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Retreatment with anti-tumor necrosis factor therapy in combination with an immunomodulator for recurrence of Crohn's disease after ileocecal resection results in prolonged continuation as compared to anti-tumor necrosis factor monotherapy

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Background A considerable proportion of Crohn's disease patients that undergo ileocecal resection (ICR) have failed anti-tumor necrosis factor (TNF) therapy preoperatively. This study aimed to assess the effectiveness of retreatment of anti-TNF therapy in patients with postoperative recurrence.

Methods A real-world cohort study was performed on Crohn's disease patients who underwent primary ICR after anti-TNF therapy failure, and who were retreated with anti-TNF therapy for postoperative symptomatic Crohn's disease. The primary outcome was treatment failure (the need for (re)introduction of corticosteroids, immunosuppressants, or biologicals or the need for re-resection). Sub-analyses were performed on the nature of preoperative anti-TNF failure (primary non-response, secondary loss of response, intolerance), indication for ICR (refractory, stricturing, penetrating disease), combination therapy with immunomodulators, retreatment with the same anti-TNF agent and preoperative exposure to 1 vs. >1 anti-TNF agents.

Results In total, 66 of 364 patients retreated with anti-TNF therapy following ICR. Cumulative rates of treatment failure at 1 and 2 years were 28% and 47%. Treatment failure rate at 2 years was significantly lower in patients receiving combination therapy as compared to anti-TNF monotherapy (30% vs. 49%, P = 0.02). No difference in treatment failure was found with regards to the nature of preoperative anti-TNF failure (P = 0.76), indication for ICR (P = 0.88) switch of anti-TNF agent (P = 0.55) agent, and preoperative exposure to 1 vs. >1 anti-TNF agents (P = 0.88).

Conclusion Retreatment with anti-TNF therapy for postoperative Crohn's disease recurrence is a valid strategy after preoperative failure. Combination therapy is associated with a lower rate of treatment failure. Eur J Gastroenterol Hepatol 35: 45–51
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Keywords: Crohn's disease, ileocecal resection, retreatment, tumor necrosis factor inhibitors

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Introduction

Although the need for surgery has decreased over time, up to 40% of patients with Crohn's disease will require an intestinal resection during the disease course [1]. Postoperative recurrence is common since up to 25% of patients will develop clinical recurrence and up to 80% will develop endoscopic recurrence within 1 year [2–6].

A majority of Crohn's disease patients have been exposed to anti-tumor necrosis factor (TNF) therapy prior to ileocecal resection (ICR). On the one hand, the previous failure of anti-TNF therapy is associated with failure of a second attempt [7,8], while on the other hand, early Crohn's disease lesions after intestinal resection may comprise a new opportunity for response to anti-TNF therapy. This hypothesis is substantiated by the observation of distinct characteristics of the immune infiltrate in the neo-terminal ileum of Crohn's disease lesions after ICR, as compared to longstanding ileitis [9].

In contrast to abundant data on anti-TNF agents for the prevention of postoperative recurrence of Crohn's disease, data regarding treatment of postoperative recurrence with anti-TNF therapy are scarce. In addition,

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medication use prior to ICR is not taken into account in current international guidelines on management strategies for postoperative Crohn's disease [10,11]. To date, only three real-world studies have assessed the effect of anti-TNF therapy as a treatment for postoperative recurrence. However, these studies comprised mostly anti-TNF naïve patients [12–14]. In addition, only one study has investigated the effect of anti-TNF treatment for postoperative recurrence in pediatric Crohn's disease patients who were refractory to anti-TNF therapy preoperatively [15]. Therefore, the effect of retreatment with anti-TNF therapy after resection of the affected bowel region in previously anti-TNF refractory adult Crohn's disease patients is unknown. This study aimed to assess the effectiveness of retreatment with anti-TNF therapy for postoperative recurrence in Crohn's disease patients who failed anti-TNF preoperatively.

Methods

Study design and patients

A retrospective, multicenter study was conducted on Crohn's disease patients who underwent primary ICR for the indication of Crohn's disease between January 2000 and January 2020. Eligible patients were identified from local hospital pathology databases of the participating centers, including four teaching and 6 academic hospitals. Patients aged 16 years and older, who were exposed to anti-TNF therapy preoperatively, were considered eligible. Patients who were retreated with anti-TNF therapy (infliximab or adalimumab) as the first treatment choice for postoperative clinical recurrence were included. Postoperative clinical recurrence was defined as symptomatic Crohn's disease after ICR necessitating initiation of medical treatment. In case corticosteroids or 5-aminosalicylates were the first treatment choice for postoperative clinical recurrence followed by anti-TNF therapy (within 3 months in case of corticosteroid use), patients were also included. Exclusion criteria included primary postoperative prophylaxis with an anti-TNF agent.

Outcome and definitions

The primary endpoint was treatment failure, defined as the (re)introduction of treatment (including 5-aminosalicylates, corticosteroid, immunosuppressants or other biologics) for symptomatic disease or the need for re-resection at 1 and 2 years following ICR. These patients were considered to have an inadequate response to the second exposure to anti-TNF therapy. Sub-analyses were performed on the nature of preoperative anti-TNF failure, indication for ICR, combination therapy with immunomodulators vs. anti-TNF monotherapy, retreatment with the same or a different anti-TNF agent postoperatively and preoperative exposure to 1 vs. >1 anti-TNF agents. Preoperative anti-TNF therapy failure types were defined as primary non-response (absent or insufficient improvement of clinical, biochemical or endoscopic inflammation after anti-TNF therapy), secondary loss of response (primary response to initial therapy which was not maintained) or intolerance (discontinuation of anti-TNF therapy due to side effects). Indications for ICR included refractory disease (non-stricturing and non-penetrating disease), stricturing disease or penetrating disease. Additionally, the association of the interval between anti-TNF initiation and treatment failure within 1 or 2 years was assessed.

Data collection

Electronic patient records were retrospectively reviewed. Data were collected until re-resection, loss to follow-up or death. Baseline characteristics (including age, sex and smoking history), disease characteristics (including Montreal classification [16], disease duration, medical treatment history, concomitant treatment), biochemical markers (anti-TNF antibodies and trough levels within 12 months prior to ICR), the time between ICR and retreatment of anti-TNF and postoperative endoscopic and radiologic data were obtained. If an endoscopy was performed within 16 weeks before the start of retreatment or treatment failure, endoscopic findings were included. Endoscopic disease activity was defined as Rutgeerts classification ≥i2a [5] and radiological disease activity was defined as active inflammation on abdominal ultrasound, computed tomography or MRI as assessed by a local radiologist. In case of anti-TNF re-treatment failure, pharmacologic data (anti-TNF antibodies and trough levels) were collected.

Statistical analysis

Continuous variables were reported as the median and interquartile range (IQR). Categorical variables were reported as frequencies and percentages. The time to event was defined as the time between anti-TNF initiation and treatment failure. Regarding patients who did not have treatment failure, the observation was censored at the time of maximal follow-up, loss to follow-up or death. A Pearson's r test was performed to assess whether there was a point-biserial correlation between time to start anti-TNF treatment and treatment failure within 1 and 2 years. The observed cumulative incidence of treatment failure following ICR was calculated using the Kaplan–Meier Method. Sub-analyses on the nature of preoperative anti-TNF failure, combination therapy with immunomodulators vs. anti-TNF monotherapy, and retreatment with the same anti-TNF agent postoperatively were compared using the Log Rank test. All data analyses were performed using IBM SPSS Statistics for Windows, version 25.0.

Ethics approval

This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its protocol was assessed and approved by the Medical Ethical Research Committee of the Erasmus University Medical Centre on 10 November 2017.

Results

Baseline characteristics

A total of 364 patients who underwent an ICR and received anti-TNF therapy prior to surgery were identified. Of these patients, 159/364 (44%) patients experienced

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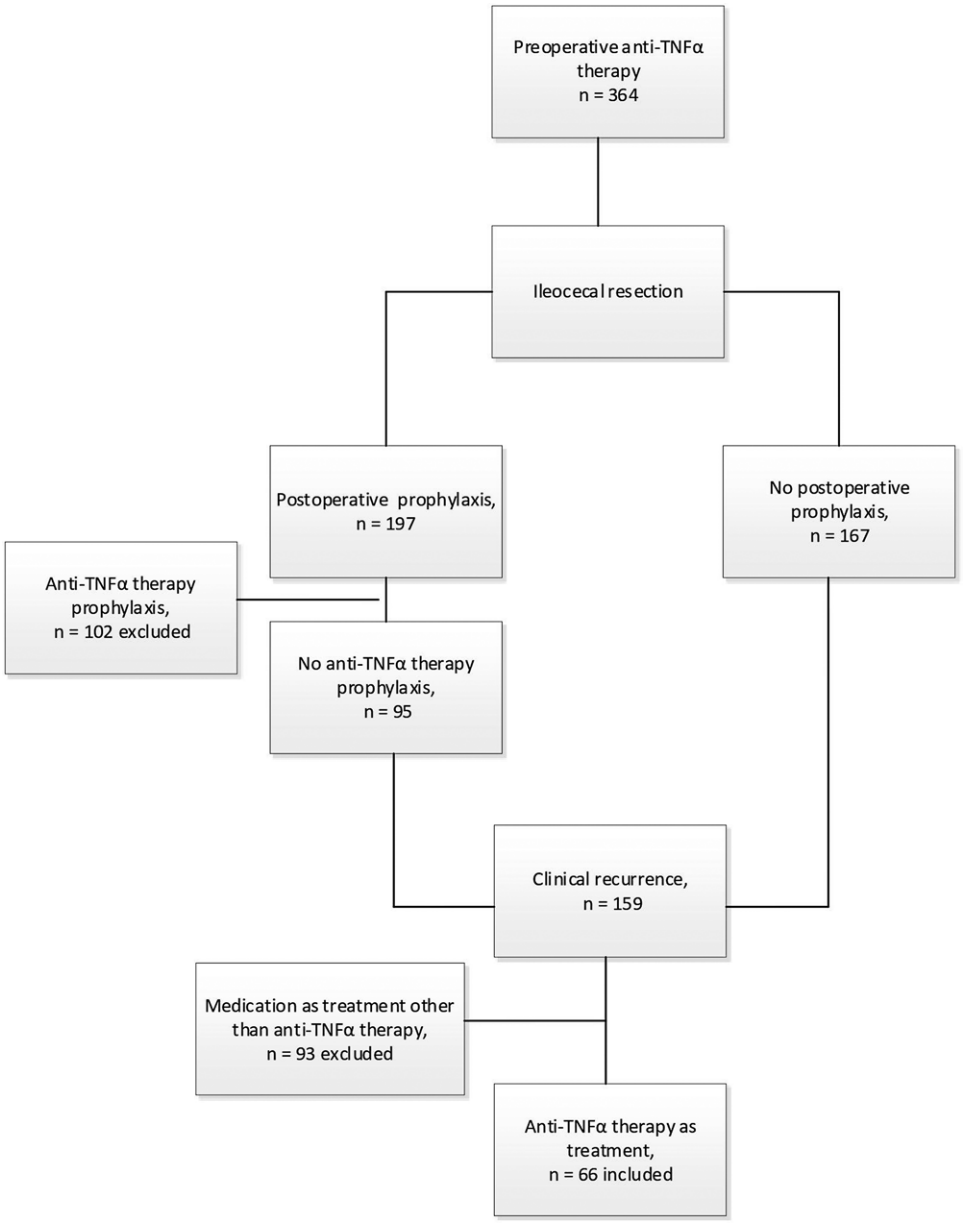

Fig. 1. Flowcharts study population.

postoperative clinical recurrence, of whom 66/159 (42%) patients received reintroduction of anti-TNF as treatment and were included in the study population (Fig. 1).

The majority of the included patients were female (62%) with a median age of 35 years (IQR 26–50) (Table 1). Median disease duration until ICR was 4.7 years (IQR 1.8–9.3). Indication for ICR was refractory disease (non-stricturing and non-penetrating disease) in 26/66 (39%) patients, stricturing disease in 28/66 (42%) patients or penetrating disease in 12/66 (18%) patients. Median total postoperative follow-up was 6.3 years (IQR 4.3–8.3). In total, 47/66 (71%) patients were exposed to one anti-TNF agent (47% infliximab, 24% adalimumab) and 19/66 (29%) patients were exposed to both anti-TNF agents alternately prior to ICR. After ICR, 22/66 (33%) patients received prophylactic immunomodulatory therapy [3/22 (14%) methotrexate, 19/22 (86%) thiopurines] postoperatively.

Preoperative anti-tumor necrosis factor failure

Regarding anti-TNF failure prior to ICR, secondary loss of response was the reason in the majority of patients ($n = 45/66$, 68%), whereas 12/66 (18%) had primary non-response and 7/66 (11%) discontinued anti-TNF treatment due to intolerance to anti-TNF therapy (Table 1). At the time of cessation of anti-TNF therapy preoperatively, the median serum level of adalimumab was 4.2 µg/mL (IQR 2.98–6.63, $n = 6$) and for infliximab 4.4 µg/mL (IQR 2.43–9.20, $n = 6$). Antibodies to anti-TNF therapy were reported in only a few patients at the time of discontinuation prior to ICR for adalimumab (12×10^{-9} g/L, IQR 12–4303, $n = 4$) and infliximab (12×10^{-9} g/L, IQR 12–12, $n = 3$).

Postoperative recurrence

Regarding postoperative clinical recurrence, 31/66 (47%) patients were treated with infliximab and 35/66 (53%)

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Table 1. Baseline characteristics

Patients characteristics		*n* = 66
Age, yearsa	Median (IQR)	34 (24–48)
Sex, female	*N* (%)	41 (62)
Smoker, yesb	*N* (%)	27 (41)
Age at diagnosis		
≤16 years	*N* (%)	13 (20)
17–40 years	*N* (%)	37 (56)
>40 years	*N* (%)	16 (24)
Disease location at ICR		
Ileum (L1)	*N* (%)	42 (64)
Colon (L2)	*N* (%)	0 (0)
Ileocolonic (L3)	*N* (%)	24 (36)
Disease, behavior at ICR		
Non-stricturing, non-penetrating (B1)	*N* (%)	22 (33)
Stricturing (B2)	*N* (%)	27 (41)
Penetrating (B3)	*N* (%)	17 (26)
Perianal disease (p)	*N* (%)	8 (12)
Preoperative anti-TNF therapy		
Infliximab	*N* (%)	31 (47)
Adalimumab	*N* (%)	16 (24)
Both	*N* (%)	19 (29)
Preoperatively ustekinumab	*N* (%)	–
Preoperatively vedolizumab	*N* (%)	1 (2)
Reason anti-TNF therapy was withdrawn		
Primary non-response	*N* (%)	12 (18)
Secondary loss of response	*N* (%)	45 (68)
Intolerance	*N* (%)	7 (11)
Missing	*N* (%)	2 (3)

ICR, ileocecal resection; TNF, tumor necrosis factor.
[a]At the time of retreatment.
[b]At the time of ICR.

were treated with adalimumab. Thirty-seven out of 66 (56%) patients received the same anti-TNF agent preoperatively and postoperatively, and 29/66 (44%) were treated with a different agent. Of these patients, 7/66 (11%) received prednisone primarily, followed by anti-TNF therapy. Median time between ICR and treatment with anti-TNF therapy following postoperative clinical recurrence was 9.4 months (IQR 6.5–18.4). In total, 44/66 (67%) patients started anti-TNF as monotherapy whereas 22/66 (33%) received concomitant immunomodulators. Regarding concomitant immunomodulators, 18/22 patients continued postoperative prophylactic immunomodulatory therapy at time of reintroduction of anti-TNF therapy and 4/22 patients started a concomitant immunomodulator in combination with anti-TNF therapy.

Endoscopic evaluation was performed in 32/66 (49%) of the patients at the time of postoperative clinical recurrence, of whom 25/32 patient (78%) had a Rutgeerts score ≥i2a [i2 = 13 (40%), i3 = 9 (27%), i4 = 3 (9%) i0 = 5 (16%), i1 = 2 (6%)].

Postoperative treatment failure

During total follow-up, treatment failure after retreatment with anti-TNF therapy was observed in 44/66 (67%) of whom 3/44 (7%) underwent a re-resection. Median time to treatment failure was 1.2 years (IQR 0.6–4.2). Kaplan–Meier estimates of the treatment failure rates were 28% and 44% after 1 and 2 years, respectively (Fig. 2). One (2%) and two (5%) patients underwent a re-resection within 1 and 2 years, respectively. Endoscopy data after anti-TNF re-introduction were available for 19/44 patients (43%) at the time of treatment failure of whom 15 patients (79%) had endoscopic disease activity (Rutgeerts score ≥ 2a). No correlation was observed between the time of the start of anti-TNF treatment for postoperative clinical recurrence and treatment failure ($P = 0.790$).

At the time of treatment failure, the median serum level of adalimumab was 6.0 µg/mL (range 0.03–12, $n = 2$) and infliximab was 3.0 µg/mL (IQR 0.30–12, $n = 11$). Antibodies to anti-TNF therapy were detected at the time of discontinuation in three patients treated with adalimumab (35×10^{-9} g/L, IQR 35–150) and in seven patients treated with infliximab (12×10^{-9} g/L, IQR 12–280) of whom seven (70%) and three (30%) patients received mono- and combination therapy, respectively.

Regarding patients with primary non-response, secondary loss of response and intolerance to anti-TNF therapy, the cumulative rate of treatment failure at 1 year was 25%, 23% and 57% (Log-Rank, $P = 0.102$), in patients with primary non-response, secondary loss of response and intolerance to anti-TNF therapy, respectively. After 2 years, the cumulative rate of treatment failure was 25%, 45% and 71% (Log-Rank, $P = 0.760$).

In patients with refractory, stricturing or penetrating disease as an indication for ICR, the 1-year cumulative rate of treatment failure was 31%, 26% and 17% (Log-Rank, $P = 0.996$), respectively. After 2 years, the cumulative rates of treatment failure were 50%, 41% and 28% (Log-Rank, $P = 0.880$), respectively.

With regard to combination therapy with immunomodulators, the cumulative rates of treatment failure after 1 year were 9% and 32% in patients receiving combination therapy with an immunomodulator as compared to patients who were exposed to anti-TNF monotherapy (Log-Rank, $P = 0.004$). After 2 years, the cumulative rate of treatment failure was 30% and 49% ($P = 0.016$, Fig. 3). Time to treatment failure was 2.1 years (IQR 1.2–4.0) in patients receiving combination therapy as compared to 1.1 years (IQR 0.4–3.1) in patients exposed to anti-TNF monotherapy.

Regarding retreatment with the same anti-TNF agent postoperatively, the cumulative rates of treatment failure at 1 year were 30% in patients who retreated with the same agent as compared with 21% in patients who were switched to another agent postoperatively (Log-Rank, $P = 0.349$). After 2 years, the cumulative rates of treatment failure were 36% and 51% (Log-Rank, $P = 0.548$).

Regarding preoperative exposure to 1 vs. >1 anti-TNF agents, the cumulative rates of treatment failure at 1 year was 26% in patients exposed to only one anti-TNF agent preoperatively as compared with 33% in patients who were switched to another agent preoperatively (Log-Rank, $P = 0.797$). After 2 years, the cumulative rates of treatment failure were 42% and 63% (Log-Rank, $P = 0.884$).

Discussion

Recurrence of symptomatic Crohn's disease after a primary ICR occurs in over 40% of patients who have been exposed to anti-TNF therapy preoperatively. Especially in the case of a therapy refractory disease course preoperatively, an important clinical question in postoperative Crohn's disease management is whether treatment, rather than prevention, of postoperative recurrence can be effectively managed with a second exposure to anti-TNF therapy. This real-world cohort study showed that retreatment with anti-TNF therapy for postoperative

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Crohn's disease recurrence after primary ICR is continued in more than half of patients after 2 years. Anti-TNF therapy in combination with an immunomodulator results in the continuation of therapy in a significantly higher proportion of patients, that is, approximately two-thirds of the patients. Therefore, retreatment with anti-TNF therapy especially in combination with an immunomodulator may be an effective strategy for postoperative clinical recurrence of Crohn's disease in patients treated with an anti-TNF agent postoperatively.

In the currently available literature, three studies, including an Italian study ($n = 13$), a Japanese study ($n = 8$) and a Spanish study ($n = 179$) investigated the impact of diagnosis and treatment with anti-TNF therapy on postoperative endoscopic recurrence after surgery and have shown beneficial effect of anti-TNF therapy for postoperative recurrence varied from 61% to 75% depending on the timing of endoscopic evaluation. Importantly, all studies reported a low overall percentage of patients who failed anti-TNF preoperative, respectively 3/13 (23%), 2/8 (25%) and 53/179 (30%) [12–14]. Only one previous study, with a pediatric cohort of patients who failed anti-TNF preoperatively despite adequate serum trough levels (pharmacodynamics failure), investigated the effectiveness

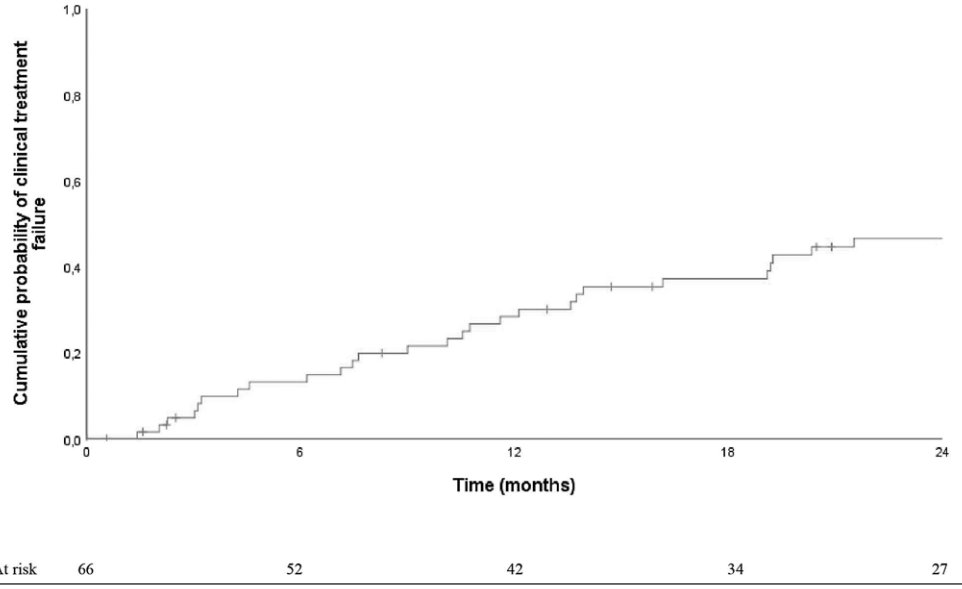

Fig. 2. Kaplan–Meier analysis of treatment failure in Crohn's disease patients in whom anti-TNF was restarted due to clinical recurrence. TNF, tumor necrosis factor.

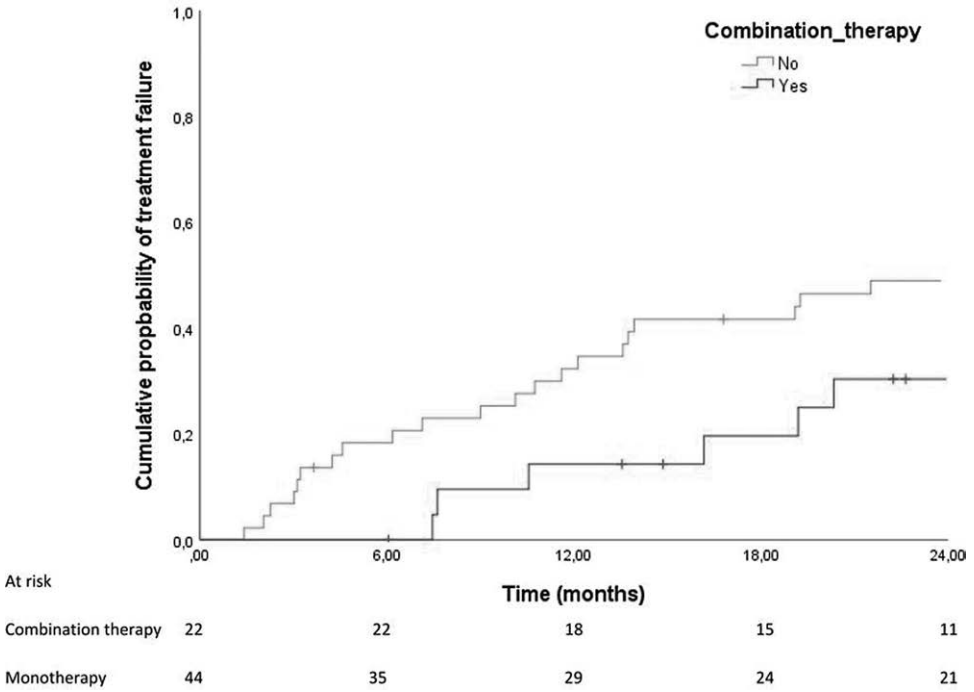

Fig. 3. Kaplan–Meier analysis of treatment failure in Crohn's disease patients who were retreated with anti-TNF therapy after diagnosis of postoperative clinical recurrence for the subgroups combination therapy with immunomodulators vs monotherapy. TNF, tumor necrosis factor.

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of retreatment with anti-TNF after ICR. Children treated with adalimumab prior to surgery and retreated with this anti-TNF agent had a similar rate of clinical remission after 12 months compared with those who had not received anti-TNF therapy prior to surgery [15]. This suggests that pediatric Crohn's disease patients who failed anti-TNF therapy and underwent ICR can retreat with the same agent for postoperative recurrence with a high success rate similar to that of anti-TNF naïve patients [15]. Our study confirms the beneficial effect of retreatment with anti-TNF therapy in adults for postoperative clinical recurrence of Crohn's disease. Unfortunately, the retrospective study design did not allow for the differentiation of pharmacokinetic, immunogenic or pharmacodynamic failure of anti-TNF therapy. Future studies are required to assess the predictive value of preoperative anti-TNF trough levels for the postoperative success of retreatment.

A possible explanation for the high success rate of retreatment could be the distinct mucosal profiles of cytokines that are produced during different stages of Crohn's disease. Macroscopically unaffected neo-terminal ileum contains elevated levels of TNF. However, these TNF levels are not increased in mucosal biopsies of the terminal ileum of Crohn's disease patients with pre-operative longstanding ileitis (taken from the resection specimens) despite histopathologically confirmed inflammation [9]. This difference in anti-TNF production might reflect a functional change in immunological pathways activated during the stage of disease, especially in patients undergoing ICR. This change in cytokine expression could support the choice of anti-TNF therapy as a treatment strategy for postoperative recurrence.

Subgroup analysis showed that treatment was more effective in patients receiving anti-TNF in combination with an immunomodulator compared to patients receiving anti-TNF monotherapy. This observation is in line with previous data which suggest that immunomodulators may need to be started or continued in Crohn's disease patients upon initiation of anti-TNF therapy, based on the presumption that immunosuppressive therapy is expected to substantially improve efficacy, increase serum drug concentrations, and reduce immunogenicity [17–20].

To the best of our knowledge, this is the first study that reports the effectiveness of retreatment with anti-TNF therapy in adult Crohn's disease patients who preoperatively failed anti-TNF therapy. A strength of the current study is the long follow-up period. Secondly, in this study all patients were treated in both academic and teaching centers, which increases its generalizability to a wider Crohn's disease population. However, some limitations need to be taken into consideration. First, no standard endoscopic evaluation was performed at the start of anti-TNF. Therefore, endoscopic recurrence was not taken into account and no correlation between anti-TNF treatment failure and endoscopic lesions could be established. Secondly, the retrospective character of the study resulted in the absence of a preoperative anti-TNF naïve control group. In addition, the small sample size did not allow for to identification of predictors of treatment failure. Another limitation is the lack of data regarding adverse events and tolerability of the treatment, including prolonged combination of anti-TNF and immunosuppressants. Although anti-TNF levels were collected, trough levels were not routinely assessed in our cohort. Therefore, we could not exemplify the exact reason for treatment failure and no conclusion can be drawn. Even with these limitations, this multicenter study sheds additional light on the role of retreatment with anti-TNF therapy for postoperative recurrence in Crohn's disease patients.

In conclusion, retreatment with anti-TNF therapy for postoperative recurrence is a valid treatment option, because half of Crohn's disease patients remain in remission 2 years after retreatment. Combination therapy with an immunomodulator is associated with lower treatment failure rates.

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S.B., E.B., and Ad.V. involved in conception and design. S.B., E.B., T.B., F.H., A.B., G.D., M.R., Nd.B., L.S., Avd.M., R.W., Ov.R., Cvd.W., and Ad.V. contributed to acquisition and interpretation of data. S.B., T.B., and Ad.V. participated in the analysis of data. All authors have participated in drafting or critically revising the manuscript and gave their final approval of the current version.

Conflicts of interest

F.H. has served on advisory boards or as speaker for Abbvie, Janssen-Cilag, MSD, Takeda, Celltrion, Teva, Sandoz and Dr Falk. Funding (Grants/Honoraria): Dr Falk, Janssen-Cilag, Abbvie, Takeda.Consulting Fees: Celgene. A.B. has served on the advisory board of Takeda, Abbvie and Janssen, outside the submitted work. G.D. reports grant support from DSM nutritional products LTD and speakers fees from Janssen Pharmaceuticals, Abbvie and Takeda, outside the submitted work. Nd.B. has served as a speaker for AbbVie and MSD and has served as consultant and principal investigator for TEVA Pharma BV and Takeda. He has received an (unrestricted) research grant from Dr. Falk, TEVA Pharma BV, MLDS and Takeda, outside the submitted work. L.S. has served as a speaker and received research support from Takeda, outside the submitted work. Avd.M. reports presentation fee from Janssen and has served on the advisory board of Takeda and Galapagos, outside the submitted work. R.W. has served on the advisory board and as invited speaker for Janssen, Pfizer and Takeda, outside the submitted work. Cvd.W. received grant support from Falk Benelux and Pfizer; received speaker fees from AbbVie, Takeda, Ferring, Dr. Falk Pharma, Hospira, Pfizer; and served as a consultant for AbbVie, MSD, Takeda, Celgene, Mundipharma and Janssen. ad.V.: Advisory board Janssen, Takeda and Abbvie. For the remaining authors, there are no conflicts of interest.

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