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Outcome of Biological Therapies and Small Molecules in Ulcerative Proctitis: A Belgian Multicenter Cohort Study

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BACKGROUND & AIMS: **Several advanced therapies (biologic therapies and small molecules) have been approved for the treatment of moderate-to-severe ulcerative colitis. The registration trials for these agents typically excluded patients with isolated proctitis, leaving an evidence gap. We evaluated efficacy and safety of advanced therapies in patients with ulcerative proctitis (UP).**

METHODS: **This multicenter retrospective cohort study included consecutive patients with active UP (Mayo endoscopy subscore of ≥2, rectal inflammation up to 15 cm) initiating advanced therapy, after failing conventional therapy. The primary end point was short-term steroid-free clinical remission (total Mayo score ≤2 with no individual subscore >1). In addition, drug persistence and relapse-free and colectomy-free survival were assessed. Both binary logistic and Cox regression analyses were performed.**

RESULTS: **In total, 167 consecutive patients (52.0% female; median age 41.0 years; 82.0% bionaive) underwent 223 courses of therapy for UP (38 adalimumab, 14 golimumab, 54 infliximab, 9 ustekinumab, 99 vedolizumab, 9 tofacitinib). The primary end point was achieved with 36.3% of the treatment courses, and based on multivariate analysis, more commonly attained in bionaive patients ($P = .001$), patients treated with vedolizumab ($P = .001$), patients with moderate endoscopic disease activity ($P = .002$), and a body mass index <25 kg/m^2 ($P = .018$). Drug persistence was significantly higher in patients treated with vedolizumab ($P < .001$) and patients with a shorter disease duration ($P = .006$). No new safety signals were observed.**

CONCLUSIONS: **Advanced therapies are also efficacious and safe in patients with ulcerative colitis limited to the rectum. Therefore, the inclusion of patients with UP in future randomized-controlled trials should be considered.**

Keywords: Advanced Therapy; Biological Therapy; Proctitis; Small Molecule; Ulcerative Colitis.

Abbreviations used in this paper: **5-ASA, 5-aminosalicylic acid; BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range; SAE, serious adverse event; TNF, tumor necrosis factor; UC, ulcerative colitis; UP, ulcerative proctitis.**

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Ulcerative colitis (UC) is a well-known chronic inflammatory disease of the colon, mainly affecting the mucosa. According to the Montreal classification, UC is divided based on the disease extent into ulcerative proctitis (UP; E1, inflammation limited to the rectum), left-sided UC (E2, inflammation limited to the colon distal to the splenic flexure), and extensive colitis (E3, inflammation extending proximal to the splenic flexure).[1] Epidemiologic studies have shown that 25%–55% of patients with UC present with UP at the time of diagnosis.[2] Although in UP only a very short segment of the colon is affected, it may be associated with discomforting symptoms, such as increased stool frequency, tenesmus, urgency, incontinence, and rectal blood loss, having a high impact on the quality of life. Furthermore, it is known that poorly controlled UP is associated with a risk of more proximal disease extension and consequently a higher risk of colectomy.[2,3] Adequate treatment is therefore crucial.

The classical treatment for UP consists of topical 5-aminosalicylic acid (5-ASA) and corticosteroids, if necessary associated with oral formulations of these compounds.[4,5] However, 1 in 3 patients fails to respond to first-line treatments. Topical tacrolimus has been investigated in 2 small randomized controlled trials, showing superior effect to placebo in inducing clinical response (73% vs 10%) in 1 study, and similar efficacy compared with beclomethasone suppositories (62.9% vs 59.9%) in another study.[6,7] In an observational study, 3 out of 21 (14.3%) patients treated with azathioprine reached steroid-free clinical remission at the short-term follow-up (between 3 and 9 months after initiation, missing in 4 patients).[8] After a median follow-up of 46.2 months, 5 out of 25 (20.0%) patients reached treatment success defined as the absence of colectomy, no need for anti-TNF, no ongoing systemic steroids use, no adverse event leading to azathioprine withdrawal, and clinically quiescent disease at last follow-up.

The effectiveness and safety profile of advanced therapies, including the small molecule tofacitinib, and biologics, such as adalimumab, golimumab, infliximab, ustekinumab, and vedolizumab, for the treatment of moderate-to-severe UC, are well proven following well-powered randomized double-blind placebo-controlled studies (OCTAVE, ULTRA, PURSUIT, ACT, UNIFI, and GEMINI).[9–16] As a consequence, these agents are widely used in patients with UC failing conventional therapies. Of note, in clinical practice these advanced therapies are also used in patients with UP (inflammation up to 15 cm of the anal margin), although such patients were systematically excluded from the pivotal trials. A recent systematic literature review could not find a single randomized controlled trial that investigated the effect of advanced therapies in UP.[17] To date, only 3 small observational studies described the effect of anti–tumor necrosis factor (anti-TNF) and vedolizumab in patients with UP, with response rates ranging between 42% and 69%, depending on the presupposed definitions of response.[18–20]

The aim of our study was to conduct a retrospective national multicenter cohort study to evaluate the short- and long-term outcome of biologic therapies (adalimumab, golimumab, infliximab, ustekinumab, and vedolizumab) and the JAK inhibitor tofacitinib for the treatment of UP.

Methods

Study Design

Nineteen Belgian centers participated in this multicenter retrospective cohort study. All sites had to maintain a database of patients with UC treated with biologic therapy (adalimumab, golimumab, infliximab, ustekinumab, or vedolizumab) or small molecules (tofacitinib). Only patients with UP (inflammation limited to the distal 15 cm from the anal margin) and an endoscopic Mayo subscore $\geq$2 at initiation of the index advanced therapy could be included. Patients with a history of a total or subtotal colectomy before initiation of the index therapy were excluded, as were patients with an ostomy at initiation of the index therapy, patients who were previously treated with the same advanced therapy, and patients who were treated with a biologic or a small molecule through a clinical study or a compassionate use program. Furthermore, patients had to have initiated the index advanced therapy before October 2021, allowing a follow-up of at least 20 weeks. The start date of the study was different for each center depending on when they started maintaining a database. The first index therapy for UP was initiated in February 2005.

Patients that initiated multiple advanced therapies for UP throughout their disease could be included more than once.

As part of the Belgian reimbursement criteria, all eligible patients had to undergo a clinical and endoscopic evaluation at baseline and after induction therapy (Week 8 for tofacitinib; Week 14 for adalimumab, golimumab, infliximab, and vedolizumab; and Week 20 for ustekinumab) allowing the short-term evaluation of the complete Mayo score in all patients. To start an advanced therapy, all patients had to fail (or be intolerant) to conventional therapy defined as a minimum of 3 months of 5-ASA and 3 months of (oral, rectal or intravenous) steroids and/or immunomodulators. Of note, in Belgium ustekinumab and tofacitinib can only be prescribed after failure of an anti-TNF agent or vedolizumab. Dose optimization was performed following daily clinical practice and could have been based on clinical symptoms, objective signs of disease activity, and/or therapeutic drug monitoring.

The following demographic and clinical data were collected: age, disease duration, sex, type of the advanced therapy, previous and concomitant UC therapy, maximal extent of the disease before index therapy, smoking behavior, extraintestinal manifestations including primary sclerosing cholangitis and spondyloarthropathy, total Mayo score, weight, length, body mass index (BMI),

C-reactive protein (CRP), hemoglobin, and serum albumin.

This study was approved by the Ethics Committee of Research of the University Hospitals Leuven (S65496). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All authors reviewed and approved the final manuscript.

Efficacy End Points

Short-term efficacy was evaluated between Weeks 8 and 20 after initiation of the index therapy. The primary end point was steroid-free clinical remission at short-term follow-up. Clinical remission was defined as a total Mayo score $\leq$2, with no individual subscore $>$1. Steroid-free status was defined as the absence of any type of steroids at time of evaluation, without taking into account how long these steroids had been discontinued. Other short-term end points included (steroid-free) clinical remission (regardless of prior need for dose optimization), (steroid-free) clinical response, endoscopic remission, and endoscopic improvement. Clinical response was defined as a decrease from baseline in the total Mayo score with $\geq$3 points and $\geq$30%, with a decrease in the rectal bleeding subscore of $\geq$1 point or an absolute rectal bleeding subscore $\leq$1. Endoscopic remission was defined as an endoscopic Mayo subscore of 0, and endoscopic improvement as an endoscopic Mayo subscore of 0 or 1. In patients with an elevated CRP at baseline (CRP $>$5 mg/L), short-term biologic remission (CRP $\leq$5 mg/L) and response (a decrease from baseline in CRP with $\geq$50% or a CRP $\leq$5 mg/L) were assessed. Nonresponder imputation was used if the short-term (endoscopic) evaluation was not performed, meaning that patients without short-term evaluation were assumed to be nonresponders regardless of actual response status.

Long-term efficacy was assessed by analyzing drug persistence, colectomy-free survival, and relapse-free survival at the time of the last follow-up visit. Although drug persistence and colectomy-free survival were evaluated in all patients, relapse-free survival was only evaluated in patients achieving short-term clinical remission. We also registered the occurrence of serious adverse events (SAEs) during the treatment period with the index biologic. SAEs were defined as any untoward medical occurrence that results in (1) death, (2) life-threatening illness or injury, (3) a permanent impairment of a body structure or function, (4) in-patient hospitalization or prolongation of existing hospitalization, and (5) fetal distress or a congenital anomaly/birth defect.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics for Windows, version 28.0 (IBM Corp, Armonk, NY). Descriptive statistics were used to analyze patient characteristics. Medians with interquartile ranges (IQR) were calculated for continuous data, and counts or percentages were computed for categorical variables. Univariate and multivariate binary logistic and Cox regression were performed to identify (independent) variables associated with both short- and long-term outcome. Variables with a P value $<$ .05 in univariate analysis were included in the multivariate analysis. A P value $<$ .05 was considered significant.

Analyses were not only performed in the overall cohort, but also in the more homogenous subgroup of bionaive patients.

What You Need To Know

Background

Several advanced therapies (including biological therapies and small molecules) have been shown efficacious for the treatment of moderate-to-severe ulcerative colitis, but patients with disease limited to the rectum were excluded from most of the registration trials.

Findings

The efficacy and safety profile of advanced therapies in patients with ulcerative proctitis is similar to that in patients with more extensive ulcerative colitis.

Implications for patient care

Patients with isolated proctitis should not be excluded from advanced therapies.

Results

Patient Characteristics

A total of 167 patients (52% female) with UP were treated with 223 courses of advanced therapies (38 adalimumab, 14 golimumab, 54 infliximab, 9 ustekinumab, 99 vedolizumab, 9 tofacitinib) between February 2005 and October 2021. In the subgroup of 137 bionaive patients, 82 initiated treatment with an anti-TNF (29 adalimumab, 10 golimumab, 43 infliximab), 1 with ustekinumab, and 54 with vedolizumab. The other 30 patients had received biologic treatment previously for a more extensive disease.

Baseline characteristics of the overall cohort and the subgroup of bionaive patients and bioexposed are displayed in Table 1. The median (IQR) age at start of index therapy was 41.0 (32.0–53.0) years and the median (IQR) disease duration was 65.4 (20.1–130.8) months. Almost all patients had failed oral or rectal 5-ASA (91.5% and 95.1%, respectively) and/or corticosteroids (98.2%) in the past. Furthermore, 119 (53.4%) had a previous

Table 1. Patient Characteristics at Initiation of Index Therapy

	Overall cohort (n = 223)	Bionaive patients (n = 137)	Bioexposed patients (n = 86)	*P* value
Female, n (%)	116/223 (52.0)	70/137 (51.1)	46/86 (53.5)	.728
Median (IQR) age at start of index therapy, *y*	41.0 (32.0–53.0)	39.0 (29.0–51.0)	43.5 (35.5–55.3)	
Median (IQR) disease duration at start of index therapy, *mo*	65.4 (20.1–130.8)	39.0 (12.9–110.1)	88.0 (50.4–167.0)	
Median (IQR) total Mayo score	8.0 (7.0–9.0)	8.0 (7.0–9.0)	8.0 (7.0–10.0)	
Endoscopic Mayo subscore (%)				
Mayo 2	123/223 (55.2)	80/137 (58.4)	43/86 (50.0)	.220
Mayo 3	100/223 (44.8)	57/137 (41.6)	43/86 (50.0)	
Median (IQR) weight, *kg*	70.0 (61.3–82.2)	70.0 (60.3–81.0)	75.0 (62.0–87.5)	
Median (IQR) length, *m*	1.72 (1.65–1.76)	1.70 (1.65–1.76)	1.72 (1.66–1.75)	
Median (IQR) BMI, kg/m^2	24.8 (21.0–28.1)	24.1 (20.9–26.9)	25.8 (21.9–29.1)	
Median (IQR) C-reactive protein, *mg/L*	2.1 (0.7–5.4)	2.1 (0.6–6.3)	2.3 (0.8–5.2)	
Median (IQR) hemoglobin, *g/dL*	13.8 (12.9–14.8)	14.0 (12.9–14.9)	13.7 (12.7–14.6)	
Median (IQR) serum albumin, *g/L*	44.2 (41.9–46.3)	44.8 (42.6–46.8)	43.3 (41.0–46.1)	
More extensive disease before index (%)	99/223 (44.4)	41/137 (29.9)	58/86 (67.4)	**< .001**
Smoking status				
Active	17/216 (7.9)	10/133 (7.5)	7/83 (8.4)	.708
Ex	75/216 (34.7)	49/133 (36.8)	26/83 (31.3)	
Never	124/216 (57.4)	74/133 (55.6)	50/83 (60.2)	
Extraintestinal manifestations (%)	29/223 (13.0)	11/137 (8.0)	18/86 (20.9)	**.005**
Index therapy (%)				
Anti–tumor necrosis factor agents	106/223 (47.5)	82/137 (59.9)	24/86 (27.9)	**< .001**
Adalimumab	38/223 (17.0)	29/137 (21.2)	9/86 (10.5)	
Golimumab	14/223 (6.3)	10/137 (7.3)	4/86 (4.7)	
Infliximab	54/223 (24.2)	43/137 (31.4)	11/86 (12.8)	
Tofacitinib	9/223 (4.0)	0/137 (0.0)	9/86 (10.5)	**< .001**
Ustekinumab	9/223 (4.0)	1/137 (0.7)	8/86 (9.3)	**.002**
Vedolizumab	99/223 (44.4)	54/137 (39.4)		.059
Concomitant UC therapy (%)				
5-ASA	141/223 (63.2)	93/137 (67.9)	48/86 (55.8)	.069
Oral 5-ASA	112/223 (50.2)	74/137 (54.0)	38/86 (44.2)	
Rectal 5-ASA	59/223 (26.5)	42/137 (30.7)	17/86 (19.8)	
Corticosteroids	101/223 (45.3)	64/137 (46.7)	37/86 (43.0)	.590
Oral topical corticosteroids	39/223 (17.5)	24/137 (17.5)	15/86 (17.4)	
Rectal topical corticosteroids	40/223 (17.9)	20/137 (14.6)	20/86 (23.3)	
Oral systemic corticosteroids	32/223 (14.3)	24/137 (17.5)	8/86 (9.3)	
Intravenous corticosteroids	0/223 (0.0)	0/137 (0.0)	0/86 (0.0)	
Immunosuppressants	62/223 (27.8)	39/137 (28.5)	23/86 (26.7)	.780
Thiopurines	56/223 (25.1)	39/137 (28.5)	17/86 (19.8)	
Methotrexate	6/223 (2.7)	0/137 (0.0)	6/86 (7.0)	

Table 1. Continued

	Overall cohort (n = 223)	Bionaive patients (n = 137)	Bioexposed patients (n = 86)	*P* value
Previous UC treatment (%)				
5-ASA	220/223 (98.7)	135/137 (98.5)	85/86 (98.9)	
Oral 5-ASA	204/223 (91.5)	122/137 (89.1)	82/86 (95.3)	1.000
Rectal 5-ASA	212/223 (95.1)	129/137 (94.2)	83/86 (96.5)	
Corticosteroids	219/223 (98.2)	133/137 (97.1)	86/86 (100.0)	
Oral topical corticosteroids	146/223 (65.5)	79/137 (57.7)	57/86 (77.9)	.301
Rectal topical corticosteroids	135/223 (60.5)	81/137 (59.1)	54/86 (62.8)	
Oral systemic corticosteroids	136/223 (61.0)	74/137 (54.0)	62/86 (72.1)	
Intravenous corticosteroids	11/223 (4.9)	4/137 (2.9)	7/86 (8.1)	
Immunosuppressants	119/223 (53.4)	61/137 (44.5)	58/86 (67.4)	**< .001**
Thiopurines	117/223 (52.5)	61/137 (44.5)	56/86 (65.1)	
Methotrexate	10/223 (4.5)	0/137 (0.0)	10/86 (11.6)	
Cyclosporine	6/223 (2.7)	1/137 (0.7)	5/86 (5.8)	
Tacrolimus	2/223 (0.9)	0/137 (0.0)	2/86 (2.3)	
Advanced therapies	86/223 (38.6)		86/86 (100.0)	
Adalimumab	38/223 (17.0)		38/86 (44.2)	**< .001**
Golimumab	15/223 (6.7)		15/86 (17.4)	**< .001**
Infliximab	52/223 (23.3)		52/86 (60.5)	**< .001**
Tofacitinib	0/223 (0.0)		0/86 (0.0)	1.000
Ustekinumab	2/223 (0.9)		2/86 (2.3)	.148
Vedolizumab	18/223 (8.1)		18/86 (20.9)	**< .001**

5-ASA, 5-aminosalicylic acid; BMI, body mass index; IQR, interquartile range; UC, ulcerative colitis.
Significant values are depicted in bold.

treatment with an immunosuppressant therapy, such as a thiopurine, methotrexate, cyclosporine, or tacrolimus. Although all patients had UP at initiation of index therapy, 44.4% of patients previously had more extensive disease. The median (IQR) total Mayo score at the start of the index therapy was 8.0 (7.0–9.0) with 55.2% and 44.8% of patients having an endoscopic Mayo subscore of 2 and 3, respectively.

Short-Term Efficacy

Short-term efficacy was evaluated after a median (IQR) follow-up of 13.7 (10.0–14.2) weeks. The primary end point of short-term steroid-free clinical remission was achieved with 81 out of 223 (36.3%) index therapies. All short-term end points, for both the overall cohort and the bionaive patients, are enlisted in Table 2. Thirteen patients (5.8%) needed a dose optimization during the induction period, including 3 patients who achieved short-term clinical remission. From the 90 patients who were receiving rectal therapy at baseline, 49 patients (54.4%) were able to discontinue them before short-term evaluation.

Factors associated with the primary end point in univariate analysis are depicted in Supplementary Table 1. In multivariate analysis, a bionaive status (odds ratio [95% confidence interval], 3.566 [1.627–7.815]; $P = .001$), treatment with vedolizumab (3.203 [1.581–6.488]; $P = .001$), a baseline Mayo endoscopic subscore of 2 versus 3 (3.123 [1.533–6.360]; $P = .002$), and a baseline BMI less than 25 kg/m^2 (2.374 [1.161–4.857]; $P = .018$) were associated with steroid-free clinical remission (Table 3). In the subpopulation of bionaive patients, treatment with vedolizumab (4.082 [1.743–9.560]; $P = .001$), a Mayo endoscopic subscore of 2 versus 3 (3.144 [1.326–7.457]; $P = .009$), and a BMI less than 25 kg/m^2 (3.208 [1.315–7.830]; $P = .010$) remained significantly associated with this outcome (Table 3).

Long-Term Efficacy

Median follow-up was (IQR) of 48.5 (28.5–72.5) months after initiating the index advanced therapy. Figure 1 shows the relapse-free survival, drug persistence, and colectomy-free survival. In the 87 patients showing short-term clinical remission, the relapse-free survival after 1 year was 88.5%. This was 87.9% in the 66 bionaive patients showing short-term clinical remission. After 1 year, drug persistence and colectomy-free survival were, respectively, 65.0% and 98.7% in the overall cohort and 67.2% and 99.3% in the bionaive patients.

No baseline parameters were associated with relapse-free or colectomy-free survival. Factors associated with drug persistence are shown in Supplementary Table 2. In multivariate analysis, drug persistence was significantly higher in patients treated with vedolizumab (2.104

Table 2. Short-Term Efficacy End Points

	Overall cohort (n = 223)	Bionaive patients (n = 137)
Steroid-free clinical remission without dose optimization	78/223 (35.0)	58/137 (42.3)
Steroid-free clinical remission	81/223 (36.3)	61/137 (44.5)
Steroid-free clinical response	129/223 (57.8)	89/137 (65.0)
Clinical remission	87/223 (39.0)	71/137 (51.8)
Clinical response	140/223 (62.8)	97/137 (70.8)
Endoscopic remission	62/223 (27.8)	50/137 (36.5)
Endoscopic improvement	120/223 (53.8)	83/137 (60.6)
Biologic remission	30/46 (65.2)	21/28 (75.0)
Biologic response	33/46 (71.7)	21/28 (75.0)

NOTE. Values are number (%).

[1.411–3.138]; $P < .001$), and in patients with a shorter disease duration (1.706 [1.168–2.492]; $P = .006$) (Table 3 and Figure 2). In the bionaive patients, both vedolizumab (2.087 [1.124–3.877]; $P = .020$) and a BMI less than 25 kg/m^2 (1.912 [1.117–3.273]; $P = .018$) were associated with drug persistence (Table 3 and Figure 2).

Safety

Three out of the 223 treatment courses had to be discontinued before the short-term evaluation because of an SAE. One patient experienced an infusion reaction during his second infusion of infliximab. In the other 2 patients, there was no clear causality. One patient treated with adalimumab experienced a transient ischemic accident, whereas another patient treated with vedolizumab had a deterioration of his underlying neurologic disease (no further details available).

During maintenance, 7 patients developed an SAE. Three of them were potentially linked to the index advanced therapy. One patient treated with adalimumab developed a tuberculosis pneumonia (without having other risk factors for tuberculosis, such as intake of other immunosuppressants or living in an endemic region) and 2 patients treated with infliximab had a bacterial pneumonia. The other 4 SAEs were not clearly correlated with

Table 3. Independent Predictors of Steroid-Free Clinical Remission at Short-Term Follow-Up (Primary End Point) and Drug Persistence on the Long-Term in the Overall Cohort and the Bionaive Patients (Multivariate Analysis)

	Overall cohort (n = 223)		Bionaive patients (n = 137)	
	Primary end point Odds ratio (95% CI) *P* value	Drug persistence Odds ratio (95% CI) *P* value	Primary end point Odds ratio (95% CI) *P* value	Drug persistence Odds ratio (95% CI) *P* value
Bionaive patients	3.566 (1.627–7.815) $P = .001$			
Vedolizumab	3.203 (1.581–6.488) $P = .001$	2.104 (1.411–3.138) $P < .001$	4.082 (1.743–9.560) $P = .001$	2.087 (1.124–3.877) $P = .020$
Baseline Mayo endoscopic subscore 2 (vs 3)	3.123 (1.533–6.360) $P = .002$		3.144 (1.326–7.457) $P = .009$	
Baseline BMI <25 kg/m^2	2.374 (1.161–4.857) $P = .018$		3.208 (1.315–7.830) $P = .010$	1.912 (1.117–3.273) $P = .018$
Disease duration <5 y		1.706 (1.168–2.492) $P = .006$		

BMI, body mass index; CI, confidence interval.

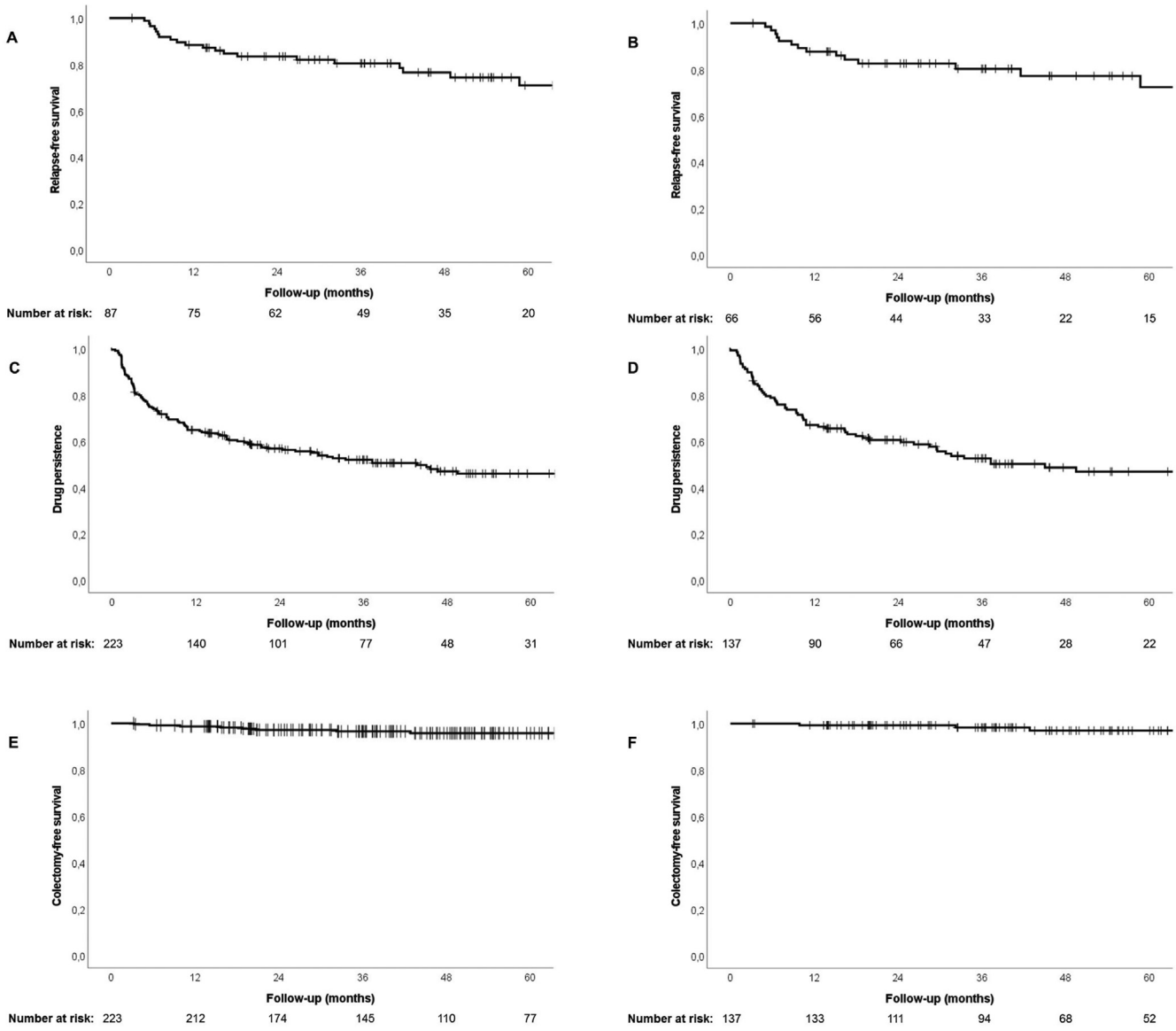

Figure 1. Relapse-free survival, drug persistence, and colectomy-free survival. Relapse-free survival in patients achieving short-term clinical remission in the overall cohort (*A*) and the bionaive patients (*B*). Drug persistence in the overall cohort (*C*) and the bionaive patients (*D*). Colectomy-free survival in the overall cohort (*E*) and the bionaive patients (*F*).

the advanced therapy and included 1 non-ST-elevation myocardial infarction, 1 appendectomy and 1 tonsillectomy during treatment with vedolizumab, and 1 hospitalization caused by worsening of UC in a patient treated with infliximab.

One patient got pregnant during treatment with the index therapy, namely golimumab. Golimumab was stopped at Week 19 of pregnancy. The patient gave birth at 38 weeks and golimumab was restarted the day thereafter. No birth defects where observed.

Discussion

In our study investigating the effect of advanced therapies for UP, 36.3% of patients reached the primary end point of steroid-free clinical remission at short-term follow-up. This number increased to 44.5% in bionaive patients. The observed efficacy data are comparable with those reported in the pivotal randomized controlled trials for biologics and tofacitinib in patients with left-sided and extensive UC.[9–16] Indeed, in these registration trials short-term clinical remission rates ranged between 15% and 69%. However, in comparison with the 3 smaller observational studies that have been performed in patients with UP so far,[18–20] our success rates were a little bit lower. This might be explained by the application of a more stringent definition for clinical remission in our study (steroid-free) and a relatively fixed time point of evaluation (between 8 and 20 weeks following the local reimbursement guidelines).

Our study supports the recent push to include patients with UP in future clinical trials on patients with moderate-to-severe UC. In the recent ELEVATE UC studies evaluating the efficacy of the S1P receptor

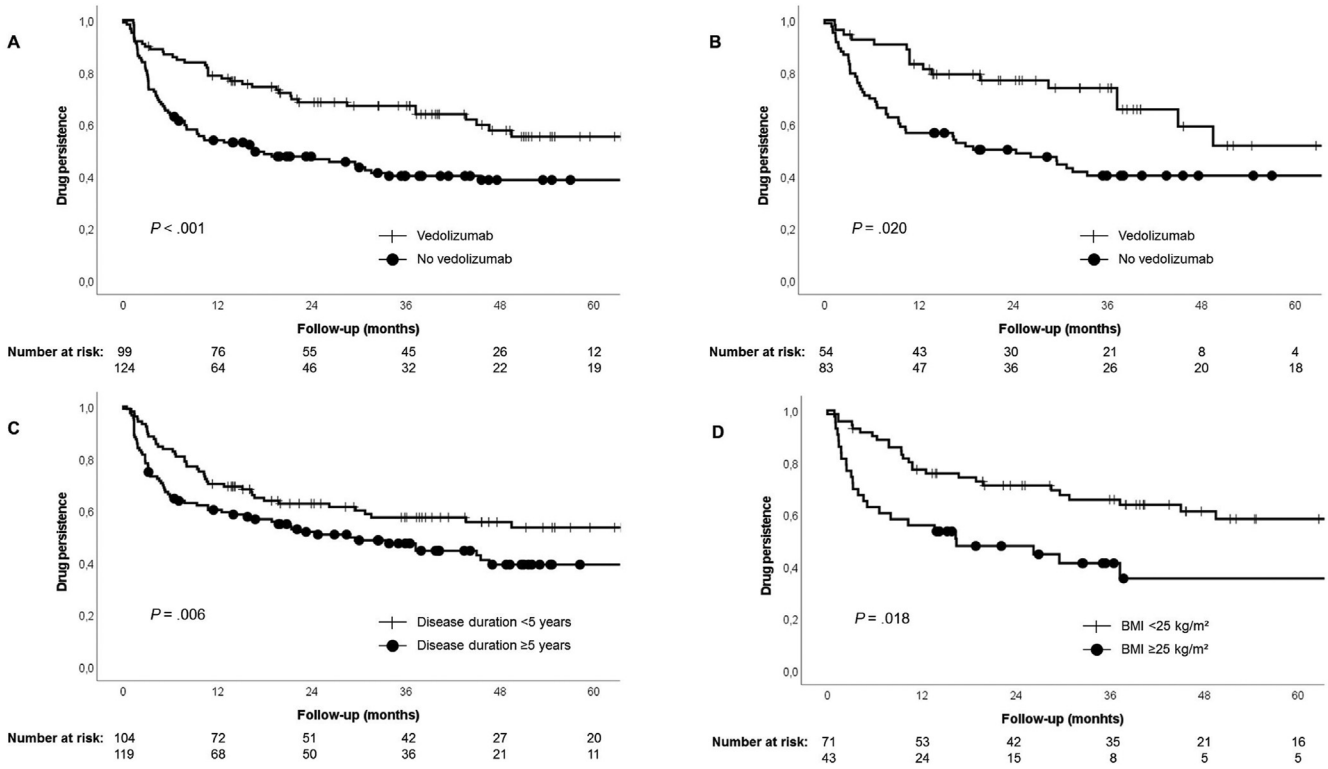

Figure 2. Independent predictors of drug persistence. Drug persistence in the overall cohort based on treatment with vedolizumab (*A*) and disease duration (*C*). Drug persistence in the bionaive patients based on treatment with vedolizumab (*B*) and body mass index (*D*).

modulator etrasimod, 15% of the recruited patients could have an isolated proctitis (<10 cm rectal involvement).[21] In the end, only 55 out of 787 patients (7%) showed to have an isolated proctitis at baseline making a comparison with the other subgroups more difficult.

After 1 year of follow-up, relapse-free survival was 88.5% in those patients achieving short-term clinical remission. In the overall cohort, drug persistence and colectomy-free survival were, respectively, 65.0% and 98.7% at 1 year. The 35.0% discontinuation rate was somewhat lower compared with what has been suggested as in large-scale studies in both Europe and the United States (40%–50%).[22–24]

Treatment with vedolizumab was independently associated with better efficacy compared with other advanced therapies, even if we combined all anti-TNF agents. So far, only 1 head-to-head trial has been performed in patients with UC, comparing vedolizumab with adalimumab.[25] The VARSITY trial in patients with moderate-to-severe UC with left-sided or extensive colitis, showed that at Week 52 clinical remission was significantly higher in the vedolizumab group than in the adalimumab group (31.3% vs 22.5%). Nevertheless, the benefit of vedolizumab was no longer significant in the bionaive patients, nor for the steroid-free clinical remission. In our study, however, vedolizumab was independently associated with short-term steroid-free clinical remission, and this in the overall cohort as in the bionaive patients. Because this study was not set up as a comparative effectiveness study, we have to be cautious with making too strong conclusions on the superiority of vedolizumab. Of note, patients treated with vedolizumab more commonly received concomitant corticosteroids, whereas the number of patients with a Mayo 3 endoscopic subscore at baseline was numerically lower in this subgroup (Supplementary Table 3).

Previous studies identified several clinical and biologic factors having a negative impact on the response to biologics in patients with UC, such as younger age, longer disease duration, more severe disease, more extensive disease, and extraintestinal manifestations.[20,26] In our study, however, only a longer disease duration was associated with a worse drug persistence in the overall cohort. Remarkably, previous more extensive disease was not predictive of short- or long-term outcome. However, this observation may have been influenced by concomitant and previous therapies because no strict washout period was used. Another remarkable finding was the fact that a BMI $\geq$25 kg/m^2 was associated with a worse short-term and long-term outcome. Although this is in agreement with a single-center Californian cohort study,[27] a pooled analysis of individual participant data from clinical trials with infliximab could not confirm this.[28]

With only 10 SAEs during a median follow-up of 46.2 months, our study showed that prescribing advanced therapies for UP is at least as safe as prescribing them for left-sided and more extensive UC.

The strengths of our study are the relatively large study size, the multicenter character, the incorporation of an endoscopic evaluation at baseline and after induction, and the longer duration of follow-up compared with previous trials.

Our study, however, also has limitations. First, the retrospective nature makes it more prone for incomplete or distorted data collection. Another limitation is the lack of a control arm. Third, the number of patients treated with golimumab, tofacitinib, and ustekinumab was quite small, making it impossible to look for significant impact of these advanced therapies on treatment outcome. Furthermore, both tofacitinib and ustekinumab could only be prescribed in patients previously exposed to anti-TNF therapy or vedolizumab. In addition, based on local reimbursement criteria, the postinduction time point was not the same among patients, and diverted according to the type of advanced therapy, ranging from 8 to 20 weeks after the first administration. Last, we were not able to collect data on fecal calprotectin and trough levels.

Conclusions

This multicenter retrospective study showed that biologics and small molecules are an efficacious and safe treatment option in patients with UP. Because these findings were comparable with data from the pivotal trials, one should consider the inclusion of UP patients in future randomized-controlled trials with investigational medical products for UC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.06.023.

References

1. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005; 19(Suppl A):5A–36A.
2. Meucci G, Vecchi M, Astegiano M, et al. The natural history of ulcerative proctitis: a multicenter, retrospective study. Gruppo di Studio per le Malattie Infiammatorie Intestinali (GSMII). Am J Gastroenterol 2000;95:469–473.
3. Kim B, Park SJ, Hong SP, et al. Proximal disease extension and related predicting factors in ulcerative proctitis. Scand J Gastroenterol 2014;49:177–183.
4. Raine T, Bonovas S, Burisch J, et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. J Crohns Colitis 2022;16:2–7.
5. Pineton de Chambrun G, Tassy B, Kollen L, et al. The treatment of refractory ulcerative colitis. Best Pract Res Clin Gastroenterol 2018;32-33:49–57.
6. Lie M, Kreijne JE, Dijkstra G, et al. No superiority of tacrolimus suppositories vs beclomethasone suppositories in a randomized trial of patients with refractory ulcerative proctitis. Clin Gastroenterol Hepatol 2020;18:1777–1784.
7. Lawrance IC, Baird A, Lightower D, et al. Efficacy of rectal tacrolimus for induction therapy in patients with resistant ulcerative proctitis. Clin Gastroenterol Hepatol 2017;15:1248–1255.
8. Mallet AL, Bouguen G, Conroy G, et al. Azathioprine for refractory ulcerative proctitis: a retrospective multicenter study. Dig Liver Dis 2017;49:280–285.
9. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011;60:780–787.
10. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012; 142:257–265.
11. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:85–95; quiz e14–15.
12. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014; 146:96–109.
13. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–2476.
14. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369:699–710.
15. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2019;381:1201–1214.
16. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2017;376:1723–1736.
17. Caron B, Sandborn WJ, Panaccione R, et al. Efficacy of pharmacological agents for ulcerative proctitis: a systematic literature review. J Crohns Colitis 2022;16:922–930.
18. Bouguen G, Roblin X, Bourreille A, et al. Infliximab for refractory ulcerative proctitis. Aliment Pharmacol Ther 2010; 31:1178–1185.
19. Dubois E, Moens A, Geelen R, et al. Long-term outcomes of patients with ulcerative proctitis: analysis from a large referral centre cohort. United European Gastroenterol J 2020; 8:933–941.
20. Pineton de Chambrun G, Amiot A, Bouguen G, et al. Efficacy of tumor necrosis factor antagonist treatment in patients with refractory ulcerative proctitis. Clin Gastroenterol Hepatol 2020; 18:620–627.
21. Sandborn WJ, Vermeire S, Peyrin-Biroulet L, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. Lancet 2023;401:1159–1171.
22. Brady JE, Stott-Miller M, Mu G, et al. Treatment patterns and sequencing in patients with inflammatory bowel disease. Clin Ther 2018;40:1509–1521.
23. Chen C, Hartzema AG, Xiao H, et al. Real-world pattern of biologic use in patients with inflammatory bowel disease:

treatment persistence, switching, and importance of concurrent immunosuppressive therapy. Inflamm Bowel Dis 2019; 25:1417–1427.

24. Armuzzi A, DiBonaventura MD, Tarallo M, et al. Treatment patterns among patients with moderate-to-severe ulcerative colitis in the United States and Europe. PLoS One 2020;15:e0227914.
25. Sands BE, Peyrin-Biroulet L, Loftus EV Jr., et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. N Engl J Med 2019;381:1215–1226.
26. Zampeli E, Gizis M, Siakavellas SI, et al. Predictors of response to anti-tumor necrosis factor therapy in ulcerative colitis. World J Gastrointest Pathophysiol 2014;5:293–303.
27. Kurnool S, Nguyen NH, Proudfoot J, et al. High body mass index is associated with increased risk of treatment failure and surgery in biologic-treated patients with ulcerative colitis. Aliment Pharmacol Ther 2018;47:1472–1479.
28. Singh S, Proudfoot J, Xu R, et al. Obesity and response to infliximab in patients with inflammatory bowel diseases: pooled analysis of individual participant data from clinical trials. Am J Gastroenterol 2018;113:883–889.

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Edouard Louis (Investigation: Supporting; Writing – review & editing: Equal)
Wouter Van Moerkercke (Investigation: Supporting; Writing – review & editing: Equal)
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Supplementary Table 1. Factors Associated With Short-Term Steroid-Free Clinical Remission (Primary End Point) in Univariate and Multivariate Analysis, in the Overall Patient Cohort, the Bionaive Patients, and the Bioexposed Patients

	Overall cohort (n = 223)		Bionaive patients (n = 137)	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
	Odds ratio (95% CI) *P* value	Odds ratio (95% CI) *P* value	Odds ratio (95% CI) *P* value	Odds ratio (95% CI) *P* value
Female	1.070 (0.619–1.847) $P = .809$		1.577 (0.800–3.109) $P = .188$	
Age >40 y	0.872 (0.505–1.505) $P = .622$		0.825 (0.419–1.627) $P = .579$	
Disease duration <5 y	0.909 (0.526–1.571) $P = .733$		0.675 (0.846–3.315) $P = .138$	
Endoscopic Mayo score 2	**2.116 (1.200–3.731) $P = .009$**	**3.123 (1.533–6.360) $P = .002$**	**2.211 (1.093–4.470) $P = .026$**	**3.144 (1.326–7.457) $P = .009$**
More extensive disease before index therapy	0.731 (0.420–1.272) $P = .267$		1.470 (0.705–3.064) $P = .303$	
Active smoking	0.941 (0.334–2.652) $P = .909$		0.496 (0.123–2.009) $P = .511$	
Extraintestinal manifestations	0.912 (0.402–2.069) $P = .825$		2.333 (0.650–8.377) $P = .217$	
Anti-TNF therapy	**0.511 (0.292–0.893) $P = .018$**	Not in the equation	**0.265 (0.129–0.545) $P < .001$**	Not in the equation
Vedolizumab therapy	**2.595 (1.482–4.545) $P < .001$**	**3.203 (1.581–6.488) $P = .001$**	**4.038 (1.954–8.347) $P < .001$**	**4.082 (1.743–9.560) $P = .001$**
Concomitant 5-ASA	0.832 (0.474–1.461) $P = .522$		0.827 (0.402–1.698) $P = .604$	
Concomitant steroids	0.948 (0.547–1.640) $P = .848$		1.517 (0.770–2.989) $P = .227$	
Concomitant immunomodulators	0.862 (0.466–1.595) $P = .637$		0.048 (0.449–2.003) $P = .889$	
Bionaive status	**2.649 (1.449–4.841) $P = .001$**	**3.566 (1.627–7.815) $P = .001$**	NA	
BMI <20 kg/m^2	1.082 (0.445–2.631) $P = .862$		1.050 (0.353–3.119) $P = .930$	
BMI <25 kg/m^2	**2.675 (1.409–5.077) $P = .002$**	**2.374 (1.161–4.857) $P = .018$**	**3.333 (1.476–7.530) $P = .003$**	**3.208 (1.315–7.830) $P = .010$**
CRP >5 mg/L	**0.402 (0.196–0.823) $P = .011$**	Not in the equation	0.533 (0.233–1.223) $P = .135$	

5-ASA, 5-aminosalicylic acid; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; NA, not applicable; TNF, tumor-necrosis factor.
Significant values are depicted in bold.

Supplementary Table 2. Factors Associated With Drug Persistence in Univariate and Multivariate Analysis, Both in the Overall Patient Cohort as in the Bionaive Patients

	Overall cohort (n = 223)		Bionaive patients (n = 137)	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
	Odds ratio (95% CI) *P* value	Odds ratio (95% CI) *P* value	Odds ratio (95% CI) *P* value	Odds ratio (95% CI) *P* value
Female	0.908 (0.628–1.314) $P = .608$		1.203 (0.750–1.931) $P = .442$	
Age >40 y	0.810 (0.560–1.172) $P = .262$		0.682 (0.425–1.095) $P = .111$	
Disease duration <5 y	**1.511 (1.040–2.198)** ***P* = .029**	**1.706 (1.168–2.492)** ***P* = .006**	1.376 (0.857–2.212) $P = .184$	
Endoscopic Mayo score 2	1.389 (0.958–2.012) $P = .081$		1.439 (0.888–2.331) $P = .137$	
More extensive disease before index therapy	**0.622 (0.430–0.898)** ***P* = .011**	Not in the equation	0.667 (0.408–1.092) $P = .104$	
Active smoking	0.770 (0.413–1.439) $P = .410$		0.772 (0.333–1.792) $P = .546$	
Extraintestinal manifestations	1.572 (0.857–2.882) $P = .140$		2.132 (0.745–6.098) $P = .150$	
Anti-TNF therapy	**0.503 (0.343–0.737)** ***P* < .001**	Not in the equation	**0.439 (0.252–0.764)** ***P* = .003**	Not in the equation
Vedolizumab therapy	**1.919 (1.294–2.841)** ***P* < .001**	**2.104 (1.411–3.138)** ***P* < .001**	**2.208 (1.269–3.846)** ***P* = .004**	**2.087 (1.124–3.877)** ***P* = .020**
Concomitant 5-ASA	0.872 (0.593–1.280) $P = .483$		0.958 (0.576–1.592) $P = .868$	
Concomitant steroids	0.902 (0.623–1.304) $P = .581$		1.105 (0.685–1.783) $P = .683$	
Concomitant immunomodulators	0.744 (0.502–1.103) $P = .139$		0.949 (0.564–1.595) $P = .842$	
Bionaive status	1.196 (0.818–1.748) $P = .355$		NA	
BMI <20 kg/m^2	0.629 (0.365–1.083) $P = .091$		0.683 (0.343–1.356) $P = .273$	
BMI <25 kg/m^2	1.304 (0.857–1.980) $P = .213$		**2.020 (1.182–3.460)** ***P* = .009**	**1.912 (1.117–3.273)** ***P* = .018**
CRP >5 mg/L	0.826 (0.535–1.279) $P = .391$		0.864 (0.488–1.531) $P = .616$	

5-ASA, 5-aminosalicylic acid; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; NA, not applicable; TNF, tumor-necrosis factor.
Significant values are depicted in bold.

Supplementary Table 3. Patient Characteristics at Initiation of Index Therapy in the Bionaive Patients

	Vedolizumab (n = 54)	Other therapies (n = 83)	*P* value
Female (%)	31/54 (57.4)	39/83 (47.0)	.233
Median (IQR) age at start of index therapy, *y*	38.0 (26.0–53.3)	40.0 (32.0–50.0)	.688
Median (IQR) disease duration at start of index therapy, *mo*	69.3 (10.9–144.4)	32.1 (12.9–96.7)	.221
Median (IQR) total Mayo score	8.0 (7.0–9.0)	8.0 (7.0–10.0)	.650
Endoscopic Mayo subscore (%) Mayo 2 Mayo 3	34/54 (63.0) 20/54 (37.0)	46/83 (55.4) 37/83 (44.6)	.382
Median (IQR) weight, *kg*	70.0 (61.0–77.0)	70.0 (60.0–84.0)	.188
Median (IQR) length, *m*	1.70 (1.64–1.76)	1.72 (1.66–1.78)	.250
Median (IQR) BMI, kg/m^2	23.4 (20.5–25.8)	24.4 (20.9–28.1)	.216
Median (IQR) C-reactive protein, *mg/L*	2.3 (0.7–6.7)	1.8 (0.6–5.4)	.456
Median (IQR) hemoglobin, *g/dL*	13.8 (12.9–14.8)	14.1 (12.9–14.9)	.562
Median (IQR) serum albumin, *g/L*	44.7 (42.8–46.8)	44.8 (42.6–46.8)	.945
More extensive disease before index (%)	14/54 (25.9)	27/83 (32.5)	.409
Smoking status Active Ex Never	4/53 (7.5) 17/53 (32.1) 32/53 (60.4)	6/80 (7.5) 32/80 (40.0) 42/80 (52.5)	.899
Extraintestinal manifestations (%)	4/54 (7.4)	7/83 (8.4)	1.000
Concomitant UC therapy (%)	38/54 (70.4)	55/83 (66.3)	.615
5-ASA	30/54 (55.6)	44/83 (53.0)	.770
Oral 5-ASA	17/54 (31.5)	25/83 (30.1)	.866
Rectal 5-ASA	34/54 (63.0)	30/83 (36.1)	**.002**
Corticosteroids	15/54 (27.8)	9/83 (10.8)	**.011**
Oral topical corticosteroids	11/54 (20.4)	9/83 (10.8)	.123
Rectal topical corticosteroids	10/54 (18.5)	14/83 (16.9)	.804
Oral systemic corticosteroids	0/54 (0.0)	0/83 (0.0)	1.000
Intravenous corticosteroids	6/54 (11.1)	33/83 (39.9)	**< .001**
Immunosuppressants	6/54 (11.1)	33/83 (39.8)	**< .001**
Thiopurines	0/54 (0.0)	0/83 (0.0)	1.000
Methotrexate			
Previous UC treatment (%)	54/54 (100.0)	81/83 (97.6)	.519
5-ASA	49/54 (90.7)	73/83 (88.0)	.609
Oral 5-ASA	51/54 (94.4)	78/83 (94.0)	1.000
Rectal 5-ASA	51/54 (94.4)	82/83 (94.4)	.300
Corticosteroids	30/54 (55.6)	49/83 (59.0)	.687
Oral topical corticosteroids	30/54 (55.6)	11/83 (61.4)	.493
Rectal topical corticosteroids	24/54 (44.0)	50/83 (60.2)	.070
Oral systemic corticosteroids	1/54 (1.9)	3/83 (3.6)	1.000
Intravenous corticosteroids	23/54 (52.6)	38/83 (45.8)	.713
Immunosuppressants	23/54 (42.6)	38/83 (45.8)	.713
Thiopurines	0/54 (0.0)	0/83 (0.0)	1.000
Methotrexate	1/54 (1.9)	0/83 (0.0)	.394
Cyclosporine	0/54 (0.0)	0/83 (0.0)	1.000
Tacrolimus			

5-ASA, 5-aminosalicylic acid; BMI, body mass index; IQR, interquartile range; UC, ulcerative colitis.