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Thiopurines Are Associated with a Reduction in Surgical Re-resections in Patients with Crohn's Disease: A Long-term Follow-up Study in a Regional and Academic Cohort

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Background: Combination therapy of thiopurines and anti–tumor necrosis factor alpha (TNF-α) antibodies is the most effective medical treatment of Crohn's disease (CD). Data on thiopurines and anti-TNF-α antibodies in preventing surgical recurrence (need for re-resection) of CD are scarce. Therefore, we analyzed which factors were involved in surgical recurrence of CD in a large cohort of patients with CD operated in a regional and a university hospital.

Methods: This is a retrospective cohort study of 567 patients who underwent surgery for CD. Clinical data and risk factors for surgical recurrence were analyzed, focusing on medical therapy and hospital type.

Results: Overall, 237 (41.8%) patients developed a surgical recurrence, after a median of 70 (2–482) months. Before surgical recurrence, 235 patients (41.4%) and 116 patients (20.5%) used thiopurines and anti-TNF-α antibodies, respectively. Multivariate analysis identified 3 independent risk factors associated with surgical recurrence of CD. A higher risk was seen in patients with colonic disease compared with patients with ileal disease (hazard ratio, 1.56; 95% confidence interval, 1.10–2.21; $P = 0.012$) and in patients using multiple types of medication (hazard ratio, 1.38; 95% confidence interval, 1.25–1.54; $P < 0.001$). However, a lower risk was seen in patients using thiopurines (hazard ratio, 0.51; 95% confidence interval, 0.34–0.77; $P = 0.001$).

Conclusions: Thiopurines are effective in preventing surgical recurrence of CD. The role of anti-TNF-α antibodies seems promising as well. Combination therapy of thiopurines and anti-TNF-α antibodies for prevention of surgical recurrence of CD should be studied in a randomized trial.

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Key Words: Crohn's disease, surgical recurrence, prevention, thiopurines, anti-TNF-α

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal tract. Most commonly, it involves the terminal ileum and proximal colon. The clinical course of CD is characterized by alternating periods of exacerbation and remission. During the past few years, knowledge of the pathogenesis of CD has increased, but it is still not fully understood. Genetic, environmental, and microbial factors play a role in the regulation of intestinal immunity, with its deviations due to CD leading to mucosal ulceration and complications such as strictures and fistula.[1–4]

The medical management of CD is changed in the last decades and is rapidly evolving from classical therapy with 5-aminosalicylates and corticosteroids to the use of immune modulators such as thiopurines and methotrexate.[5] Unfortunately, these drugs have considerable side effects and only a moderate effect on mucosal healing. Therefore, there is definitely a need for new agents that are more effective and safer.[3,6] These modern agents can be functionally classified as tumor necrosis factor alpha (TNF-α) blockers, other cytokines modulators, T-cell blockers, and blockers of inflammatory cell migration and adhesion.[6,7] Monoclonal antibodies directed against the proinflammatory cytokine TNF-α (anti-TNF-α), such as infliximab and adalimumab, are safe and efficacious in the treatment of CD.[8,9]

Infliximab and adalimumab were registered for CD in the Netherlands in 2000 and 2003, respectively. Anti-TNF-α antibodies, particularly when used in combination with thiopurines, can achieve mucosal healing and hold promise to reduce the need for surgery and recurrence after previous surgery.[10,11] However, the influence of anti-TNF-α antibodies and immune modulators on the need for surgery for CD in regional practice has been poorly evaluated.[7,12] The aim of this study was to analyze which risk

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factors play a role in surgical recurrence and re-resection for CD in a large regional hospital and a university hospital cohort of patients with CD.

MATERIALS AND METHODS

Patients and Methods

We hypothesized that more patients with aggressive or therapy-resistant disease course are referred to a university hospital. To avoid selection bias, we performed a retrospective cross-sectional cohort study in 567 patients who underwent surgery for CD in a large regional hospital (Medical Center Leeuwarden, Leeuwarden, the Netherlands) or in the regional university hospital (University Medical Center, Groningen, the Netherlands). All patients were identified from the medical records with the *ICD-9* codes 555.1 (regional enteritis of colon, large bowel, rectum), 555.2 (regional ileocolitis), 555.9 (regional enteritis, not otherwise specified), and 556.0 (idiopathic proctocolitis and ulcerative enterocolitis). All patients who underwent at least 1 intestinal resection because of CD before January 2010 (from January 1951 through September 2009) were included. Patients without an intestinal resection and those in whom the surgical intervention was limited to intestinal bypass surgery, abscess drainages, or surgery for fistulae were excluded. The date of last follow-up was December 31, 2010.

All medical charts were reviewed for demographic data; date of diagnosis; Montreal classification[13] (age of diagnosis, location of disease, and disease behavior); family history of IBD; extraintestinal manifestations (arthritis, eye involvement, skin disorders, and primary sclerosing cholangitis); use of oral contraceptives; smoking history (nonsmoker, quit smoking before diagnosis, quit smoking after diagnosis, or current smoker); medication use; date, indication and type of first and, if applicable, second surgical resection, including as if it was an open or laparoscopic procedure; and the total number of resections. Not included were long-term metabolic or endocrine effects of CD such as vitamin B12 deficiency, secondary amyloidosis, renal stones, and osteoporosis. For the use of medication, we recorded the use of 5-aminosalicylates, corticosteroids, cyclosporine, methotrexate, thiopurines (azathioprine and 6-mercaptopurine), or anti-TNF-α antibodies (infliximab and adalimumab), both before and after the resection.

The objective of this study was to evaluate the impact of the introduction of thiopurines and anti-TNF-α antibodies on the prevention of surgical recurrence of CD. Because this is a retrospective study, there was no strict protocol for starting postoperative medical treatment. According to the Dutch guidelines, postoperative medication was not started immediately after surgery but only after clinical or endoscopic recurrence. In such cases, treatment was started according to a step-up approach. Initially, thiopurines were started and only in case of disease progression or intolerance for thiopurines, anti-TNF-α antibodies were added. The primary outcome of this study was surgical recurrence, which was defined as a second intestinal resection for CD at any time during follow-up. Surgery for complications directly related to the first intestinal resection, leading to a second resection, was not considered as surgical recurrence. Secondary outcomes were time to surgical recurrence and the total number of surgical interventions. To identify any differences between the 2 cohorts, the regional hospital cohort was compared with the cohort from the university hospital.

To investigate the influence of anti-TNF-α antibodies on surgical recurrence, patients were divided into 2 subgroups: (1) patients who used anti-TNF-α antibodies before their first or second resection (anti-TNF-α cohort) and (2) patients who did not use anti-TNF-α antibodies or only after their second resection (non–anti-TNF-α cohort).

Statistical Analysis

All statistical analyses were performed by PASW statistics 18 Statistical Package for the Social Sciences (SPSS, Chicago, IL). Statistical difference was defined as $P \leq 0.05$.

Univariate analyses of frequencies, medians, and means were performed to describe the study population. To identify statistical differences between the 2 groups in demographic and preoperative characteristics, χ^2 or Fisher's exact test was used for categorical variables and a Student's t test or Mann–Whitney U test for continuous variables.

To identify variables associated with surgical recurrence, a Cox regression analysis was performed. Proportional hazards with 95% confidence intervals (CI) were calculated. All variables with univariate $P < 0.2$ and predefined variables with clinical importance (smoking history, the use of thiopurines and anti-TNF-α, and total number of medication types) were considered for the multivariate model. The multivariate model was determined using Cox proportional hazard regression analysis with stepwise backward elimination to identify predictors for surgical recurrence. Survival curves were used to illustrate the surgical recurrence rate during 20 years follow-up.

RESULTS

Study Population

In total, 567 patients (regional hospital = 140, university hospital = 427) with CD underwent at least 1 intestinal resection during the study period, with a median follow-up of 11 years after the first intestinal resection. Patient characteristics are listed in Table 1. Overall, the majority of patients were women (59%), both in the regional hospital and university cohort (64% and 58%, respectively). The median age at diagnosis was 26 (20–38) years. In the university cohort, patients were significantly younger at the time of diagnosis than in the regional hospital, with a mean age of 29 versus 35 years, respectively ($P < 0.001$).

More than 80% of the patients had ileal (L1) or ileocecal (L3) disease. In both cohorts, the majority (55%) of patients suffered from stricturing disease. In the regional hospital cohort,

TABLE 1. Baseline Characteristics of Patients with Focus on Hospital and Anti-TNF-α Use

	All Patients (n = 567)	Academic Cohort (n = 427)	Regional Cohort (n = 140)	*P*	Anti-TNF-α Cohort (n = 116)	Non–Anti-TNF-α Cohort (n = 451)	*P*
Female, n (%)	337 (59.4)	247 (57.8)	90 (64.3)	NS	74 (63.8)	263 (58.3)	NS
Age at diagnosis, n (%), yr							
A1, <16	75 (13.2)	67 (15.7)	8 (5.7)	0.001	24 (20.7)	51 (11.3)	0.001
A2, 17–40	372 (65.6)	282 (66)	90 (64.3)		79 (68.1)	293 (65.0)	
A3, >40	120 (21.2)	78 (18.3)	42 (30)		13 (11.2)	107 (23.7)	
Location CD, n (%)							
L1, ileal	240 (42.3)	164 (38.4)	76 (54.3)	<0.001	40 (35.4)	200 (45.5)	NS
L2, colonic	88 (15.5)	60 (14.1)	28 (20)		22 (19.5)	66 (15.0)	
L3, ileocolonic	219 (38.6)	183 (42.9)	36 (25.7)		49 (43.4)	170 (38.6)	
L4, isolated upper disease	6 (1.1)	6 (1.4)	0		2 (1.8)	4 (0.9)	
Missing	14 (2.5)	14 (3.3)	0		3 (2.6)	11 (2.4)	
Disease behavior, n (%)							
B1, inflammatory	88 (15.5)	55 (12.9)	33 (23.6)	0.009	24 (20.7)	64 (14.2)	0.027
B2, stricturing	312 (55)	229 (53.6)	83 (59.3)		55 (47.4)	257 (57)	
B3, penetrating	119 (21)	97 (22.7)	22 (15.7)		33 (28.4)	86 (19.1)	
Missing	48 (8.5)	46 (10.8)	2 (1.4)		4 (3.4)	44 (9.8)	
Smoking history, n (%)							
Current	170 (30)	123 (28.7)	47 (33.6)	0.001	36 (31.0)	134 (29.7)	0.046
Quit after diagnosis	126 (22.2)	109 (25.7)	17 (12.1)		23 (19.8)	103 (22.8)	
Quit before diagnosis	35 (6.2)	20 (4.7)	15 (10.7)		3 (2.6)	32 (7.1)	
Never	170 (30)	126 (29.4)	44 (31.4)		47 (40.5)	123 (27.3)	
Missing	66 (11.6)	49 (11.4)	17 (12.1)		7 (6.0)	59 (13.1)	
Disease duration in years from diagnosis until first resection, mean (SD)	3.45 (5.75)	3.36 (5.65)	3.74 (6.03)	NS	4.12 (5.80)	3.28 (5.73)	NS
Surgical approach of first resection, n (%)							
Open	439 (77.4)	363 (85)	6 (54.3)	<0.001	79 (68.1)	360 (79.8)	<0.001
Laparoscopic	88 (15.5)	36 (8)	52 (37.1)		31 (26.7)	57 (12.6)	
Missing	40 (7.1)	28 (6)	12 (8.6)		6 (5.2)	34 (7.5)	
No. of medications, mean (range)	3.05 (0–12)	3.16 (0–12)	2.73 (0–8)	0.007	4.53 (2–12)	2.66 (0–8)	<0.001
Use of medications, n (%)							
5-aminosalicylates	434 (79.9)	335 (82.7)	99 (71.7)	0.007	89 (78.8)	345 (80.2)	NS
Corticosteroids	444 (81.5)	335 (82.5)	109 (78.4)	NS	107 (93.9)	337 (78.2)	<0.001
Cyclosporine	10 (1.8)	8 (2.0)	2 (1.4)	NS	3 (2.6)	7 (1.6)	NS
Methotrexate	54 (9.8)	49 (11.9)	5 (3.6)	0.003	23 (19.8)	31 (7.1)	<0.001
Anti-TNF-α, n (%)							
Before first or second resection	116 (20.5)	102 (23.9)	14 (10.0)	<0.001	N/A	N/A	N/A
Never or after second resection	451 (79.5)	325 (76.1)	126 (90.0)				
Thiopurines, n (%)							
Before first or second resection	235 (41.4)	188 (44.0)	47 (33.6)	0.008	105 (90.5)	130 (28.8)	<0.001
Never or after second resection	316 (55.7)	223 (52.2)	93 (66.4)		11 (9.5)	305 (67.6)	
Missing	16 (2.8)	16 (3.7)	0		0	16 (3.6)	

N/A, not applicable; NS, not significant.

significantly more patients had the relatively benign inflammatory behavior type (B1) disease than in the university hospital cohort (24% versus 13%; $P = 0.009$). The mean duration of disease from diagnosis until first resection was 3.5 years. There was no difference in disease duration between both hospital cohorts. In 77% of the patients, the first resection was an open procedure. This was more often the case in the university hospital cohort (85% versus 54%; $P < 0.001$). In both cohorts, the first resection in the majority (60%) of patients was an ileocecal resection.

A minority (30%) of the patients never smoked. In the university cohort, significantly more patients ceased smoking after their diagnosis of CD than patients in the regional hospital cohort (26% versus 12%; $P = 0.001$).

The majority of patients (77%) did not have a first- or second-degree relative with IBD. Nearly one-third of all patients (32%) suffered from extraintestinal disease.

In the university cohort, significantly more different medication types were used compared with the regional hospital cohort (3.2 versus 2.7; $P = 0.007$). In the university hospital cohort, significantly more patients used anti-TNF-α antibodies (24% versus 10%; $P < 0.001$) or thiopurines (44% versus 34%; $P = 0.008$) before their first or second resection than in the regional hospital cohort. Overall, 116 patients (20.5%) used anti-TNF-α antibodies. Of those patients, 45 (38.8%) used anti-TNF-α antibodies before the first resection.

Patients in the anti-TNF-α cohort were significantly younger at diagnosis than patients in the non–anti-TNF-α cohort (mean age, 26 versus 32 yr; $P < 0.001$) and suffered more often from penetrating disease behavior (28% versus 19%, respectively; $P = 0.027$). Patients in the anti-TNF-α cohort used significantly more different medication types compared with the non–anti-TNF-α cohort (4.5 versus 2.7; $P < 0.001$), and they used significantly more often thiopurines (91% versus 29%; $P < 0.001$). In the anti-TNF-α cohort, significantly more patients never smoked compared with the non–anti-TNF-α cohort (41% versus 27%; $P = 0.046$). There was no statistical significant difference between the anti-TNF-α and non–anti-TNF-α cohort in disease location, family history, extraintestinal manifestations, or surgical approach of the first resection.

Surgical Recurrence

A total of 237 (41.8%) patients developed a surgical recurrence after a median of 70 (range, 2–482) months. In the university cohort, more patients developed a surgical recurrence than in the regional hospital cohort (188 patients [44%] versus 49 patients [35.0%]; $P = 0.037$). There was no significant difference between both the hospital cohorts or the anti-TNF-α cohorts in the time interval between the first and second resection.

Overall, the mean number of surgical resections was 1.76 (SD, 1.18), with no significant difference between both cohorts. In the anti-TNF-α cohort, patients had significantly fewer surgical resections than in the non–anti-TNF-α cohort, with a mean of 1.32 versus 1.88, respectively ($P < 0.001$).

We then performed a univariate analysis to identify predictors of surgical recurrence (Table 2). The following 3 variables

TABLE 2. Univariate Analysis of Predictors of Surgical Recurrence of CD

	HR (95% CI)	*P*
Hospital		
Regional	1.10 (0.80–1.52)	0.567
Academic	1.00	
Gender		
Male	1.11 (0.85–1.45)	0.429
Female	1.00	
Age at diagnosis	1.00 (0.99–1.01)	0.827
Age at first resection	1.00 (0.99–1.01)	0.448
Time between diagnosis and first resection	0.99 (0.96–1.01)	0.205
Smoking history		
Never	1.00	
Current	1.39 (0.98–1.97)	0.066
Quit after diagnosis	1.33 (0.92–1.90)	0.127
Quit before diagnosis	1.49 (0.80–2.79)	0.208
OAC in women		
Yes	0.71 (0.47–1.08)	0.105
No	1.00	
Family history		
No IBD	1.00	
First degree versus no IBD	0.88 (0.54–1.42)	0.590
Second degree versus no IBD	1.01 (0.54–1.88)	0.979
CD location		
L1, ileal	1.00	
L2, colonic	1.68 (1.09–2.59)	0.019
L3, ileocolonic	1.55 (1.15–2.08)	0.004
Disease behavior		
B2, stricturing	1.00	
B1, inflammatory	0.69 (0.44–1.10)	0.116
B3, penetrating	1.27 (0.93–1.73)	0.137
Extraintestinal manifestations		
Yes	0.83 (0.73–1.28)	0.826
No	1.00	
No. of medications	1.21 (1.12–1.31)	<0.001
Surgical approach of first resection		
Open	1.46 (0.86–2.49)	0.159
Laparoscopic	1.00	
Anti-TNF-α		
Before first or second resection	0.83 (0.58–1.21)	0.338
Never or after second resection	1.00	
Thiopurines		
Before first or second resection	0.75 (0.56–1.00)	0.046
Never or after second resection	1.00	

OAC, oral contraceptive.

were identified and were subsequently included in the multivariate analysis. First, patients with colonic or ileocolonic disease had a significantly higher risk of surgical recurrence than patients with only ileal disease (hazard ratio [HR], 1.68; 95% CI, 1.09–2.59; $P = 0.019$; and HR, 1.55; 95% CI, 1.15–2.08; $P = 0.004$). Second, the total number of medication types was associated with a higher risk of surgical recurrence (HR, 1.21; 95% CI, 1.12–1.31; $P < 0.001$). Finally, patients who never used thiopurines or who used them after their second resection had a higher risk of surgical recurrence than patients who used thiopurines before their first or second resection (HR, 1.33; 95% CI, 1.00–1.79; $P = 0.046$).

Three additional variables were identified with a P value <0.2 and therefore also included in the multivariate analysis: smoking history, disease behavior, and the surgical approach. The use of anti-TNF-α antibodies did not reach statistical significance in univariate analysis, with a HR of 0.834. However, because this was a predefined variable with clinical importance, and we think it is potentially related to the risk of surgical recurrence of CD, it was also included in the multivariate analysis.

The multivariate model identified 3 variables as independent risk factors associated with surgical recurrence of CD (Table 3). A higher risk of surgical recurrence was seen in patients with colonic disease compared with patients with ileal disease (HR, 1.56; 95% CI, 1.10–2.21; $P = 0.012$), and in patients who used more different types of medications (HR, 1.38; 95% CI, 1.25–1.54; $P < 0.001$). However, a lower risk of surgical recurrence was seen in patients who used thiopurines before their first or second resection (HR, 0.51; 95% CI, 0.34–0.77; $P = 0.001$) (Fig. 1). Patients who used anti-TNF-α antibodies before their first or second resection also had a trend toward a statistical significant lower risk of surgical recurrence (HR, 0.60; 95% CI, 0.34–1.04; $P = 0.068$) (Fig. 2).

TABLE 3. Multivariate Analysis of Predictors of Surgical Recurrence of CD

	HR (95% CI)	*P*
CD location		
L1, ileal	1.00	
L2, colonic	1.56 (1.10–2.21)	0.012
L3, ileocolonic	1.31 (0.74–2.33)	0.358
Disease behavior		
B2, stricturing	1.00	
B1, inflammatory	0.70 (0.41–1.22)	0.206
B3, penetrating	1.40 (0.96–2.05)	0.083
No. of medications	1.38 (1.25–1.54)	<0.001
Anti-TNF-α		
Before first or second resection	0.60 (0.34–1.04)	0.068
Never or after second resection	1.00	
Thiopurines		
Before first or second resection	0.51 (0.34–0.77)	0.001
Never or after second resection	1.00	

DISCUSSION

Prevention of postoperative recurrence is a well-defined important outcome parameter in the treatment of CD. Unfortunately, evidence-based data concerning the best strategy to prevent postoperative recurrence is lacking. Surgical recurrence and thus reoperation has a great impact on patients. There is an ongoing search for risk factors that affect surgical recurrence. Despite the increased use of immune modulators, such as thiopurines and anti-TNF-α antibodies, surgical recurrence has remained a major clinical problem in the long-term follow-up, with 46% and 55% recurrence rate at 20 years reflecting the disabling course of CD.[14]

In this study, with a large group of 576 operated patients with CD with a median follow-up of 11 years, we found that thiopurines are effective in preventing surgical recurrence of CD. In addition, treatment with anti-TNF-α, especially when used in combination with thiopurines, seems to reduce surgical recurrence as well.

At the time of introduction, anti-TNF-α antibodies were a promising option in the prevention of postoperative recurrence because of their ability to heal intestinal ulcers. Evidence, however, is based only on one marginally powered randomized controlled trial with 24 patients with CD in which infliximab prevented endoscopic recurrence of CD. Surgical recurrence was not evaluated in this trial.[15] For an accurate assessment of surgical recurrence, it requires a longer follow-up than for assessing clinical and endoscopic recurrence, and until now, the effect of anti-TNF-α antibodies on surgical recurrence remains unclear.[16–19]

In univariate analysis, use of anti-TNF-α antibodies was not a significant risk factor for surgical recurrence; however, in multivariate analysis, patients who used anti-TNF-α antibodies before their first or second resection had a lower risk of surgical recurrence, with a trend toward statistical significance. This suggests that the use of anti-TNF-α antibodies might be effective in preventing surgical recurrence. To substantiate this, probably larger numbers ought to be included.

In the multivariate analysis, the use of thiopurines proves to be an independent risk factor of surgical recurrence. Combination therapy of thiopurines and anti-TNF-α antibodies could be effective in preventing clinical and endoscopic recurrence.[10,20] Because in our study 91% of the patients who used anti-TNF-α antibodies before their first resection also used thiopurines, our findings suggest that the combined use of anti-TNF-α antibodies and thiopurines is more effective than thiopurines alone in preventing surgical recurrence. This is enhanced by the fact that patients in the anti-TNF-α cohort needed less resections. In addition, patients in the anti-TNF-α cohort had a longer lag time between diagnosis and first surgery, leading to the assumption that the use of anti-TNF-α antibodies may delay the natural course of CD. The multivariate analysis demonstrated that patients who used multiple types of IBD medication had an increased risk of surgical recurrence. This can be explained by the fact that patients in our cohort

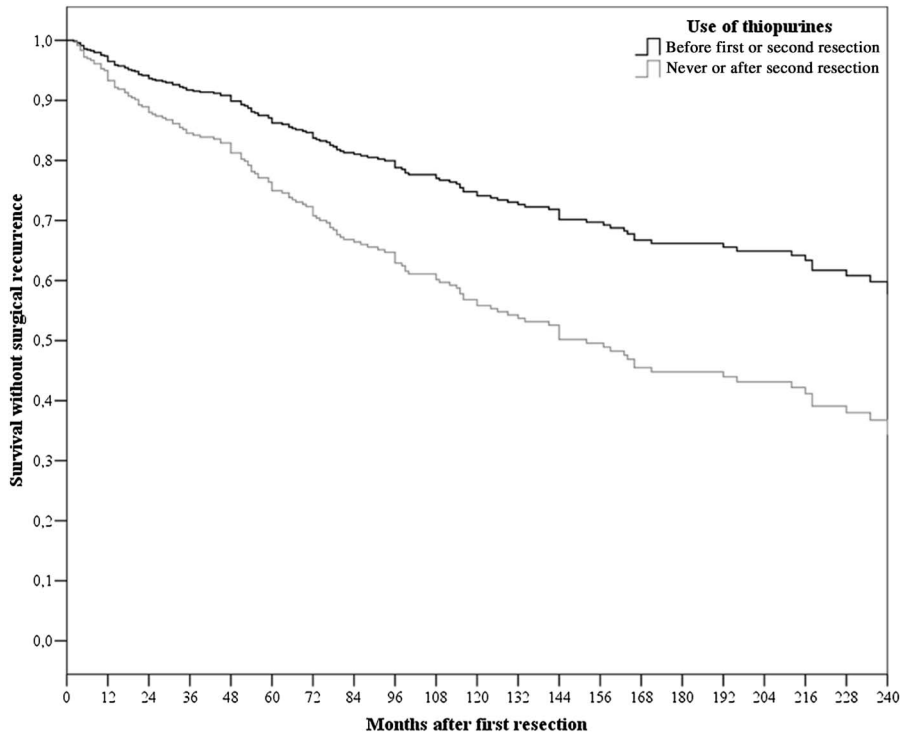

FIGURE 1. Cumulative risk of surgical recurrence of CD with use of thiopurines before the second resection, or never or after the second resection ($P = 0.001$).

were treated according to the step-up approach, and thus patients with a more severe disease are prescribed multiple different types of medication. This result, however, could also be biased by a prescription policy indicating earlier application of different types of medication in patients at risk of a more progressive course of CD. In addition, another bias could be that we also scored the use of 5-aminosalicylates as a type of different medication, although this seems not to be effective in preventing recurrence in CD.[21,22]

In our study, surgical recurrence occurred in 41.8% of patients after a median of 5.8 years. These findings are comparable with a study by Yamamoto,[14] who reported surgical recurrence rates of 11% to 32%, 20% to 44%, and 46% to 55% at 5, 10, and 20 years, respectively.

Patients with colonic disease had a significantly higher risk of surgical recurrence than patients whose CD was limited to the terminal ileum. This result is in line with a study by Sahmoud et al[23] reporting a higher risk of recurrence with involvement of the colon, although patients with concurrent small bowel disease should have been included as well. Furthermore, a study by Bitton et al[24] showed that patients with colonic CD also had an earlier clinical recurrence.

Patients in the university hospital cohort were significantly younger at the time of presentation of symptoms and at time of surgery than patients in the regional hospital cohort, and they were more often treated with anti-TNF-α antibodies. The age difference can be explained by the fact that most pediatric patients are treated and operated in the university hospital and not in the regional hospital, with 5 pediatric patients operated in the regional hospital versus 41 in the academic hospital. However, age was not an independent risk factor for surgical recurrence in the Cox regression model. This finding is in line with other studies.[25,26]

In earlier studies, penetrating disease behavior (B3) seemed to be associated with a higher risk of surgical recurrence.[18,25,27,28] In the present study, disease behavior according to the Montreal classification proved to be a risk factor in univariate analysis but not in multivariate analysis. This confirms the studies by Borley et al[29] and Unkart et al,[16] who did not find any evidence for the existence of a separate, early recurring, and aggressive disease type.

Because of the retrospective approach, we are not able to present Crohn's Disease Activity Index scores or Rutgeerts scores as indicators of disease severity. However, patients who used thiopurines or anti-TNF-α antibodies used significantly more types of medication, which reflects a more severe type of disease. Secondly, penetrating disease (B3) as a relatively more aggressive disease type was more frequent in the anti-TNF-α antibodies group.

Smoking has repeatedly shown to be an independent risk factor for surgical recurrence in CD.[2,14–19,25,30,31] In this study, smoking and quitting smoking immediately before diagnosis were associated with an increased risk for surgical recurrence compared with nonsmoking in the univariate analysis. However, in the multivariate analysis, the habit of smoking did not affect the surgical recurrence.

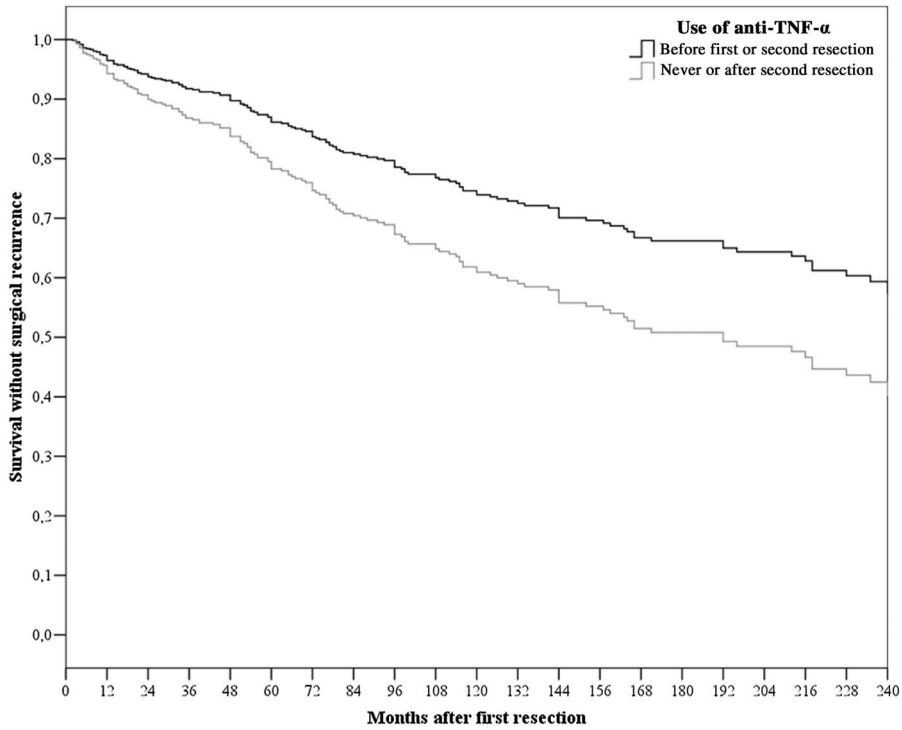

FIGURE 2. Cumulative risk of surgical recurrence of CD with the use of anti-TNF-α antibodies before the second resection, or never or after the second resection ($P = 0.068$).

We realize that our study has limitations. First, the study design is retrospective and we were not able to collect all the data from the medical charts (overall 6.5% missing data; see Table 1). Second, during the study period, medical management of CD has been rapidly evolved. Almost 75% of the patients, however, had their first surgical resection after January 1990, so after the introduction of thiopurines. Furthermore, we could not evaluate the duration of (combined) use of thiopurines and anti-TNF-α antibodies. This might be relevant, because thiopurines could have the most influence on surgical recurrence, when used for at least 36 months.[17] We examined anti-TNF-α antibodies and thiopurines separately, but 91% of the patients who used anti-TNF-α antibodies also used thiopurines at some point during their treatment.

However, this study contains a large number of patients from both a large regional and university hospital with a long-term follow-up of medication use and other risk factors for surgical recurrence. Also, our cohort contains all patients who underwent surgery for CD in both hospitals, whereas many trials use inclusion and exclusion criteria that limit frequently extrapolation to general hospital practice.

The use of anti-TNF-α antibodies on prevention of surgical recurrence in CD is promising. The findings in our study suggest that the combined use of anti-TNF-α antibodies and thiopurines may prevent surgical recurrence, which is in line with the SONIC trial showing that combination therapy of anti-TNF-α antibodies and thiopurines resulted in more clinical remission and mucosal healing.[10]

As evidence is scarce, albeit very much needed, larger prospective studies are necessary to investigate the results of anti-TNF-α antibodies in the long-term follow-up. In this context, the PREVENT study, an international multicenter trial, is being conducted. In this trial, patients who underwent ileocolonic resection will be randomized to treatment with infliximab or placebo every 8 weeks through week 200, with the aim of preventing recurrence of the disease after surgical resection. The primary endpoints will be clinical or endoscopic recurrence at 76 weeks.[32]

Most studies on the effect of different factors involved in CD limit their endpoints to clinical or endoscopic recurrence of CD. However, surgical recurrence has a great physical and psychological impact on patients, and therefore surgical recurrence needs to be studied in a randomized controlled trial as well.

In conclusion, this large cohort study shows that 41.8% of patients with CD need a re-resection with a median of 5.8 years after the first intestinal resection and identified colonic disease and the use of different medication types as risk factors for surgical recurrence of CD. Furthermore, we show that thiopurines are effective in the prevention of this surgical recurrence of CD. The role of anti-TNF-α antibodies seems promising as well, albeit not significant in our numbers. The combination of thiopurines and anti-TNF-α antibodies might be even more effective in the prevention of surgical recurrence of CD and should be studied in a randomized controlled trial.

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