoscopic assessment was performed after a median of 31 months (IQR, 13–54). At the last endoscopic assessment performed while on anti-TNF therapy, 109 of 179 patients (61%) had achieved endoscopic improvement, including 65 patients (42%) who achieved endoscopic remission. Infliximab-treated patients showed significantly higher rates of endoscopic response (70% vs 53%; P = 0.02) and endoscopic remission (57% vs 29%; *P* < 0.01) (Figure 1).

Among the 39 patients who also had clinical POR at the beginning of anti-TNF therapy, 23 (59%) achieved clinical remission at the end of the follow-up (61% with infliximab and 57% with adalimumab; *P* = 0.80). On the other hand, among the 140 patients who were asymptomatic despite having mucosal lesions at the beginning of anti-TNF therapy, 15 (11%) met the criteria for clinical POR (12% with infliximab and 9% with adalimumab) after a median time of 31 months (IQR, 7–44). The cumulative probability of remaining free of clinical POR was 96%, 91%, and 86% at 1, 3, and 5 years, respectively. No differences were observed between infliximab and adalimumab-treated patients.

Factors associated with treatment outcomes

The results of the univariable and multivariable factors associated with endoscopic improvement and endoscopic remission are shown in Table 4. Infliximab therapy (as opposed to adalimumab) for endoscopic POR (OR 3.16 [95% CI 1.65–6.05]; P < 0.01), concomitant thiopurines (OR 2.15 [95% CI 1.04–4.46]; P = 0.03), and the presence of clinical POR at the start of anti-TNF therapy (OR 3.31 [95% CI 1.51–7.28]; *P* = 0.03) were the factors independently associated with endoscopic remission in the multivariable analysis. Moreover, endoscopic improvement was independently associated with having advanced endoscopic POR

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Table 1. Baseline characteristics of patients including clinical features at index surgery

	Overall (n = 179)	Infliximab (n = 83)	Adalimumab (n = 96)	*P* Value
Male gender	98 (55)	51 (61)	47 (49)	0.09
Familial with inflammatory bowel disease	18 (10)	8 (10)	10 (11)	0.85
Active smoking at CD diagnosis	103 (58)	53 (64)	50 (52)	0.11
Disease location				
Ileal	97 (54)	47 (57)	50 (52)	0.54
Ileocolonic	82 (46)	36 (43)	46 (48)	0.54
Upper gastrointestinal involvement	5 (3)	2 (2)	3 (3)	0.77
Disease behavior				
Inflammatory	14 (8)	6 (7)	8 (8)	0.78
Stricturing	78 (44)	38 (46)	40 (42)	0.58
Penetrating	87 (49)	39 (47)	48 (50)	0.69
Extraintestinal manifestations	50 (28)	19 (23)	31 (32)	0.16
Rheumatologic	40 (22)	15 (18)	25 (26)	0.20
Cutaneous	13 (7)	5 (6)	8 (8)	0.55
Ocular	5 (3)	4 (5)	1 (1)	0.13
Thrombotic	1 (1)	1 (1)	0 (0)	0.28
Age group at diagnosis				
<18 yr	19 (11)	7 (8)	12 (13)	0.38
18–40 yr	130 (73)	60 (72)	70 (73)	0.92
>40 yr	30 (17)	16 (19)	14 (15)	0.40
Indication of index surgery				
Intestinal stenosis	92 (51)	48 (58)	44 (46)	0.11
Intra-abdominal penetrating complication	67 (37)	25 (30)	42 (44)	0.06
Refractoriness to medical therapy	20 (11)	10 (12)	10 (10)	0.73
Thiopurines exposure before index surgery	100 (56)	50 (60)	50 (52)	0.27
Anti-TNF exposure before index surgery	53 (30)	21 (25)	32 (33)	0.24
Active smoking at index surgery	86 (48)	44 (53)	42 (44)	0.22
Heavy smokers (>10 cigarettes/d)	54 (75)	27 (77)	27 (73)	0.68
Penetrating behavior	87 (49)	39 (47)	48 (50)	0.69
Perianal disease before index surgery	30 (17)	16 (19)	14 (15)	0.40
Intestinal resections before index surgery	30 (17)	14 (17)	16 (17)	0.97
Median (range)	1 (1–3)	1 (1–2)	1 (1–3)	
At least 1 risk factor for POR	136 (76)	63 (76)	73 (76)	0.75
>1 known risk factor for POR	66 (37)	31 (37)	35 (36)	0.90
Primary prevention for POR after index surgery				
None	51 (28)	20 (24)	31 (32)	0.23
Mesalazine	11 (6)	2 (2)	9 (9)	0.06
Metronidazole	17 (10)	10 (6)	7 (4)	0.58
Thiopurines	81 (45)	40 (48)	41 (43)	0.46
Thiopurines + metronidazole	19 (11)	11 (13)	8 (8)	0.29

CD, Crohn's disease; POR, postoperative recurrence; TNF, tumor necrosis factor.

Table 2. Main features at the beginning of anti-TNF therapy for endoscopic POR

	Overall (n = 179)	Infliximab (n = 83)	Adalimumab (n = 96)	*P* Value
Time from index surgery to index ileocolonoscopy (mo)	41 (13–78)	40 (18–77)	46 (12–81)	0.85
Rutgeerts score at the beginning of anti-TNF				
Rutgeerts i2	65 (36)	30 (36)	35 (36)	0.96
Rutgeerts i3	47 (26)	23 (28)	24 (25)	0.68
Rutgeerts i4	67 (37)	30 (36)	37 (39)	0.74
Median time (IQR) from surgery to anti-TNF (mo)	44 (18–87)	41 (20–84)	47 (15–96)	0.82
Clinical POR at anti-TNF start	39 (22)	18 (22)	21 (22)	0.98
Exposure to the same anti-TNF prior to index surgery	24 (45)	14 (67)	10 (31)	**0.01**
Anti-TNF induction schedule	176 (98)	82 (99)	94 (98)	0.65
Concomitant immunosuppressants				
Thiopurines	124 (69)	62 (75)	62 (65)	0.14
Methotrexate	11 (6)	6 (7)	5 (5)	0.57
C-reactive protein >5 mg/L	55 (31)	24 (29)	31 (33)	0.63
Hemoglobin < 12 g/dL (men) or <11 g/dL (women)	23 (13)	11 (13)	12 (13)	0.88
Faecal calprotectin >100 mg/kg[a]	36 (65)	17 (71)	19 (61)	0.46

Bold indicates statistical significance with a *P* value less than 0.05.
IQR, interquartile range; POR, postoperative recurrence; TNF, tumor necrosis factor.
[a]Only available for 55 patients.

(OR 2.63 [95% CI 1.37–5.07]; *P* < 0.01), concomitant use of thiopurines (OR 2.34 [95% CI 1.18–4.62]; *P* = 0.01), and infliximab therapy for endoscopic POR (OR 2.01 [95% CI 1.05–3.88]; *P* = 0.04). In a secondary analysis, and to establish the association of infliximab with the outcome in an unbiased manner, a propensity score analysis was performed. Propensity score yielded 65 matched pairs of patients from both groups (infliximab and adalimumab). The distribution of created propensity score is presented in Supplemental Digital Content 3 (see Figure, http://links.lww.com/CTG/A341). Infliximab therapy for POR was significantly associated with endoscopic improvement and remission (OR 2.2 [95% CI 1.1–4.5]; *P* = 0.03, and OR 2.2 [95% CI 1.1–4.6]; *P* = 0.03, respectively).

DISCUSSION
Current guidelines on the postoperative management of CD recommend the primary prevention of POR in all patients except those with pure fibrotic and short ileal stenosis (8,9). However, the need for systematic primary prophylaxis for POR is under debate, with some authors posing the use of an endoscopic-driven strategy in which only those patients showing mucosal lesions would be treated (6). With this strategy, up to 55% of patients without primary prevention will need rescue therapy within the first year after surgery. On the other hand, even in patients who start thiopurines early after surgery, endoscopic POR occurs in up to 40% within 1 year (11,20,21). Beyond the early postoperative management of CD, it is a fact that approximately half of these patients develop early mucosal lesions that put them at risk of clinical POR. Mesalazine has demonstrated a very limited efficacy

in this setting (14–16,22). Thiopurines, although useful (14), are hampered by a high rate of intolerance and their slow active mechanism, and they may not be the most suitable option in patients with already existing clinical POR. Therefore, biological agents seem to be the best potential choice in this clinical scenario. In previous small series, the reported rate of endoscopic remission with infliximab ranged from 47% to 52% (15,17). To the best of our knowledge, this is the largest cohort assessing the usefulness of anti-TNF agents as rescue therapy for endoscopic POR in CD, and we observed that anti-TNFs are able to improve or revert recurrent mucosal lesions in more than half of the patients.

As expected, most of our patients were at a high risk of POR. Although smoking is probably the greatest and most repeatedly found risk factor for POR, a great proportion of patients keep on smoking after surgery, reflecting that beyond the prescription of efficient drug therapies, there is still room for improvement in preventive measures by physicians and nurses in this particularly risky clinical scenario. We also observed that half of the patients in our cohort were treated with anti-TNF agents for endoscopic POR despite preventive therapy with thiopurines. This might explain that in a high proportion of our patients, anti-TNF agents were initiated beyond the first year after the index surgery; in fact, it has been recently reported that there is a steady risk of endoscopic POR over time among those patients on preventive thiopurines with a first ileocolonoscopy without mucosal lesions (23). In fact, almost half of those patients who started anti-TNF beyond 18 months after surgery had an initial ileocolonoscopy with a Rutgeerts score < i3. Anyway, preventive thiopurine therapy for POR, and exposure to thiopurines or anti-TNF agents before the

Table 3. Follow-up features and outcomes of anti-TNF therapy for endoscopic postoperative recurrence

	Overall (n = 179)	Infliximab (n = 83)	Adalimumab (n = 96)	*P* Value
Median (IQR) follow-up time on anti-TNF (mo)	51 (30–79)	58 (30–83)	47 (27–64)	0.08
Median (IQR) time between anti-TNF start and first endoscopic assessment (mo)	16 (11–31)	17 (11–29)	14 (10–32)	0.32
Time between anti-TNF start and first endoscopic assessment < 18 mo	99 (55)	45 (54)	54 (56)	0.79
Median (IQR) time between anti-TNF start and last endoscopic assessment (mo)	31 (13–54)	32 (16–58)	31 (12–47)	0.24
Anti-TNF dosemescalation	66 (37)	27 (33)	39 (41)	0.26
Reasons for anti-TNF dose escalation (could be more than one)				
Lack of endoscopic improvement	30 (45)	7 (26)	23 (59)	**0.01**
Digestive symptoms	42 (64)	19 (70)	23 (59)	0.34
Raised inflammatory biomarkers	10 (15)	3 (11)	7 (18)	0.35
Anti-TNF discontinuation	53 (30)	25 (30)	28 (29)	0.89
Main reasons for anti-TNF discontinuation				
Clinical, biological or endoscopic worsening	23 (49)	11 (48)	12 (50)	0.88
Adverse events	14 (30)	7 (30)	7 (29)	0.92
Other	10 (21)	5 (22)	5 (20)	0.94
Any C-reactive protein >5 mg/L[a]	21 (12)	11 (13)	10 (11)	0.57
Any fecal calprotectin >100 mg/kg[b]	29 (30)	13 (33)	16 (29)	0.68

Bold indicates statistical significance with a *P* value less than 0.05.
IQR, interquartile range; TNF, tumor necrosis factor.
[a]Available for 176 patients.
[b]Available for 96 patients.

index surgery, were not associated with a lower efficacy of anti-TNF therapy once POR occurred. Another reason for the delay in starting anti-TNF agents could have been the fact that treatment escalation for POR in Spain is advised only for advanced endoscopic POR (8); for that matter, almost two-thirds of our patients had advanced endoscopic POR at the index ileocolonoscopy,
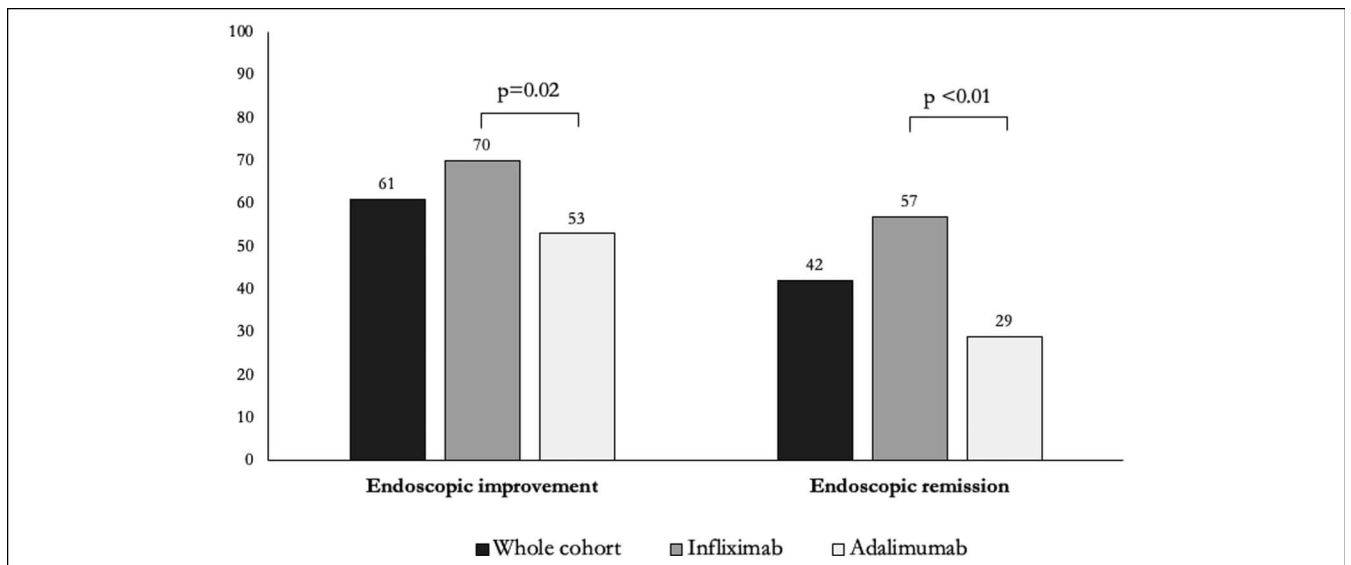

Figure 1. Proportion of treatment success per type of antitumor necrosis factor.

Table 4. Factors associated with treatment outcomes

| | Endoscopic remission | | | | Endoscopic improvement | | | |
| | Univariable analysis | | Multivariable analysis | | Univariable analysis | | Multivariable analysis | |
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Age at surgery	1.02 (0.99–1.05)	**0.05**			1.02 (0.99–1.04)	0.16		
Female gender	0.90 (0.29–1.64)	0.75			0.70 (0.38–1.29)	0.26		
Penetrating behavior	0.89 (0.44–1.45)	0.46			0.69 (0.38–1.26)	0.22		
Perianal disease before surgery	1.26 (0.57–2.78)	0.56			1.35 (0.59–3.08)	0.48		
Extraintestinal manifestations	2.36 (0.74–7.53)	0.14			1.53 (0.77–3.05)	0.23		
Active smokers at index surgery	0.91 (0.50–1.65)	0.75			1.33 (0.97–1.83)	0.08		
Previous intestinal resections	0.91 (0.41–2.02)	0.82			0.96 (0.43–2.13)	0.91		
Anti-TNF exposure before a surgery	1.22 (0.64–2.33)	0.55			1.96 (0.98–3.93)	0.06		
Advanced endoscopic POR	0.68 (0.37–1.28)	0.24			2.38 (1.27–4.45)	**<0.01**	2.63 (1.37–5.07)	**<0.01**
Postoperative prevention with thiopurines	1.95 (1.06–3.6)	**0.03**			1.63 (0.89–2.98)	0.12		
Concomitant thiopurines	2.21 (1.12–4.37)	**0.02**	2.15 (1.04–4.46)	**0.03**	2.26 (1.18–4.32)	**0.01**	2.34 (1.18–4.62)	**0.01**
At least 1 risk factor for POR	0.75 (0.39–1.46)	0.40			0.60 (0.29–1.25)	0.17		
Clinical POR at anti-TNF start	2.79 (1.34–5.80)	**<0.01**	3.31 (1.51–7.28)	**0.03**	2.18 (0.98–4.81)	0.06		
Infliximab therapy for POR	3.17 (1.71–5.88)	**<0.01**	3.16 (1.65–6.05)	**<0.01**	2.05 (1.10–3.79)	**0.02**	2.01 (1.05–3.88)	**0.04**
Time from index surgery to anti-TNF start[a]	0.99 (0.99–1.00)	0.96			1.00 (0.99–1.01)	0.99		
Time from CD diagnosis to index surgery[a]	1.00 (0.99–1.00)	0.65			1.00 (0.99–1.00)	0.72		
Endoscopic POR >12 mo from surgery	0.85 (0.42–1.73)	0.65			0.92 (0.44–1.89)	0.81		

Bold indicates statistical significance with a P value less than 0.05.
CD, Crohn's disease; CI, confidence interval; OR, odds ratio; POR, postoperative recurrence; TNF, tumor necrosis factor.
[a]Time expressed in months.

whereas most of early endoscopic POR correspond to i2 in reported series (13,20).

One of the most interesting findings of this study are those factors associated with a higher efficacy of anti-TNF for improving or reverting postoperative mucosal lesions. We found that concomitant use of thiopurines increased the efficacy of anti-TNF agents. Two RCTs comparing, respectively, infliximab and adalimumab in monotherapy or in combination with azathioprine for the treatment of active luminal CD showed that combination therapy increased the rate of mucosal healing after 6 months (24,25). Moreover, combination therapy is associated with higher trough levels of anti-TNF, preventing underexposure to the drug and potentially increasing their efficacy, particularly when mucosal healing is the therapeutic end point (26). Hence, it seems reasonable that in patients with endoscopic POR in whom anti-TNF will be started, this should be in combination with thiopurines whenever possible, and regardless, the patients was on preventive thiopurine therapy.

We also found a greater efficacy of infliximab over adalimumab. Despite the lack of face-to-face studies, both drugs have shown similar results in inducing mucosal healing in the setting of RCTs in luminal CD (27). In our study, there was a significant higher proportion of patients who had been previously exposed to the same anti-TNF in the infliximab group; this would have been an advantage (if any) for the adalimumab-treated patients who might benefit the most from a "switch strategy," although we lack the information on immunogenicity data. To confirm the results of the logistic regression analysis, we performed a propensity score analysis using 16 covariates for matching and treatment with infliximab as the dependent variable, including 130 matched patients (65 treated with infliximab and 65 with adalimumab), and the results remained the same. Therefore, it seems that at least in the postoperative setting, infliximab is superior to adalimumab for improving recurrent lesions.

Finally, we are aware of some additional limitations of our study. First, the lack of therapeutic drug measurements. This might affect in several ways: treatment dosing was not changed because of therapeutic drug monitoring in most patients, and we do not know whether those patients who discontinued therapy before surgery did it because of primary or secondary loss of response, with or without dosing adjustments based on therapeutic drug monitoring findings. Moreover, we did not have data on immunogenicity that might be particularly relevant in the case of reinitiation of infliximab, which might have favored adalimumab. However, recent studies showed controversial results regarding the utility of trough drug levels to predict the efficacy of anti-TNF in preventing endoscopic POR (28–30). Second, endoscopic images were not recorded, and no central reading was possible; therefore, the information regarding

the Rutgeerts endoscopic score relied on local endoscopic reports. Finally, the time point for endoscopic assessment was not pre-established and the response to treatment was not homogenously assessed in all patients. Despite this, there were no differences between the 2 treatment groups regarding the time to therapeutic endoscopic assessment.

In summary, anti-TNF therapy for endoscopic POR resulted in a complete reversal of mucosal lesions in half of the patients and clinical improvement in more than half of the symptomatic patients. We also found that the combination therapy of infliximab and thiopurines resulted in a higher rate of mucosal improvement.

CONFLICTS OF INTEREST

Guarantor of the article: Eugeni Domènech, MD, PhD.

Specific author contributions: F.C. and E.D. designed the study, performed statistical analyses, interpreted the results, and drafted the manuscript. Germán Cediel designed, performed, and helped in the interpretation of the statistical analysis. The remaining authors collected data and critically reviewed the manuscript. All authors are aware and agree to the content of the manuscript and accept their authorship.

Financial support: None to report.

Potential competing interests: F.C. has served as a speaker or has received educational grants from Takeda, Janssen, MSD, and Ferring. M.M. has served as a speaker, has received research or educational funding or advisory fees from Danone, Allergan, Almirall, MSD, AbbVie, Takeda, Janssen, and Ferring. R.C.G.-S. has served as a speaker or has received educational grants from AbbVie, Takeda, and Janssen. M.B.d.A. has served as a speaker, a consultant, and an advisory member for or has received research funding from MSD, AbbVie, Hospira, Takeda, Janssen, Kern Pharma, Ferring, FaesFarma, ShirePharmaceuticals, Dr. FalkPharma, Chiesi, Gebro-Pharma, OtsukaPharmaceuticals, and TillottsPharma; Pilar Nos. Educational activities, research projects, and scientific meetings sponsored by AbbVie, MSD, Janssen, Takeda, Otsuka, Kern Pharma, and Pfizer. E.I.-F. has served as a speaker or has received educational funding or advisory fees from Takeda, Janssen, MSD, and AbbVie. A.G. has served as a speaker, a consultant or advisory member for MSD, AbbVie, Hospira, Pfizer, Takeda, Janssen, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, and Tillots Pharma. M.J.C. has received education funding from Pfizer, Janssen, MSD, Ferring, and AbbVie. M.N.-L. has served as a speaker, has received research or educational funding or advisory fees from MSD, AbbVie, Takeda, Janssen, and Ferring. A.V. has served as a speaker, or has received educational funding from MSD, AbbVie, Takeda, Tillots, and Shire Pharmaceuticals. C.T. has served as a speaker, a consultant or advisory member for MSD, AbbVie, Hospira, Pfizer, Takeda, Janssen, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Gebro Pharma, and Tillots Pharma. M.V.D. has served as a speaker, has received research or educational funding from MSD, AbbVie, Takeda, Janssen, Kern Pharma, and Ferring. A.H.C. has served as a speaker or has received educational funding from AbbVie, Takeda, Pfizer, Janssen, Ferring, Shire Pharmaceuticals, and Kern Pharma. L.R. has served as a speaker, or has received educational funding from MSD, AbbVie, Takeda, Pfizer, Janssen, Ferring, and Shire Pharmaceuticals; Ramón Pajares has received fees as a speaker from Janssen and Salvat. M.D.M.-A. has received fees as a speaker, consultant, an advisory member for, and has received research funding from MSD, AbbVie, Hospira, Pfizer, Takeda, Janssen, Shire Pharmaceuticals, Tillotts Pharma, and Faes Pharma. A.A. has served as a speaker, has received research grant or advisory fees from MSD, Lilly, Roche,

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Study Highlights

WHAT IS KNOWN

✓ Seventy percent of patients with CD develop POR within the first year if no therapy is prescribed early after surgery.

✓ Thiopurines and anti-TNF agents have proven to be efficient in preventing endoscopic and clinical POR.

✓ Whether universal prevention or endoscopy-driven therapy is the best strategy is still under debate.

✓ No data are available on the efficacy of anti-TNF agents in the setting of asymptomatic patients with endoscopic POR.

WHAT IS NEW HERE

✓ Anti-TNF therapy for endoscopic POR achieves a complete reversal of mucosal lesions in almost half of the patients.

✓ Combination therapy with thiopurines increases the likeliness of improving mucosal lesions.

✓ In the postoperative setting, infliximab seems to be superior to adalimumab for improving recurrent lesions. However, face-to-face prospective studies are needed in this setting.

TRANSLATIONAL IMPACT

✓ Since this article is not a pre-clinical study we have not made a translational impact.

✓ In the instructions and guidelines of the original article, said "if your manuscript is pre-clinical, briefly explain how the results may impact future clinical practice."

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