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Alimentary Tract

Prevention of post-operative recurrence of Crohn's disease among patients with prior anti-TNFα failure: A retrospective multicenter study

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ABSTRACT

Background: Anti-TNFα are recommended for preventing Crohn's disease (CD) postoperative recurrence (POR) in patients with risk factors. However, few data exploring anti-TNFα efficacy in patients with pre-operative anti-TNFα failure are available so far.

Aims: The aim of the present study was to compare the efficacy of anti-TNFα with other biologics and immunosuppressants to prevent POR in this setting.

Methods: Consecutive CD patients who underwent bowel resection between January 2010 and December 2019 after failure of at least one anti-TNFα were retrospectively included among three tertiary centers if they started a postoperative medical prophylaxis within the three months after index surgery. The main outcome was to compare rates of objective recurrence (endoscopic or radiological recurrence in absence of colonoscopy) between patients treated with an anti-TNFα agent or another treatment as prevention of POR.

Results: Among the 119 patients included, 71 patients received an anti-TNFα (26 infliximab, 45 adalimumab) and 48 another treatment (18 ustekinumab, 7 vedolizumab, 20 azathioprine and 3 methotrexate) to prevent POR. Rates of objective recurrence at two years were 23.9% in patients treated with anti-TNFα and 44.9% in the others ($p = 0.011$).

Conclusion: Anti-TNFα remained an effective option to prevent POR for patients operated upon with previous anti-TNFα failure.

1. Introduction

The course and prognosis of Crohn's Disease (CD) has been substantially altered by the improvement in medical and surgical managements since the 90's [1]. Real-life studies have reported that among patients initially responding to infliximab, sixty percent will be in deep remission [2]. On the other hand, 40% of patients will stop this treatment due to different cause of failure: primary non-response (10%), secondary loss of response (20%) and intolerance (10%) [3]. New biologics have emerged during the last ten years and offer new options in case of anti-TNFα failure such as vedolizumab and ustekinumab [4,5]. Those progresses have allowed to decrease hospitalization incidence and the need for bowel resection [6,7]. Yet, twenty-five to fifty percent of patients will still need surgery within the first ten years of their disease course [8,9]. Two out of three surgeries will consist in an ileocecal resection.

Although the surgical option is initially very efficient, half of the patients will suffer from symptomatic post operative recurrence within 3 years without medical prophylaxis [10]. The prevention strategy is based on a systematic colonoscopy, 6 to 12 months after surgery, looking for an endoscopic recurrence which theoretically precedes the clinical recurrence [11]. Moreover, the European Crohn's and Colitis organisation (ECCO) guidelines recommend to start a prophylactic treatment within 2 to 8 weeks after surgery in presence of recurrence risk factors [12]. In a second time, the

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treatment is modulated according to ileocolonoscopy' results. According to a recent meta-analysis, the best therapeutic option to prevent CD recurrence after surgery is anti-TNFα [13].

However, an increasing rate of patients is operated upon after failure of at least one anti-TNFα. Furthermore, preoperative use of anti-TNFα had been associated with an increased risk of clinical recurrence in the PREVENT study [14]. Similarly, a French retrospective study has reported the association of the previous use of two or more anti-TNFα with a higher risk of postoperative recurrence (45.5% vs 29.1%; $p = 0.07$) [15].

Therefore, prophylaxis of postoperative recurrence for those patients with high risk profile is a major issue. Neither consensus nor guideline are available to help practicioners in their therapeutic choice in case of previous anti-TNFα failure. The aim of our study was to compare the efficacy of two strategies aiming at reducing the risk of post operative recurrence: start over an anti-TNFα or start another treatment (another biologic or conventional immunosuppressant).

2. Materials and methods

2.1. Study design

This was a retrospective, observational study conducted in three tertiary IBD French centers (centres hospitaliers universitaires de Toulouse, Montpellier and Bordeaux).

2.2. Study population

Consecutive adult CD patients were included when they underwent a surgery between January 2010 and December 2019 among the three participating centers. Index surgery consisted in an ileocecal resection, a repetitive ileocolic resection or a small bowel resection. Patients were eligible if they had CD diagnosis based on usual criteria [16], preoperative anti-TNFα failure, a postoperative medical prophylaxis (infliximab, adalimumab, certolizumab pegol, azathioprine, methotrexate, ustekinumab, vedolizumab) started within the three months after index surgery and a follow up of at least two years after index surgery including at least one colonoscopy and/or one magnetic resonance enterography (MRE). Anti-TNFα failure was defined by drug discontinuation due to loss of response (absence of improvement or worsening of symptoms), intolerance or allergy after at least 12 weeks of treatment exposure.

The exclusion criteria were : isolated colonic resection, drug discontinuation for intolerance with counter-indication of reintroduction this therapeutic class, for pregnancy and by patient choice; surgery without anastomosis within the first stage (e.g. double-barreled ileocolostomy) and patients treated with 5 aminosalicylates and steroids after the surgery.

2.3. Data collection

The identification of patients hospitalized have been carried out by extracting the files from digestive surgical and gastroenterology departments. The anonymous collection of data for each patient included has been done through an electronic Case Report Form (eCRF) in the form of an Excel file. It has been carried out retrospectively by consulting the computerized patient record on ORBIS® and Dxcare® chosen by our hospitals as medical record software.

The characteristics of patients recorded at the time of index surgery were the followings: gender, age, smoking status, body mass index (BMI), serum C-reactive protein (CRP) and albumin levels, fecal calprotectin level (if available within 3 months before surgery), localization and behavior of CD [17], duration of CD, extra intestinal manifestation and Harvey Bradshaw index at the last visit before surgery (if not available, it was retrospectively determined based on the medical records).

Data on the previous therapeutic lines (notably the last treatment before surgery) have been analyzed including the cause of interruption (loss of response, intolerance and allergy). The underlying mechanism of anti-TNFα failure was recorded when available: immunogenicity (presence of antibodies to infliximab or adalimumab), pharmacokinetic (low serum trough concentration), pharmacodynamic (adequate serum concentration without antibodies to infliximab or adalimumab) and intolerance. The adequate trough concentrations were defined as between 3–7 and 5–7 μg/mL for infliximab and adalimumab respectively [18].

Surgical data were also collected: indication, presence of lesions upstream the main resection site (excluding "victim" segments), type of procedure, post operative complications and histological data. Lesions upstream the main resection site could have been treated with strictureplasty, segmental resection or not surgically treated.

2.4. Follow-up

Postoperative follow-up data from medical visits have been recorded for 2 years: smoking status, serum CRP level, serum albumin level, fecal calprotectin level (if available), BMI and Harvey Bradshaw index at each visit. The modified Rutgeerts score has been retrospectively determined based on the endoscopic reports and pictures if available (supplementary Table 1) [10].

Data on the post operative treatment were analyzed: type, date of the first administration, need for discontinuation. In case of discontinuation, the delay since the first administration, the reason for discontinuation were recorded (clinical and/or objective recurrence, intolerance).

2.5. Postoperative recurrence

Clinical recurrence was defined by the presence of symptoms (abdominal pain and/or accelerated bowel movement and/or symptoms of bowel obstruction) associated with objective signs of inflammation (fecal calprotectin level equal or greater than 100 µg/g of stool and/or endoscopic and/or radiological signs of activity). Endoscopic recurrence was defined by a modified Rutgeerts' score ≥i2b. Radiological recurrence was defined by trained radiologists at multidisciplinary specialized consultation meeting and based on the presence of a least one of the following criteria on MRE: bowel wall thickening, mural contrast enhancement (T1-weighted gadolinium), presence of ulcers and restricted diffusion (defined by high signal intensity and reduced Apparent Diffusion Coefficient) [19,20]. The need of another surgery more than 1 month after the index surgery defined the surgical recurrence.

2.6. Study objectives

The objective of the present study was to compare rates of objective (endoscopic or radiological recurrence in absence of colonoscopy) CD recurrence between patients receiving postoperative prevention with anti-TNFα to other treatments (other biologic or conventional immunosuppressant).

Secondary objectives were to compare the cumulative survival rates without clinical recurrence, without treatment discontinuation, without surgical recurrence between the two groups and to identify risk factors for objective recurrence. Patients' preoperative characteristics, rates of objective recurrence and cumulative survival rates without clinical recurrence, without treatment discontinuation and without surgical recurrence were compared

between patients treated with other biologics (vedolizumab of ustekinumab) and conventional immunosuppressants (thiopurines or methotrexate) within the second group, in a sub-analysis. Rates of objective recurrence according the mechanism of failure of the last anti-TNFα administered before surgery in patients postoperatively treated with anti-TNFα were also compared.

2.7. Statistical analysis

Continuous variables have been reported as medians and ranges and compared using the Student's *t*-test. Categorical variables have been indicated as proportions and percentages and comparison was drawn by a chi-squared test. Cumulative survival rates without treatment discontinuation and without clinical recurrence have been calculated with a Kaplan-Meier method (log-Rank test). The first day has been set as the date of the first administration of medical prophylaxis. The time to discontinuation has been calculated as the interval between the first administration of medical prophylaxis and the date of the treatment discontinuation (or first mention of clinical recurrence respectively).

Among preoperative data collected, we investigated risk factors for objective post operative recurrence. Variables with p-value below 0.20 in univariate regression (univariable Cox regression) were included in a multivariate Cox model. Manual stepwise elimination was performed to find the best suitable model of factors predicting objective post operative recurrence. Results are presented as hazard ratio (HR) with 95% confidence intervals (95% CI).

Two-sided statistical tests have been used for all analyses and a p value < 0.05 have been considered significant. The statistical analyses have been performed with the Jamovi software (version 1.6.15.0).

3. Ethical considerations

The study was conducted in accordance with the principles of good clinical practice and the declaration of Helsinki at all times. According to the French ethic and regulatory law (public health code) retrospective studies based on the exploitation of usual care data do not require submission to an ethical committee but they have to be declared or covered by reference methodology of the French National Commission for Informatics and Liberties (CNIL). A collection and computer processing of personal and medical date was implemented to analyze the results of the research. After evaluation and validation by the data protection officer and according to the General Data Protection Regulation, this study completing all the criteria, it is recorded in the register of retrospective studies of the Toulouse University Hospital (RnIPH 2021–143) and covered by the MR-004 (CNIL number: 2,206,723 v 0). This study was approved by Toulouse University Hospital and confirm that ethical requirements were totally respected in the above report.

4. Results

4.1. Patients' preoperative characteristics

A total of 119 patients were included. Among them, 71 patients were treated postoperatively with anti-TNFα and 48 were treated with other treatments. The sex ratio was well balanced (60 women/59 men) and the median age at diagnosis was 23 years old (10–57). The main locations of disease were by frequency : ileal (65 patients; 54.6%), ileocolonic (49; 41.2%) and colonic (5; 4.2%). Thirty-eight patients (31.9%) also presented a perineal disease and 39 (32.8%) had at least one extra-intestinal manifestation. Only three patients had a non-stricturing non-penetrating disease behavior (2.5%) whereas 64 (53.8%) and 52 (43.7) suffered from penetrating and stricturing disease respectively. At the time of surgery, 41 patients were active smokers (36.1%). The median preoperative CRP and albumin serum levels were respectively 16.4 mg/L (0–245) and 35 g/L (20–49). The median preoperative BMI was 21.7 kg/m² (ranging from 13.1 to 33.3). Both groups had a median number of two postoperative recurrence risks factors according to ECCO guidelines (ranging from 0 to 6; $p = 0.145$) [12]. All patients' preoperative characteristics were similar between the two groups (Table 1).

4.2. Previous therapeutic lines

The most preoperatively prescribed lines were anti-TNFα (100% of patients) and thiopurines in monotherapy (85 patients; 71.4%). Exposition to the different therapeutic lines is detailed in supplementary Table 2. Patients postoperatively treated with anti-TNFα had previously received a median of two anti-TNFα while patients treated with other treatments had received a median of one (ranging from 1 to 3 in both groups; $p = 0.534$). Table 2 summarizes the data on the different anti-TNFα (molecule, use in combotherapy, length of prescription, failure mechanism). There was no difference between the two groups regarding preoperative anti-TNFα exposure. The median time between the last administration of treatment and surgery was one month in both groups (ranging from 0 to 11 months in anti-TNFα groups vs 0 to 20 months; $p = 0.182$).

4.3. Surgical outcomes

Surgery procedures were comparable between the two groups and consisted in an ileocecal resection for 59.2% of patients under anti-TNFα (vs 52.1%), a repetitive ileocolic resection for 36.6% (vs 37.5%), a small bowel resection for 2.8% (vs 8.3%) and a small bowel resection associated with a segmental colonic resection for 1.4% (vs 2.1%; $p = 0.559$). All surgical outcomes are presented in supplementary Table 3. There was no difference between the two groups.

4.4. Postoperative prophylaxis

Seventy-one patients were treated with anti-TNFα (26 with infliximab, 45 with adalimumab). Forty-eight patients were treated with other medications: 18 with ustekinumab, 7 with vedolizumab, 20 with azathioprine and 3 with methotrexate. The median time between surgery and first administration of prophylactic treatment was one month in both groups (ranging from 0 to 3 months; $p = 0.932$). Among patients postoperatively treated with anti-TNFα, eleven patients received a new molecule (more details on the successive anti-TNFα in supplementary Table 4). Fourteen patients had quitted smoking postoperatively (6 vs 8 patients ; $p = 0.375$), there was no difference between the two groups regarding the proportion of postoperative smokers (25.4 vs 20.8%; $p = 0.569$).

4.5. Objective recurrence

101 patients had a colonoscopy (61 in anti-TNFα groups vs 40) while 18 had an MRE (10 vs 8 ; $p = 0.700$). The median time between surgery and recurrence screening by colonoscopy (or MRE) was longer for patients treated with anti-TNFα (8 vs 7 months, ranging respectively from 4 to 23 months and 4 to 15 months respectively; $p = 0.003$). Patients postoperatively treated with anti-TNFα had significantly less objective recurrence than patients under other treatments (Fig. 1). This result remained significant for endoscopic recurrence only (21.3 vs 47.5% ; $p = 0.006$). Forty percent of patients under other treatments had a Rutgeerts score i3 or i4 vs only one in ten under anti-TNFα (Supplementary Fig. 1). Postoperative active smoking, primary non-response for the first

Table 1
Patients' preoperative characteristics.

Characteristic	Anti-TNFα (n = 71)	Other treatments (n = 48)	p
Gender			0.653
Male	34 (47.9)	25 (52.1)	
Female	37 (52.1)	23 (47.9)	
Median age at surgery (y)	33 (15–72)	38 (19–59)	0.200
Median duration of the disease at surgery (m)	91(3–553)	129 (7–415)	0.539
Disease behavior according Montreal classification			0.740
Non-stricturing, non-penetrating (B1)	2 (2.8)	1 (2.1)	
Stricturing (B2)	29 (40.8)	23 (47.9)	
Penetrating (B3)	40 (56.3)	24 (50)	
Disease location (according Montreal classification)			0.389
Ileal (L1)	42 (59.2)	23 (47.9)	
Colonic (L2)	2 (2.8)	3 (6.3)	
Ileocolonic (L3)	27 (38)	22 (45.3)	
Associated upper tract location (L4)	6 (8.5)	9 (18.8)	0.097
Perianal disease	19 (26.8)	19 (39.6)	0.141
Age at surgery according Montreal classification			0.235
<16 years (A1)	16 (22.5)	5 (10.4)	
Between 17–40 years (A2)	51 (71.8)	40 (83.3)	
> 40 years (A3)	4 (5.6)	3 (6.3)	
Extra intestinal manifestations	24 (33.8)	16 (33.3)	0.958
Skin disease	7 (9.9)	3 (6.3)	0.486
Arthropathy	18 (25.4)	13 (25)	0.965
Eye disease	2 (2.8)	1 (2.1)	0.802
Primary sclerosing cholangitis	3 (4.2)	1 (2.1)	0.525
History of surgical resection	25 (35.2)	19 (37.5)	0.799
Smoking status			0.729
Non-smokers	39 (54.9)	23 (47.9)	
Former smokers	8 (11.3)	7 (14.6)	
Active smokers	24 (33.8)	18 (37.5)	
Median Harvey Bradshaw score	5 (2–13)	5 (1–10)	0.274
Preoperative symptoms			
Abdominal pain	68 (95.8)	43 (89.6)	0.186
Symptoms of bowel obstruction	489 (69)	35 (72.9)	0.647
Accelerated bowel movement	21 (29.6)	13 (27.5)	0.786
BMI (kg/m²)	20.4 (13.1–32)	21.1 (13.8–33.3)	0.915
Serum albumin level (g/L)*	35 (20–49)	34.5 (27–48)	0.205
Serum CRP level (mg/L)†	15 (0–245)	17 (0–145)	0.862
Fecal calprotectin level (µg/g)‡	319 (100–2239)	1516 (1000–2209)	0.087

BMI, Body Mass Index; CRP, C reactive protein.
Data are represented as median (range) for continuous variables and n (%) for categorial variables.
*: 53 under anti-TNFα, 32 under other treatments.
†: 63 under anti-TNFα, 37 under other treatments.
‡: 9 under anti-TNFα, 3 under other treatments.

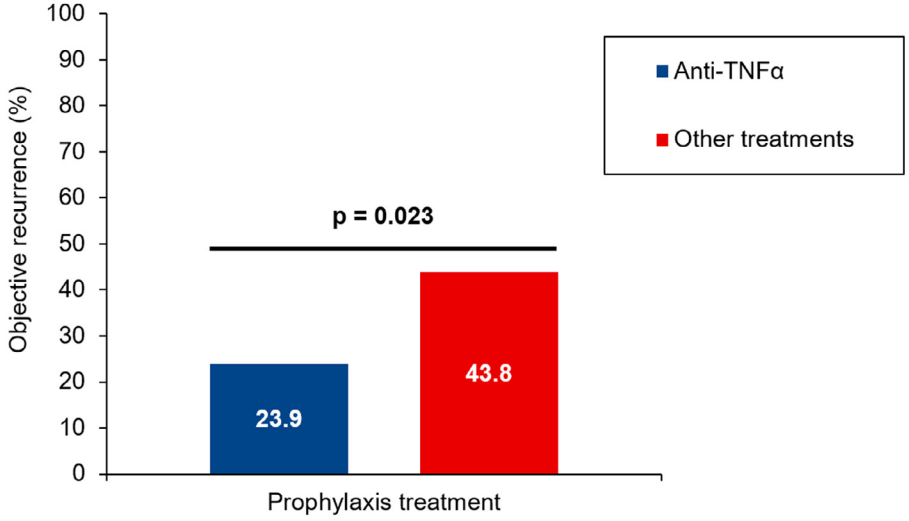

Fig. 1. Objective recurrence.
Anti-TNFα were represented by infliximab and adalimumab. Other treatments were azathioprine, methotrexate, vedolizumab and ustekinumab.

Table 2
Anti-TNFα administrated before surgery.

Outcomes	Anti-TNFα ($n = 71$)	Other treatments ($n = 48$)	p
First line			0.066
Infliximab	40 (56.3)	35 (72.9)	
Adalimumab	31 (44.3)	13 (26.5)	
Use in combotherapy	25 (35.2)	25 (52.1)	0.067
Median 1st line duration (months)	18 (1–90)	12 (0–147)	0.701
Type of failure			0.969
Primary non-response	15 (21.1)	10 (20.8)	
Secondary	55 (78.9)	39 (79.2)	
Failure mechanism			0.084
Pharmacodynamic	12 (16.9)	3 (6.3)	
Pharmacokinetic	1 (1.4)	0 (0)	
Immunogenicity	3 (4.2)	5 (10.4)	
Absence of TDM	48 (66.2)	28 (58.3)	
Intolerance	4 (5.6)	9 (18.8)	
Allergy	4 (5.6)	3 (6.3)	
Second line ($n = 56$ patients)			0.279
Infliximab	9 (29)	8 (32)	
Adalimumab	19 (61.3)	17 (68)	
Certolizumab pegol	3 (9.7)	0 (0)	
Use in combotherapy	14 (45.2)	12 (48)	0.832
Median 2nd line duration (months)	6 (0–50)	12 (0–78)	0.227
Type of failure			0.990
Primary non-response	5 (16.1)	4 (16)	
Secondary	25 (83.9)	22 (84)	
Failure mechanism			0.151
Pharmacodynamic	5 (16.1)	2 (8)	
Pharmacokinetic	4 (12.9)	2 (8)	
Immunogenicity	0 (0)	3 (12)	
Absence of TDM	20 (64.5)	13 (52)	
Intolerance	2 (6.5)	3 (12)	
Allergy	0 (0)	2 (8)	
Third line ($n = 7$ patients)			0.350
Infliximab	1 (25)	0	
Adalimumab	1 (25)	0	
Certolizumab pegol	2 (50)	3 (100)	
Use in combotherapy	2 (50)	1 (33.3)	0.659
Median 3rd line duration (months)	5 (0–67)	8 (4–35)	0.503
Type of failure			0.540
Primary non-response	1 (25)	1 (50)	
Secondary	3 (75)	1 (50)	
Failure mechanism			0.269
Pharmacokinetic	1 (25)	0 (0)	
Absence of TDM	3 (75)	1 (50)	
Intolerance	0	1 (50)	

TDM: Therapeutic Drug Monitoring.
Data are represented as median (range) for continuous variables and n (%) for categorial variables.

anti-TNFα, macroscopic invasion at surgical margins and lesions upstream the main resection site were associated with the risk of objective recurrence in multivariate analysis (Table 3).

There was no significant difference on the risk of objective recurrence according the mechanism of failure of the last anti-TNFα administered before surgery among patients postoperatively treated with anti-TNFα ($p = 0.224$). Among the 15 patients postoperatively treated with anti-TNFα whom experienced a preoperative pharmacodynamic failure, four had a objective recurrence (26.7%). Objective recurrence occurred in two patients out of five with previous history of pharmacokinetic failure (40%). Ten patients out of forty with preoperative loss of response without therapeutic drug monitoring data had a objective recurrence (20%). The only patient who experienced intolerance to the last anti-TNFα administered before surgery experienced a objective recurrence (100%).

4.6. Clinical and surgical recurrence, and treatment discontinuation

There was a trend in favor of less clinical recurrence in patients treated with anti-TNFα than those treated with other medications (Fig. 2). Clinical and biological follow-up is detailed in supplementary Table 5. No surgical recurrence occurred during the follow-up. Regarding treatment discontinuation, it was significantly less frequent in the group of patients under anti-TNFα (Fig. 3). Indications for discontinuation were similar within the two groups ($p = 0.169$): clinical recurrence (40% in anti-TNFα group vs 35%), objective recurrence (33.3 vs 55%), immunogenicity (20 vs 0%), Rutgeerts score i2a (6.7 vs 0%), colonic aphthous lesions (0 vs 10%).

4.7. Other treatments group sub-analysis

The two subgroups (patients treated with other biologics and with conventional immunosuppressants) were comparable regarding preoperative characteristics and surgical outcomes (Supplementary Table 6 and 7). Regarding objective recurrence, patients treated with vedolizumab and ustekinumab did not differ from patients treated with conventional immunosuppressants (40 vs 47.8%; $p = 0.585$). There was no difference regarding survival rate clinical recurrence between those two subgroups (Supplementary Fig. 2). There was a trend in favor of less treatment discontinuation in other biologics arm (Supplementary Fig. 3).

Table 3
Associated risks factors associated with objective recurrence.

	Univariate analysis			Multivariate analysis		
	HR	CI 95%	p	HR	CI 95%	p
Arthropathy (presence)	1.96	[0.83–4.61]	*0.121*			
Upper digestive tract lesions* (presence)	2.06	[0.69–6.18]	*0.190*			
Primary non-response to the first anti-TNFα (vs secondary loss)	2.41	[0.98–5.97]	*0.053*	3.70	[1.32–10.35]	*0.013*
Previous use of two (or more) anti-TNFα (presence)	2.23	[1.02–4.90]	*0.044*			
History of surgical resection (presence)	2.38	[1.07–5.26]	*0.031*			
Lesions upstream the resection site † (presence)	2.34	[0.92–5.94]	*0.069*	3.20	[1.16–8.85]	*0.025*
Granuloma on surgical piece (presence)	1.86	[0.82–4.22]	*0.134*			
Macroscopic lesions at surgical margins (presence)	2.27	[0.87–5.95]	*0.089*	2.92	[1.01–8.41]	*0.047*
Postoperative complications (presence)	2.29	[0.96–5.48]	*0.060*			
Postoperative active smoking (presence)	2.29	[0.96–5.48]	*0.060*	2.62	[1.01–6.80]	*0.048*

CRP: C reactive protein; BMI: Body Mass Index; HR, Hazard ratio; CI 95% : 95% confidence intervals.
* Upper lesions according Montreal classification [17].
† Lesions discovered at the time of surgery or previously described on radiological examinations.

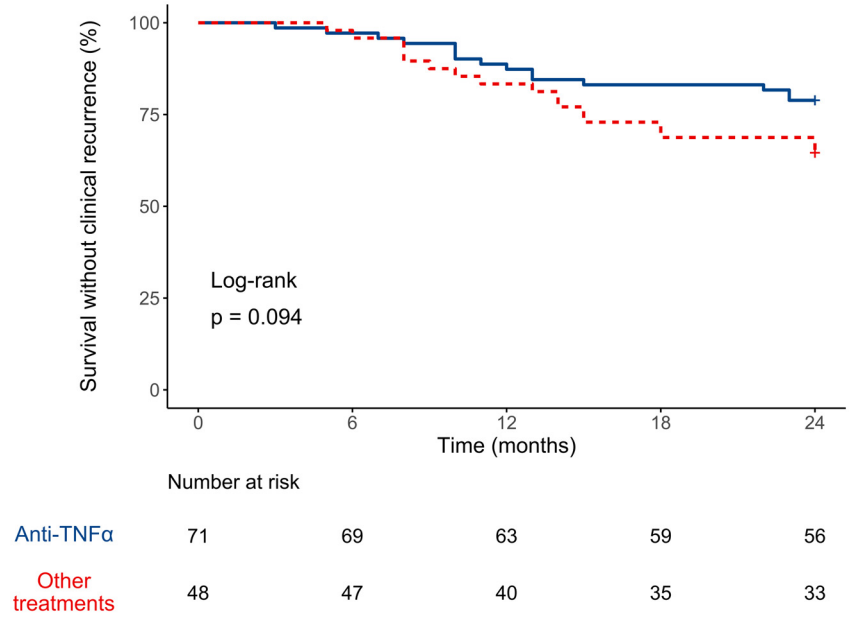

Fig. 2. Survival without clinical recurrence.
Survival curves without clinical recurrence of patients treated with anti-TNFα (blue curve) and other treatments (red curve), calculated with Kaplan-Meier method.

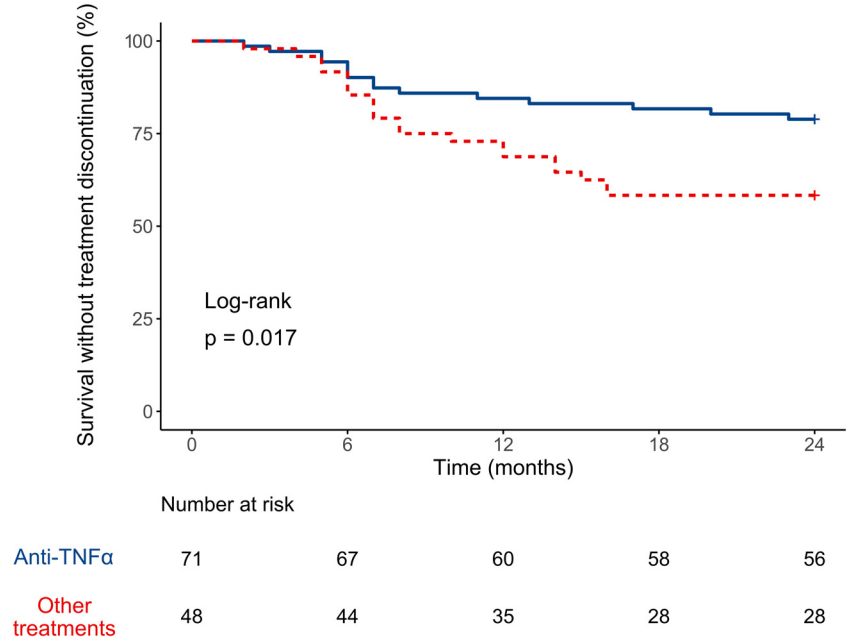

Fig. 3. Survival without treatment discontinuation.
Survival curves without treatment discontinuation of patients treated with anti-TNFα (blue curve) and other treatments (red curve), calculated with Kaplan-Meier method.

5. Discussion

In this study, we found that patients with history of preoperative anti-TNFα failure experienced less objective recurrence when they were treated with anti-TNFα. Our results are consistent with previous data on endoscopic recurrence rate with anti-TNFα, such as in PREVENT study (22.4%) and POCER study (21%) [14,21]. Yet, there were less patients preoperatively exposed to anti-TNFα in those trials (22.6 and 21.8% respectively). Moreover, subgroup analysis on patients treated with adalimumab in POCER study showed that the preoperative use of anti-TNFα was associated with a higher endoscopic recurrence risk (56 vs 5% : $p = 0.007$) [22].

There was less treatment discontinuation in the group of patients postoperatively treated with anti-TNFα. Endoscopic recurrence, defined by a Rutgeerts score more or equal to i2b, was one of the most frequent discontinuation reasons. However, nowadays the medical management of i2 lesions is debated more than ever. Rivière et al. reported the absence of benefit after therapeutic intensification on the clinical recurrence risk for those lesions [23]. One way to overcome this difficulty might be to improve the definition of endoscopic lesions. Some have proposed a new classification which differentiate ileal and anastomotic lesions [24]. Their hypothesis is that anastomotic lesions might be due to postoperative ischemia and will lead to obstruction symptoms and therefore don't need drug escalation. The POMEROL study (NCT05072782), coordinated by the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID) will give us more data on this topic.

We observed a trend in favor of anti-TNFα on the clinical recurrence risk. Our results are in accordance with the study of Savarino et al. where the risk of clinical recurrence at 1 year (defined by CDAI score $\geq$ 200) was 6.3% under adalimumab (vs 70.6% under azathioprine) [25]. The mechanism of preoperative anti-TNFα failure might influence its postoperative efficacy. Regarding the low rate of objective recurrence among patients with previous history of pharmacodynamic failure, our results are in accordance with the literature. Assa et al. reported no significant differences between anti-TNFα naive pediatric patients and patients with previous history of pharmacodynamic failure on the risk of endoscopic and clinical recurrence at 1 year [26]. This phenomenon might be explained by the definition of preoperative failure. Some patients might have symptoms due to fibrostenotic structure or too severe lesions to benefit from medical treatment. After surgery and removal of most severe (or fibrostenotic) lesions, those patients might respond to anti-TNFα. Regarding patients with history of immunogenicity, Auzolle et al. reported a high risk of endoscopic recurrence (80% vs 30% in absence of history of immunogenicity) [27]. Yet, no conclusion can be drawn on the influence of the underlying mechanism of failure of the last anti-TNFα on the objective recurrence risk because of the small number of patients with therapeutic drug monitoring data in our study.

Among our population of anti-TNFα non responders, we found previously identified risk factors of objective recurrence. Yet, history of primary non-response to a first of anti-TNFα had never been reported before [28–31]. It might be explained by our inclusion criteria and the previous exposition of the whole population to this therapeutic class. Moreover, this data might be a surrogate marker of more severe disease behavior. Indeed, a meta-analysis by Singh et al. showed that primary non-response to anti-TNFα was associated with inferior response to other biologics [32].

Our study has several limitations. First, our primary endpoint is based on recurrence screening with endoscopy and MRE. However, others have described a high consistency between radiological (based on MRE) and endoscopic recurrence [20,33]. Based on the absence of standardized therapeutic attitude after anti-TNFα failure, we chose to merge results for all other treatments. Sub-analysis in this subgroup showed no significant differences in terms of objective and clinical recurrence between patients treated with conventional immunosuppressants and other biologics. Furthermore, no treatment has proved its superiority over another one in this indication [21,34–36]. Buisson et al. found a lower risk of endoscopic recurrence (defined as lesions $\geq$ i2) under ustekinumab than azathioprine (28.0 vs 54.5% ; $p = 0.029$), yet it was not significant for lesions $\geq$ i2b or $\geq$ i3 [37]. Among the 18 patients postoperatively treated with ustekinumab in our study, 8 experienced objective recurrence (44.4%). Although the suspected longer delay of action of vedolizumab might explain worse outcomes, a recent study showed no difference between vedolizumab and ustekinumab in terms of prevention of endoscopic, clinical and surgical recurrence [38]. Among the 7 patients postoperatively treated with vedolizumab in our study, 2 experienced objective recurrence (28.6%). Regarding objective recurrence rate under thiopurines, our results are concordant with literature, notably with the randomized double blinded trial TOPPIC (mercaptopurine vs placebo; 43% of endoscopic recurrence) [39]. The retrospective design of the study exposed us to recall and indication bias. The first bias had been limited by high standardization of medical records in our specialized units. Although preoperative characteristics might have influenced the choice of postoperative treatment, there were no significant differences between the two groups on those characteristics (including all postoperative risks factors according to ECCO guidelines) [12]. Similarly, we analyzed together patients treated with the same or with another TNFα inhibitor postoperatively. Indeed, the only published study did not reported any difference of efficacy between switch anti-TNFα and start over the same molecule [40].

6. Conclusion

Our results showed that anti-TNFα remained an efficient treatment to prevent objective postoperative recurrence even for patients that had experienced anti-TNFα failure. This therapeutic option was also less interrupted during the follow-up and seemed to expose less to clinical recurrence than other treatments. Furthermore, it supports previous findings on the limited efficacy of thiopurines on severe CD. Yet, future prospective head-to-head clinical trials will be needed to firmly conclude on the superiority of anti-TNFα in this more and more frequent situation.

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Authors contributions

GL: performed data collection, research and statistical analysis, interpreted data, drafted the manuscript. RA, PR, BB, LBo, FP, AB, LBu, DL, CG: revised the article for important intellectual content. All authors approved the final version of the manuscript.

Declaration of Competing Interest

GL: no conflict-of-interest.

RA: counseling, boards, transports or fees from Abbvie, Amgen, Biogen, Ferring, Janssen, MSD, Pfizer, Takeda, Tillotts.

PR: consultancy fees from Amgen and Janssen.

BB: no conflict-of-interest.

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AB: no conflict-of-interest.

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CG: consultant/lecture fees from Abbvie, Celltrion, Ferring, Fresenius, Janssen, MSD, Pfizer and Takeda.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.09.004.

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