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Observations and Research

The Use and Efficacy of Biological Therapies for Inflammatory Bowel Disease in a Danish Tertiary Centre 2010–2020

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Background: Patients with inflammatory bowel disease (IBD) who receive biologicals frequently experience lack or loss of response. Our aim was to describe the use and efficacy of biological therapy in a tertiary IBD center.

Methods: We included all bio-naive IBD patients who initiated biological therapy between 2010 and 2020 at our centre. Their medical records were reviewed.

Results: The population consisted of 327 Crohn's disease (CD) patients, 291 ulcerative colitis (UC) patients, and 3 patients with IBD unclassified (IBDU). The median follow-up was 3 years (interquartile range = 2–5) after initiating therapy. The annual number of patients initiating biological therapy rose from 29 (2010) to 85 (2019). Most patients (457, 73.6%) received 1 biological drug; 164 (26.4%) patients received 2 or more biologicals. Primary lack of response was observed in 36.4% (106/291) and 17.4% (57/327) of UC and CD patients; loss of response was observed in 27.1% (79/291) and 31.5% (103/327) of UC and CD patients, respectively. The 5-year surgery rates were 26.6% and 20.4% in UC and CD patients, respectively. Multivariate Cox regression showed that treatment with thiopurine reduced the likelihood of needing to switch biological therapy, requiring surgery or corticosteroids in UC patients (HR: 0.745, 95% CI: 0.559–0.993), but not in CD patients (HR: 0.996, 95% CI: 0.736–1.349).

Conclusions: The annual number of IBD patients initiated on biological therapy increased considerably between 2010 and 2020. One-quarter of these patients required surgery after 5 years. Our findings suggest a beneficial effect of concurrent thiopurines for UC patients receiving biologicals, but this was not found for CD patients. This effect in UC patients was not observed when we included patients initiating thiopurines up to 6 months after the introduction of biological therapy.

Lay Summary

We included all inflammatory bowel disease (IBD) patients, who started biological therapy between 2010 and 2020 at our department in Denmark. One-quarter of these patients required surgery after five years. Concurrent medication with thiopurines seemed to be beneficial in some patients.

Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, biological therapy

Introduction

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC), Crohn's disease (CD) and IBD unclassified (IBDU), are progressive, immune-mediated diseases characterized by chronic, recurring gastrointestinal inflammation.[1,2] Biological therapy is a cornerstone of inducing and maintaining remission in patients with moderate-to-severe IBD, fistulizing CD, and acute severe UC. For patients treated with infliximab, combination therapy with thiopurines is advised due to a beneficial reduction in immunogenicity. There is currently only sparse evidence for the efficacy of combination therapy with biological drugs other than infliximab.[3,4]

The direct health care costs for IBD have shifted in recent years from being driven primarily by hospitalizations and surgery toward drug-related expenditures, especially the increasing use of biological therapy.[5,6] The arsenal of biological therapies has expanded considerably since the introduction of tumor necrosis factor-α inhibitors. In Denmark, the Danish Medical Council provides recommendations about new medicines, including their sequence of use and priority in

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treatment schedules, by balancing efficacy and costs. During the study period, infliximab was recommended as the first drug of choice for all indications of IBD.[7,8]

Since the introduction of biological therapy for IBD, there has been a decline in surgical rates observed in both randomized clinical trials and population-based cohort studies. The 5-year surgery rates decreased from 12% to 8% in UC patients and 45% to 25% in CD patients after the introduction of biological therapy.[9–11] However, the impact of the increasing use of biological therapies has proven difficult to demonstrate as monitoring strategies and the availability of treatments have also improved during the same period.[12] A recent Danish study found that the risk of surgery has stabilized despite the increased use of biological therapy, and its authors suggest that these drugs may have postponed the first surgical interventions, rather than preventing them.[13] Another important clinical question is when to introduce biological therapy. In a meta-analysis of randomized clinical trials using biological therapies, its authors found that longer disease duration tended to reduce the response to treatment in CD patients, but not in UC patients.[14]

The aim of the present study was to describe the use, and evaluate the efficacy, of biological therapy. We investigated the need for switching biological drugs, the use of corticosteroids, and surgery rates in a Danish tertiary centre over a 10-year period.

Materials and Methods

Study Population and Covariates

The study population consisted of all bio-naive IBD patients whose treatment with infliximab, adalimumab, vedolizumab, ustekinumab, golimumab, certolizumab pegol, or tofacitinib started between January 1st, 2010 and February 19th, 2020 at the Gastro Unit of Hvidovre University Hospital. Tofacitinib was included, despite being a small molecule, as it is considered being at the same treatment intensity level in Denmark. This is a tertiary IBD centre situated in the Capitol Region of Denmark, covering approximately 530 000 inhabitants in 2020. Pediatric patients having received biological therapy at the pediatric department prior to transitioning to the adult department, as well as patients that started biological therapy before referral to our unit, were excluded. Patients receiving biological therapy for reasons other than IBD were also excluded. The electronic medical records of included patients were reviewed and data about their diagnosis, sex, age at diagnosis of IBD, disease duration and location, as well as medical and surgical treatments, were systematically extracted for study. Patients with perianal disease were identified using registrations of perianal surgical procedures before initiating biological therapy. Patients were followed until December 31st, 2020, or their emigration or death.

Outcomes

The follow-up period was defined according to the date of the patient's first biological treatment and the final medical record made logged for them during the study period. Primary non-response (PNR) to first-line biological therapy was defined as a switch of therapy due to lack of response, the need for additional corticosteroids, or surgery, within the induction period. Switching therapy due to a lack of response outside of the induction period was defined as a loss of response (LOR). We stratified patients according to the type of IBD diagnosis and whether thiopurines were combined with their biological therapy. For combination therapy, thiopurines had to be administered within a month of the first dose of the biological therapy. Patients who had failed to stay in remission on thiopurine maintenance therapy and who were subsequently started on biological therapy were included in the combination group. When calculating the sequential use of biological drugs, switches to biosimilars were not included. However, switching biological therapies with the same mechanism of action, for example, switches from infliximab to adalimumab, were considered a part of the sequence. The subgroup of patients treated with first-line infliximab were also stratified according to dosage. Treatment intensification was defined as increasing either the dose of infliximab to 10 mg/kg or treatment more frequent than every 8 weeks. Surgery as an outcome included small bowel, colonic, and perianal surgery, but excluded endoscopic dilatations. Simple clinical colitis activity index (SCCAI) and Harvey–Bradshaw index (HBI) scores of 4 or less were taken to indicate remission.[15,16]

Statistical Analysis

Descriptive data are shown as numbers, percentages, medians, and interquartile ranges (IQRs), as appropriate. Multivariate Cox regression analysis was used to investigate biological treatment and the subsequent need for surgery. Covariates were concomitant thiopurines, sex, smoking status at diagnosis, age at the time of IBD diagnosis, prior bowel surgery, perianal disease, disease duration, location, and behavior. Sensitivity analyses of combination therapy with thiopurine were performed as we altered the definition of thiopurine combination therapy to include patients starting thiopurine within either 3 or 6 months. A generalized linear model was used to analyze the 1-year surgery rates.

A level of $P < .05$ was considered statistically significant. All statistical analyses were performed with RStudio Team (2021) (RStudio: Integrated Development for R. RStudio Inc., Boston, MA).

Ethical Considerations

According to Danish law, retrospective studies based on medical records for quality assurance do not require ethical approval.

Results

The Use of Biological Therapy

A total of 621 IBD patients initiated biological therapy at the Gastro Unit of Hvidovre Hospital between January 1st, 2010 and February 19th, 2020. They were followed up for a median of 2 years (IQR = 3–5) after their first treatment. The median annual number of patients initiating biological therapy was 60 patients (IQR = 39–80). Patient characteristics can be found in Table 1. Approximately 1-in-10 patients had undergone small bowel or colonic surgery prior to their first treatment with biologicals, and this figure was considerably higher in patients with CD than with UC (55/327, 16.8% vs. 18/291, 6.2%). All patients with UC had undergone a colectomy, with the exception of 1 case of ileocecal resection, where the patient was initially diagnosed with CD. Subsequent ileal pouch-anal anastomosis was performed in 13 of the 17 UC patients with colectomy, and 2 patients underwent an

Table 1. Patient characteristics.

	All patients	%	Ulcerative colitis	%	Crohn's disease	%	IBDU	%
Number of patients	621		291	46.9	327	52.7	3	0.5
Male sex	312	50.2	147	50.5	162	49.5	3	100.0
Median age at diagnosis (Q1–Q3)	26 (21–34)		26 (21–33)		26 (20–34)		47 (44–53)	
Median age at the start of biological therapy (Q1–Q3)	31 (24–41)		31 (25–41)		31 (24–41)		51 (48–56)	
Median time in years from diagnosis to start of biological therapy (Q1–Q3)	2 (0.4–8)		3 (0.6–8)		2 (0.4–8)		3 (1–4)	
Median follow-up in years from start of biological therapy (Q1–Q3)	3 (2–5)		1 (3–5)		3 (2–6)		1 (1–1)	
Smoking status at diagnosis								
Never	240	38.6	129	44.3	111	33.9	0	0.0
Stopped	108	17.4	53	18.2	55	16.8	0	0.0
Currently	77	12.4	14	4.8	61	18.7	2	66.7
Unknown	196	31.6	95	32.6	100	30.6	1	33.3
Deaths	5	0.8	1	20.0	4	80.0	0	0.0
Montreal classification at diagnosis								
Age at diagnosis (*N*, %)								
A1: < 17 years	71	11.4	27	9.3	44	13.5	0	0.0
A2: 17–40 years	454	73.1	220	75.6	234	71.6	0	0.0
A3: >40 years	96	15.5	44	15.1	49	15.0	3	100.0
Localization in Crohn's disease patients (*N*, %)								
L1: ileal					46	14.1		
L2: colon					133	40.7		
L3: ileocolonic					85	26.0		
L4: isolated upper disease					5	1.5		
L1 + L4					18	5.5		
L2+L4					4	1.2		
L3+L4					18	5.5		
Unknown					18	5.5		
Phenotype (*N*, %)								
B1: non-stricturing, non-penetrating					288	88.1		
B1 + perianal disease					5	1.5		
B2: stricturing					13	4.0		
B2 + perianal disease					0	0.0		
B3: penetrating					26	8.0		
B3 + perianal disease					4	1.2		
Perianal disease in total					9	2.8		
Disease localization in ulcerative colitis patients (*N*, %)								
E1: proctitis			31	10.6				
E2: left sided			103	35.4				
E3: extensive			143	49.1				
Unknown			14	4.8				
Number of patients with surgery prior to biological therapy (*N*, %)								
Small bowel or colonic surgery	73	11.8	18	6.2	55	16.8	0	0.0
Perianal surgery	10	1.6	1	0.3	9	2.8	0	0.0
Treatment at the time of initiating biological therapy (*N*, %)								
5-Aminosalicyclic acid	207	33.3	163	56.0	44	13.5	0	0.0
Topical steroids	22	3.5	14	4.8	8	2.4	0	0.0
Systemic steroids	214	34.5	124	42.6	90	27.5	0	0.0
Thiopurine	254	40.9	107	36.8	147	45.0	0	0.0
Number of different biological drugs administered (*N*, %)								
1	457	73.6	207	71.1	248	75.8	2	66.7
2	126	20.3	67	23.0	58	17.7	1	33.3
3 or more	38	6.1	17	5.8	21	6.4	0	0.0

Abbreviation: IBDU, inflammatory bowel disease unclassified.

ileo-rectal anastomosis. In total, 13 patients were treated with biological therapy for pouchitis and 4 patients were treated for inflammation in the rectal remnant.

At the start of biological therapy, 124 (42.6%) patients with UC and 90 (27.5%) patients with CD were treated with systemic corticosteroids.

Most patients (457/621, 73.6%) received only 1 biological drug during the observation period; 126 (20.3%) patients received 2 drugs, and 38 (6.1%) received 3 or more different biological drugs. The annual number of bio-naive IBD patients initiating biological therapy increased during the study period, as did the share of patients who had UC (Figure 1). The median disease duration from diagnosis until initiation of biological treatment did not differ over the 10 years in UC patients, but showed a trend towards shorter time to treatment in CD patients (Table S1).

First-, second-, and third-line biological therapies are described in Table 2. Infliximab was the first-line biological treatment in 561 of 621 (90.3%) patients. The second-line therapy was most frequently vedolizumab (40/84, 47.6%) in UC patients and adalimumab (55/79, 69.6%) in CD patients. Ustekinumab and vedolizumab were equally frequent (8/19, 42.1%, for both) as the third-line treatment for UC patients, and ustekinumab (11/24, 45.8%) was the most common third-line treatment for CD patients. A total of 122 (41.9%) UC and 87 (26.6%) CD patients had SCCAI or HBI data available at the time of their first treatment with biologicals; the median SCCAI score was 7 (5–9) and the median HBI score was also 7 (3–9).

The Efficacy of Biological Therapy

The first biological therapy was discontinued after a median of 7 months (IQR = 2–17) for IBD patients; it was 5 months (2–13) for UC and 10 months (4–20) for CD patients. PNR was observed in 164 out of 621 (26.4%) patients and LOR in 184 out of 621 (29.6%) patients. PNR and LOR were observed in 36.4% (106/291) and 27.1% (79/291) of UC patients, respectively. In CD patients, PNR occurred in 17.4% (57/327) and LOR in 31.5% (103/327) of them. In total, 49 out of 621 patients (8.4%) discontinued their first biological therapy due to adverse events (UC: 16/291, 5.5%; CD: 33/327, 10.1%). In total 28 out of 49 (57.1%) adverse events were infusion reactions, 3 (6%) patients discontinued due to infection. The last 18 (37.7%) patients had other adverse events such as debut of psoriasis, arthritis, or peripheral neuropathy.

In UC patients who completed the induction period and had SCCAI data available for the 5 months or more before initiating biological therapy (N = 44), 90.9% (40/44) of patients responded with a decrease of 2 or more points in SCCAI, and 72.7% (32/44) had a SCCAI score lower than 5 after induction. In CD patients who completed the induction period and had HBI data available for the 5 months or more before initiating therapy (N = 35), 71.4% (25/35) of patients responded with a decrease of 2 or more points in HBI, and 62.9% (22/35) had a HBI score lower than 5 after induction.

In total, 99 out of 621 (15.9%) patients initiated systemic corticosteroids after beginning their biological therapy, which included 33 out of 99 (33.3%) patients during their first treatment with biologicals. Systemic corticosteroids were initiated during the induction period for 18 of the 33 patients (54.5%), with 16 of those 18 patients having at least 90 days of follow-up after initiating systemic corticosteroids. At the 90-day follow-up, 9 of these 16 patients (56.2%) were continuing with biological therapy. In the 15 patients who required systemic corticosteroids after the induction period, 13 were followed for at least 90 days; 11 of these (84.6%) were continuing with biological therapy at the 90-day follow-up after initiating systemic corticosteroids.

Surgery

Surgery rates are shown in Figures 2 and 3. The 1-, 2-, and 5-year surgery rates for IBD patients undergoing biological therapy were 12.4%, 17.3%, and 23.5%, respectively. For

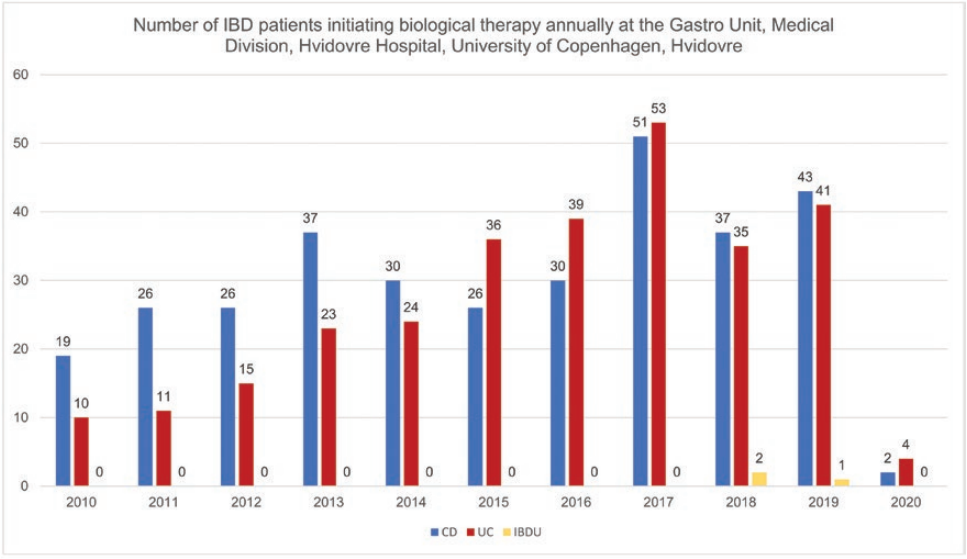

Figure 1. Number of IBD patients initiating biological therapy annually at the Gastro Unit, Medical Division, Hvidovre Hospital, University of Copenhagen, Hvidovre. Abbreviation: IBD, inflammatory bowel disease.

Table 2. Use of treatment duration and sequence of biological therapy in a Danish tertiary centre cohort.

	All patients	%	Ulcerative colitis	%	Crohn's disease	%	IBDU	%
First biological drug								
Infliximab	561	90.3	272	93.5	286	87.5	3	100.0
Adalimumab	52	8.4	13	4.5	39	11.9	0	0.0
Golimumab	0	0.0	0	0.0	0	0.0	0	0.0
Certolizumab pegol	1	0.2	0	0.0	1	0.3	0	0.0
Vedolizumab	7	1.1	6	2.1	1	0.3	0	0.0
Ustekinumab	0	0.0	0	0.0	0	0.0	0	0.0
Tofacitinib	0	0.0	0	0.0	0	0.0	0	0.0
Median duration of biological treatment until discontinuation, in months (Q1–Q3)	7 (2–17)		5 (2–13)		10 (4–20)		5 (3–7)	
Number of patients undergoing intensification of treatment with infliximab (*N*, %)	249	44.4	144	52.9	105	36.7	0	0
Number of patients undergoing combination treatment with thiopurine and biological therapy (*N*, %)	278	44.8	132	45.4	146	44.6	0	0
Number of patients undergoing combination treatment 6 months after initiating biological treatment (*N*, %)	192	30.9	77	26.5	115	35.2	0	0
Number of patients undergoing combination treatment 1 year after initiating biological treatment (*N*, %)	167	26.9	64	22.0	103	31.5	0	0
Second biological drug								
Infliximab	5	3.0	3	3.6	2	2.5	0	0.0
Adalimumab	81	49.4	26	31.0	55	69.6	0	0.0
Golimumab	10	6.1	10	11.9	0	0.0	0	0.0
Certolizumab pegol	1	0.6	0	0.0	1	1.3	0	0.0
Vedolizumab	53	32.3	40	47.6	12	15.2	1	100.0
Ustekinumab	9	5.5	1	1.2	8	10.1	0	0.0
Tofacitinib	4	2.4	4	4.8	0	0.0	0	0.0
Risankizumab	1	0.6	0	0.0	1	1.3	0	0.0
Median duration of biological treatment until discontinuation, in months (Q1–Q3)	6 (3–14)		6 (3–13)		7 (3–19)			
Number of patients undergoing combination treatment with thiopurine and biological therapy (*N*, %)	12	7.3	42	50.0	31	39.2	0	0.0
Number of patients undergoing combination treatment 6 months after initiating biological treatment (*N*, %)	9	5.5	28	33.3	24	30.4	0	0.0
Number of patients undergoing combination treatment 1 year after initiating biological treatment (*N*, %)	7	4.3	26	31.0	21	26.6	0	0.0
Third biological drug								
Infliximab	4	9.3	1	5.3	3	12.5	0	0
Adalimumab	2	4.7	1	5.3	1	4.2	0	0
Golimumab	1	2.3	0	0.0	1	4.2	0	0
Certolizumab pegol	0	0.0	0	0.0	0	0.0	0	0
Vedolizumab	15	34.9	8	42.1	7	29.2	0	0
Ustekinumab	19	44.2	8	42.1	11	45.8	0	0
Tofacitinib	1	2.3	1	5.3	0	0.0	0	0
Risankizumab	1	2.3	0	0.0	1	4.2	0	0

Table 2. Continued

	All patients	%	Ulcerative colitis	%	Crohn's disease	%	IBDU	%
Median duration of biological treatment until discontinuation, in months (Q1–Q3)	4 (1–9)		1 (1–18)		7 (3–9)		—	
Number of patients undergoing combination treatment with thiopurine and biological therapy (*N*, %)	0	0.0	11	57.9	7	29.2	0	0
Number of patients undergoing combination treatment 6 months after initiating biological treatment (*N*, %)	0	0.0	10	52.6	6	25.0	0	0
Number of patients undergoing combination treatment 1 year after initiating biological treatment (*N*, %)	0	0.0	10	52.6	5	20.8	0	0

Abbreviation: IBDU, inflammatory bowel disease unclassified.

UC patients the 1-, 2-, and 5-year surgery rates were 18.8%, 20.3%, and 26.6%, respectively, and for CD patients they were 10.4%, 14.1%, and 20.4%. No significant difference was observed in a generalized linear model of the 1-year surgery rates throughout the study period among patients with at least 1 year of follow-up (Table S2).

In total, 132 UC patients were treated with thiopurine within the first month of biological therapy and were thus considered to be undergoing combination therapy; however, after 3 and 6 months a total of 164 and 181 patients, respectively, had received thiopurine. In UC patients, combination treatment with thiopurines within the first month of the first treatment with biologicals was found to reduce the risk of surgery (HR: 0.536, 95% CI: 0.317–0.904), as did longer disease duration (HR: 0.940, 95% CI: 0.897–0.985). Advancing age at the start of biological treatment was associated with an increased risk of surgery (HR: 1.027, 95% CI: 1.009–1.046). Prior bowel surgery, sex, smoking, and disease location at diagnosis were not associated with the risk of surgery after initiating biological therapy. In a sensitivity analysis of combination therapy with thiopurine, changing the definition of thiopurine combination therapy to include patients starting thiopurine within 3 or 6 months after initiating biological therapy did not change the results.

In total, 146 CD patients were treated with thiopurine within the first month of being treated with biologicals; after 3 and 6 months a total of 169 and 191 patients, respectively, had received thiopurine. In CD patients, combination therapy with thiopurines in the first month of the first treatment with biologicals was not found to be associated with the risk of surgery (HR: 1.123, 95% CI: 0.720–2.101), nor were age at initiation of biological therapy, sex, disease duration, disease location and behavior, perianal disease, smoking, or prior bowel surgery. In a sensitivity analysis of patients started on thiopurine within 3 or 6 months of initiating biological therapy, no association with the risk of surgery was found.

The need for treatment intensification did not appear to influence the risk of surgery in an analysis adjusted for age at initiation of biological therapy, sex, disease duration, location and behavior, perianal disease, smoking, or prior bowel surgery (UC: HR: 0.619, 95% CI: 0.360–1.065; CD: HR: 0.630, 95% CI: 0.361–1.096).

Need for second-line biological therapy, corticosteroids, and/or surgery as a combined outcome

In total, 398 out of 621 (64.1%) patients required either a switch in biological therapy, corticosteroids, or surgery. The 1-, 2-, and 5-year failure of therapy rates, defined according to this combined outcome, were 45.9%, 57.9%, and 71.6%, respectively (UC: 56.2%, 65.6%, and 76.6%; CD: 36.4%, 50.9%, and 67.1%). Table 3 summarizes the time to failure of therapy and the number of patients requiring corticosteroids and surgery. In a multivariate Cox regression analysis, UC patients receiving combination treatment with thiopurines within 1 month of starting treatment with biologicals had a lower risk of a failure of therapy (HR: 0.745, 95% CI: 0.559–0.993). No other variables were associated with the risk of surgery after initiating biological therapy. A sensitivity analysis was performed for combination therapy with thiopurines, changing the thiopurine initiation to either 3 or 6 months after starting biological therapy. Thiopurine therapy

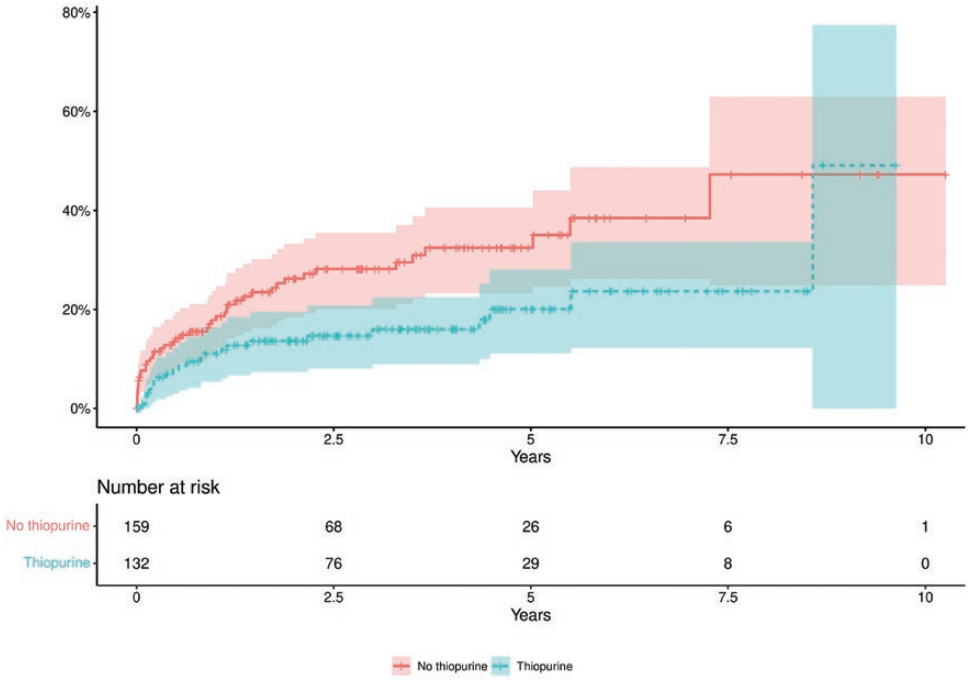

Figure 2. Risk of surgery according to treatment with thiopurine in ulcerative colitis patients undergoing biological therapy.

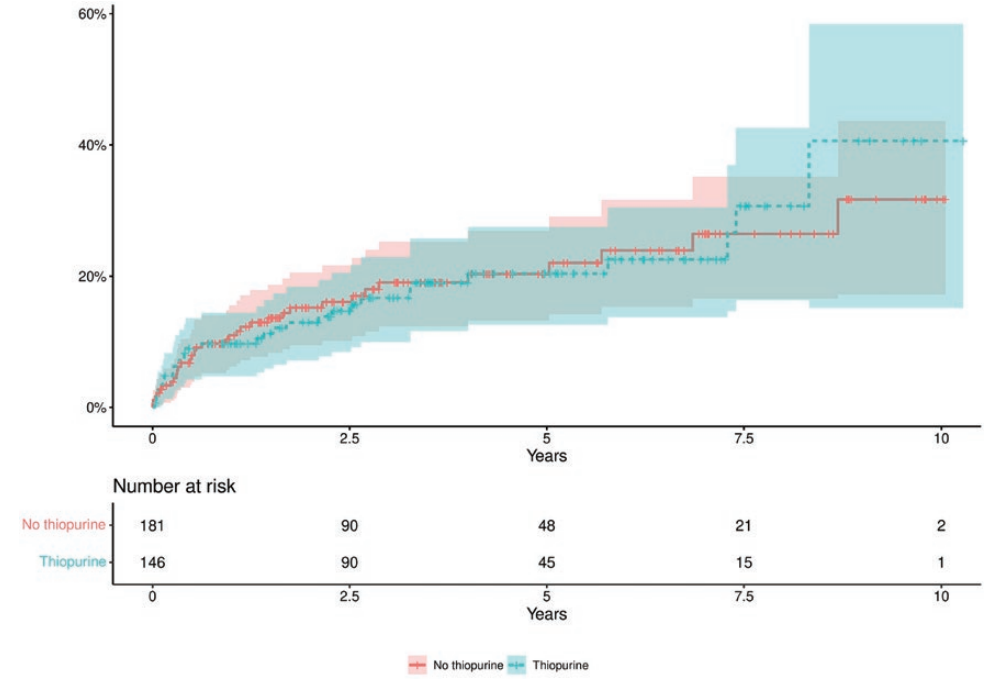

Figure 3. Risk of surgery according to treatment with thiopurine in Crohn's disease patients undergoing biological therapy.

was found to reduce the risk of failure of therapy when initiated within 3 months of starting biological therapy, but the reduction was not found to be significant when including patients who initiated thiopurines within 6 months of starting biological therapy (HR: 0.765, 95% CI: 0.566–1.034).

In CD patients, advanced age at initiation of biological therapy was found to be associated with an increased risk of failure of therapy (HR: 1.017, 95% CI: 1.004–1.029); however, being male lowered the risk (HR: 0.663, 95% CI: 0.493–0.893). No association was found with any of the other variables, including combination treatment with thiopurines within the first month of starting on biologicals (HR: 0.996, 95% CI: 0.736–1.349). In a sensitivity analysis of combination therapy with thiopurines that changed the initiation to within 3 or 6 months of starting biological therapy, no associations with the risk of failure of therapy were found.

Multivariate Cox regression analyses of infliximab intensification showed a reduced risk of requiring second-line

Table 3. Rates of failure of biological therapy in a Danish tertiary centre cohort.

	All patients	%	Ulcerative colitis	%	Crohn's disease	%	IBDU	%
Median time to failure of therapy, in months (Q1–Q3)	5.9 (1.4–14.5)		3.7 (1.3–11.0)		8.5 (2.5–18.3)		0.4 (0.3–0.6)	
Patients in need of systemic corticosteroids during biological treatment (*N*, %)	99	15.9	60	20.6	38	11.6	1	33.3
Median number of flare-ups treated with systemic steroids per patient after their first treatment with biologicals (Q1–Q3)	1 (1–2)		1 (1–1)		1 (1–2)		1 (1–1)	
Number of patients started on topical steroids after their first treatment with biologicals (*N*, %)	20	3.2	10	3.4	10	3.1	0	0,0
Number of patients undergoing major abdominal surgery after their first treatment with biologicals (*N*, %)	125	20.1	65	22.4	60	18.3	0	0.0
Number of patients undergoing perianal surgery after their first treatment with biologicals (*N*, %)	11	1.8	5	1.7	4	1.2	2	66.7

Abbreviation: IBDU, inflammatory bowel disease unclassified.

biological therapy, corticosteroids, and surgery in CD patients, but this association was not significant for UC (UC: HR: 0.748, 95% CI: 0.554–1.011; CD: HR: 0.558, 95% CI: 0.406–0.767). These analyses were adjusted for age at initiation of biological therapy, sex, disease duration, location, prior bowel surgery, and smoking.

Discussion

We have described the use and efficacy of biological therapies during the past 10 years at our tertiary centre in Denmark. The use of biological therapy increased year-on-year throughout the study period and the annual number of IBD patients initiating biological therapy was approximately 3 times higher in 2019 than it was in 2010. After 2017 we observed a decline in the number of patients initiating biologicals therapy at our centre. There is no apparent explanation of this, as the tendency on a national level in this period was an increased use of biologicals which was described previously by our group.[5] About 90% of our patients received infliximab as a first-line biological therapy, as per the recommendations of the Danish Medical Council. One quarter of our patients received at least one other biological drug, and three-quarters of patients required second-line biological therapies, surgery, or corticosteroids.

A Swedish study of 250 UC patients found the PNR of infliximab after 3 months to be 24%,[17] whereas we observed PNR in UC patients to be 36.4%; however, our study was not restricted to chronic active disease as an indication for biological therapy. In a recent Danish nationwide cohort study of bio-naive IBD patients, 32.8% of IBD patients switched to a second biological drug as an indicator of failure of therapy, whereas we observed this in about one quarter of our patients.[5] These differences may be due to study design, as our study was based on case record forms, while the Danish nationwide cohort study was registry based.

A Belgian referral centre study found that 23.5% of CD patients treated with infliximab underwent major abdominal surgery after a median of 55 months of follow-up.[18] Likewise, we found that in the 5 years after initiating biological therapy 21.4% of CD patients had undergone surgery; however, this figure included perianal surgery. In two European cohort studies, the 5-year surgery rates were 6% in UC and 22% in CD patients. Interestingly, biological therapy was not associated with a reduced risk of surgery in either of these studies.[19,20] The previous mentioned Swedish UC study reported a comparable colectomy rate of 17.0% after 1 year and 22.5% after 3 years of biological treatment in UC patients.[5] We observed major surgery rates in surgery-naive CD patients was 8.5% and 16.6% after 1 and 3 years, respectively.

We could not demonstrate any significant changes in the 1-year surgery rates among patients treated with biologicals in the study period. This is in contrast to the Danish nationwide cohort study, conducted between 2011 and 2018, in which the authors observed a significant decline, from 21.1% to 14.8%, in 1-year colectomy rates among UC patients and a significant decline in 1-year major surgery rates among surgery-naive CD patients, from 10.1% to 5.5%, all of whom were treated with biologicals.[5]

We found that UC patients started on concurrent thiopurine treatment within 1 month of initiating biological therapy had a reduced risk of needing second-line biological

therapy, surgery, or corticosteroids. However, this was not the case when we included patients whose treatment with thiopurines started within 6 months of initiating biological therapy, thus suggesting that the benefit of combination therapy in UC patients depends on starting thiopurines early on. The UC SUCCES randomized controlled trial evaluating corticosteroid-free remission after 16 weeks in 239 UC patients found that a combination of thiopurine and infliximab was superior to either of the 2 medications as a monotherapy.[21] Similarly, the SONIC study reported that infliximab in combination with thiopurine was more efficacious than either of the two given as a monotherapy in 508 CD patients, with higher rates of clinical remission and mucosal healing at week 26.[22] However, we did not find any significant difference in the risk of needing a second-line biological therapy, surgery, or corticosteroids among CD patients undergoing combination treatment with thiopurine vs biological monotherapy in their first month of treatment.

The major strength of this study is the Danish health care setting, which provides free and universal services, thereby reducing selection bias. Furthermore, we had detailed information about patients' treatment regime and disease location at the time of their diagnosis. However, there are also limitations to the study. First, instead of data for endoscopic activity, mucosal healing, and therapeutic drug monitoring, we relied on a switching of biological therapy, the need for surgery or treatment with corticosteroids as surrogate markers for the efficacy of biologicals. Second, this was a retrospective study and we were missing data for some of the patients, including symptom scores before and after beginning biological therapy.

In conclusion, by the end of a 10-year period at a Danish tertiary centre, approximately three times as many IBD patients initiated biological therapy each year than at the beginning. Around three-quarters of IBD patients undergoing first-line biological therapy required a second-line biological therapy, surgery, or corticosteroids. Our findings suggest there is a benefit in combining thiopurine with biological therapy in UC patients; however, we were not able to find an association for CD patients.

Supplementary Data

Supplementary data is available at *Crohn's and Colitis 360* online.

Conflicts of Interest

I.V.: Fees for lecturing from Takeda, Tillotts, MSD, and Janssen-Cilag. K.T.: Advisory board: Janssen-Cilag A/S. Clinical trials: Ferring Lægemidler A/S, Pharmacosmos A/S, AbbVie A/S, and Pfizer ApS. Lectures: Ferring Lægemidler A/S, Janssen-Cilag A/S, and Takeda Denmark. All unrelated to the work submitted. Consultancy: Pfizer ApS. A.M.P.: Fees for lecturing from Ferring. F.B.: Research grants from Ferring and Tillotts. Personal fee from Ferring. All unrelated to the work submitted. J.B.: Personal fees from AbbVie, Janssen-Cilag, and Celgene. Grants and personal fees from MSD. Personal fees from Pfizer. Grants and personal fees from Takeda for participating in advisory boards. Grants and personal fees from Tillotts Pharma. Personal fees from Samsung Bioepis. Grants from Bristol Myers Squibb and Novo Nordisk. All unrelated to the work submitted. M.D.W., L.A., M.S., O.K.F., G.P., A.M.-N., M.K.-K., T.B., and I.N.-L.: none declared.

Data Availability

Data available upon reasonable request due to privacy/ethical restrictions.

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