The Real-World Effectiveness and Safety of Ustekinumab in the Treatment of Crohn's Disease: Results From the SUCCESS Consortium

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INTRODUCTION: **We evaluated the real-world effectiveness and safety of ustekinumab (UST) in patients with Crohn's disease (CD).**

METHODS: **This study used a retrospective, multicenter, multinational consortium of UST-treated CD patients. Data included patient demographics, disease phenotype, disease activity, treatment history, and concomitant medications. Cumulative rates of clinical, steroid-free, endoscopic, and radiographic remissions were assessed using time-to-event analysis, and clinical predictors were assessed by using multivariate Cox proportional hazard analyses. Serious infections and adverse events were defined as those requiring hospitalization or treatment discontinuation.**

RESULTS: **A total of 1,113 patients (51.8% female, 90% prior antitumor necrosis factor exposure) were included, with a median follow-up of 386 days. Cumulative rates of clinical, steroid-free, endoscopic, and radiographic remissions at 12 months were 40%, 32%, 39%, and 30%, respectively. Biologic-naive patients achieved significantly higher rates of clinical and endoscopic remissions at 63% and 55%, respectively. On multivariable analyses, prior antitumor necrosis factor (hazard ratio, 0.72; 95% confidence interval, 0.49–0.99) and vedolizumab exposure (hazard ratio, 0.65; 95% confidence interval, 0.48–0.88) were independently associated with lower likelihoods of achieving endoscopic remission. In patients who experienced loss of remission, 77 of 102 (75%) underwent dose optimization, and 44 of 77 (57%) achieved clinical response. An additional 152 of 681 patients (22.3%) were dose-optimized because of primary nonresponse incomplete response to UST, of whom 40.1% (61 of 152) responded. Serious infections occurred in 3.4% of patients while other noninfectious adverse events (lymphoma [n = 1], arthralgia [n = 6], rash [n = 6], headache [n = 3], hepatitis [n = 3], hair loss [n = 3], neuropathy [n = 1], and vasculitis [n = 1]) occurred in 2.4% of patients.**

DISCUSSION: **UST represents a safe and effective treatment option for CD, with 40% of patients from a highly refractory cohort achieving clinical remission by 12 months. The greatest treatment effect of UST was seen in biologic-naive patients, and dose escalation may recapture clinical response.**

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory condition, which has the potential to affect the entirety of the gastrointestinal tract (1). Tumor necrosis factor alpha (TNF-α) antagonists have been the mainstay of therapy in patients with moderate-to-severe disease activity, with demonstrated efficacy on clinical, endoscopic, and histologic parameters (2,3). However, their use may be limited because of lack of response or loss of response and carry the potential for serious adverse events including opportunistic infections and malignancies (3,4). The development of other biologic agents in recent years has offered not only the prospect of additional therapeutic options but also the potential to avoid some of the risks and side effects commonly associated with TNF-α antagonists (5).

Ustekinumab (UST) is the first and only clinically available biologic agent targeting the p40 subunit of interleukin-12 and interleukin-23. The UNITI-IMUNITI randomized controlled trials (RCTs) demonstrated efficacy and safety of UST in both induction and maintenance therapies for patients with moderately to severely active CD, independent of their prior response to TNF-α antagonists (6). The approval of UST provided a much needed expansion to the current armamentarium of therapeutic options for CD. However, data on real-world effectiveness and safety remain limited. This multicenter, multinational cohort aimed to examine the effectiveness and safety of UST and to identify the predictors of treatment response for patients with CD in routine clinical practice.

METHODS

Study design

We performed a retrospective review of the IBD Health Outcomes Consortium substudy group (SUCCESS), a multicenter consortium of patients with IBD treated with UST. Detailed data for the consortium have been previously published (7,8). IRB approval was obtained at each respective site for ongoing data collection and transfer to create the consortium. Patients at each site were identified through a review of electronic medical records and/or examination of infusion center records. Retrospective data collection was performed at each site using a standardized data collection form between May 1, 2014, and March 2019, and ultimately, all deidentified data were transferred to the coordinating site for analysis. The SUCCESS substudy group data set was restricted to patients with CD treated with on-label UST after approval in September 2016. The study results are reported in accordance with the Strengthening and Reporting of Observational Studies in Epidemiology guidelines for cohort studies (9).

Variables

Data were collected on variables of interest to include patient characteristics (sex, age at both diagnosis and UST initiation, body mass index, and smoking status), disease characteristics (disease duration, prior hospitalizations, prior surgeries, extraintestinal manifestations, and phenotype based on the Montreal subclassifications for CD of A1 through A3, L1 through L4, B1 through B3, and the presence or absence of perianal disease) (10), treatment history (corticosteroids, immunomodulators, TNF-α antagonists, α4β7-integrin or α4-integrin inhibitors), treatment duration, and reason for discontinuation. Variables of interest specific to UST included disease activity at baseline (clinical severity based on chart review and physician's global assessment, and any endoscopic and radiographic assessments in the 12 weeks before UST initiation), date of initial UST infusion, and concurrent therapies at the time of UST initiation (corticosteroids and/or immunomodulators). Follow-up assessments including clinical evaluations, laboratory studies, and endoscopic and radiographic assessments were also recorded.

Participants

Patients were included in the analysis if they met the following criteria: (i) confirmed diagnosis of CD based on clinical, endoscopic, radiographic, and/or histologic data; (ii) active clinical symptoms attributed to CD before initiation of UST; and (iii) at least one clinical, endoscopic, and/or radiographic follow-up after initiation of UST. We excluded patients treated with subcutaneous injection induction dosing as opposed to intravenous (IV) induction dosing, those treated with off-label UST before US Food and Drug Administration (FDA) approval, those with CD of the ileoanal pouch, and those in whom UST was started for an indication other than CD (e.g., psoriasis).

Outcomes

Our primary effectiveness outcomes of interest were cumulative rates of clinical and endoscopic remissions at 6 and 12 months. Secondary effectiveness outcomes included cumulative rates of corticosteroid-free remission, radiographic remission, loss of remission, and durable remission (achievement of clinical remission and the absence of loss of remission at the last follow-up). Clinical remission was defined as complete resolution of all CD-related symptoms as assessed by the site providers in routine practice, and endoscopic remission was defined by the absence of ulcers and/or erosions, which was confirmed by a rereview of endoscopic reports. Endoscopic remission outcome analyses were limited to patients with documented mucosal ulcers at baseline before initiation of UST. Achievement of corticosteroid-free remission (in those patients who were on either budesonide or prednisone at the time of UST initiation) was defined as having completely tapered from corticosteroids, achieving clinical remission, and having no documented repeat corticosteroid prescription within the first 4 weeks of completing the taper. Radiographic remission was defined as the absence of imaging features of active inflammation based on interpretation by a local radiologist, using the available baseline imaging as a comparator, with confirmation by a rereview of imaging reports. Deidentified endoscopy and radiographic reports were reviewed by the coordinating site investigator (P.S.D.) to confirm the accuracy of structured coding performed by sites. Loss of remission was defined as the recurrence of CD-related symptoms, need for surgery, need to switch therapy, or need to modify UST dosing in patients achieving clinical remission. Durable remission was defined as the achievement of clinical remission and maintenance of clinical remission through the end of the follow-up period.

Safety outcomes included infectious and noninfectious adverse events which required antibiotics, hospitalization, and/or therapy discontinuation or interruption. Serious infections were specifically defined as those requiring hospitalization and/or therapy discontinuation. No deaths were observed during the period of observation of treatment exposure.

Statistical analysis

Statistical analyses were performed using SPSS. Continuous variables were presented as means (and SDs) or medians (and

Table 1. Patient demographics

Demographics based on prior biologic exposure status, n; median follow-up in d (IQR)	All UST-treated, n = 1,113; 386 d (204–562)	Biologic-naive, n = 106; 340 d (200–545)	1 biologic, n = 289; 407 d (205–549)	2 biologics, n = 437; 368 d (194–546)	3 biologics, n = 187; 469 d (235–706)	4 biologics, n = 94; 444 d (223–603)
Age diagnosis, median yr (IQR)	23 (16–33)	30 (22.8–44.3)	26 (19–40)	21 (15–31)	20 (14–30)	18.5 (13–27.3)
Age at UST initiation, median yr (IQR)	38 (28–52)	48 (32–52)	40 (28–55)	37 (26–49)	38 (28–51)	34 (26–45.3)
Disease duration, median yr (IQR)	11 (5–20)	5 (1–26)	9 (4–18)	12 (6–19)	15 (8–22)	13 (9–20)
BMI (kg/m^2), median (IQR)	24.4 (21.3–28.3)	26 (21.2–28.1)	24.9 (21.8–30)	23.3 (21–28.2)	23.5 (21.1–30)	24.9 (21.7–28)
C-reactive protein, median (IQR)	1.7 (0.5–6.7)	1.1 (0.1–3.7)	1.2 (0.4–5.1)	2.0 (0.5–8.6)	2.6 (0.7–6.2)	1.9 (0.5–8.9)
Albumin, median (IQR)	4.0 (3.5–4.3)	4.1 (3.5–4.3)	4.2 (3.7–4.3)	4.0 (3.5–4.3)	3.8 (3.4–4.2)	3.9 (3.5–4.1)
Female sex, n (%)	576 (51.8)	36 (34)	154 (53.3)	217 (49.7)	122 (65.2)	47 (50.0)
Never smoker, n (%)	835 (75)	80 (75.5)	222 (76.8)	314 (71.9)	140 (74.9)	79 (84.0)
Prior CD-related hospitalization, n (%)	805 (72)	52 (49.1)	180 (62.3)	339 (77.6)	153 (81.8)	81 (86.2)
Disease extent[a]						
L1, n (%)	217 (19.5)	32 (30.2)	73 (25.3)	74 (16.9)	23 (12.3)	15 (16.0)
L2, n (%)	173 (15.5)	12 (11.3)	57 (19.7)	72 (16.5)	21 (11.2)	11 (11.7)
L3, n (%)	723 (65.0)	62 (58.5)	159 (55.0)	291 (66.6)	143 (76.5)	68 (72.3)
Stricturing/penetrating disease history, n (%)	678 (60.9)	48 (45.3)	163 (56.4)	272 (62.2)	134 (71.7)	61 (64.9)
Perianal disease, n (%)	413 (37.1)	22 (20.8)	74 (25.6)	200 (45.8)	70 (37.4)	47 (50.0)
Baseline ulceration, n (%)	915 (82.2)	92 (86.8)	238 (82.4)	353 (80.8)	154 (82.4)	78 (83.0)
Prior surgery, n (%)	658 (59.1)	34 (32.1)	135 (46.7)	284 (65.0)	133 (71.1)	72 (76.6)
Prior *Clostridioides difficile*, n (%)	181 (16.3)	8 (7.5)	30 (10.4)	82 (18.8)	42 (22.5)	19 (20.2)
Prior malignancy, n (%)	94 (8.4)	16 (15.1)	33 (11.4)	25 (5.7)	14 (7.5)	6 (6.4)
Prior 5-ASA, n (%)	739 (66.4)	28 (26.4)	194 (67.1)	310 (70.9)	142 (75.9)	65 (69.1)
Prior steroid, n (%)	983 (88.3)	78 (73.6)	241 (83.4)	394 (90.2)	178 (95.2)	92 (97.9)
Prior thiopurine, n (%)	838 (75.3)	40 (37.7)	193 (66.8)	349 (79.9)	167 (89.3)	89 (94.7)
Prior methotrexate, n (%)	470 (42.2)	18 (17.0)	92 (31.8)	183 (41.9)	114 (61.0)	63 (67.0)
Prior anti-TNF, n (%)	987 (88.7)	0 (–)	269 (93.1)	437 (100)	187 (100)	94 (100)
Prior PNR to anti-TNF, n (%)	385 (34.6)	0 (–)	64 (22.1)	169 (38.7)	101 (54.0)	51 (54.3)
Last anti-TNF failure						
PNR, n (%)	287 (25.8)	0 (–)	56 (19.4)	122 (27.9)	73 (39.0)	36 (38.3)
LOR, n (%)	268 (26.1)		79 (27.3)	101 (23.1)	64 (34.2)	24 (25.5)
LOR + escalation, n (%)	251 (22.6)		59 (20.4)	144 (33.0)	28 (15.0)	20 (21.3)
Intolerance, n (%)	189 (17.0)		83 (28.7)	70 (16.0)	22 (11.8)	14 (14.9)
Drug monitoring with last anti-TNF, n (%)	616 (55.3)	0 (–)	171 (59.2)	280 (64.1)	94 (50.3)	69 (73.4)
Prior vedolizumab, n (%)	265 (23.8)	0 (–)	20 (6.9)	69 (15.8)	82 (43.9)	94 (100)
Concomitant IS, n (%)						
None	485 (43.6)	52 (49.1)	150 (51.9)	192 (44.0)	67 (35.8)	24 (25.5)
Steroids alone, n (%)	254 (22.8)	30 (28.3)	69 (23.9)	91 (20.8)	41 (21.9)	23 (24.5)
IM alone, n (%)	191 (17.2)	14 (13.2)	44 (15.2)	77 (17.6)	39 (20.9)	17 (18.1)
Steroids + IM, n (%)	183 (16.4)	10 (9.4)	26 (9.0)	77 (17.6)	40 (21.4)	30 (31.9)

5-ASA, 5-aminosalicylate; anti-TNF, antitumor necrosis factor; BMI, body mass index; CD, Crohn's disease; IM, immunomodulator; IQR, interquartile range; IS, immunosuppression; LOR, loss of response; PNR, primary nonresponse; UST, ustekinumab.
[a]Based on the Montreal classification: L1 = ileal; L2 = colonic; and L3 = ileocolonic.

Table 2. Cumulative rates of clinical, endoscopic, and steroid-free remissions with UST at 6 and 12 mo

	Cumulative rates	Entire cohort	0 biologics	1 biologic	2 biologics	3 biologics	4 biologics
Clinical remission	6-mo	21%	25%	24%	21%	14%	18%
	12 mo	40%	63%	43%	40%	26%	34%
Endoscopic remission[a]	6 mo	17%	22%	20%	17%	14%	15%
	12 mo	39%	55%	37%	31%	26%	24%
Steroid-free remission[b]	6 mo	15%	19%	19%	19%	10%	8%
	12 mo	32%	62%	35%	37%	20%	15%

[a]Endoscopic remission—evaluated in those who had available endoscopy with ulcerations at baseline.
[b]Steroid-free remission—able to taper off steroids with no repeat steroid prescription within 4 weeks of tapering off and achieved clinical remission.

interquartile ranges [IQRs]) if the distribution was skewed, and categorical or binary variables were presented as proportions or percentages. For the comparison of baseline continuous variables, we used the independent sample Student *t* test (2 group comparisons) or 1-way ANOVA with Bonferroni correction (3 or more group comparisons), and for the comparison of baseline binary variables we used the Pearson χ^2 or Fisher exact test. Primary and secondary effectiveness outcomes were described quantitatively as cumulative rates using Kaplan-Meier survival and time-to-event analyses.

Proportional hazard analyses (Cox regression) were performed to identify factors independently associated with treatment outcomes. Baseline variables from the univariable analyses with a *P* value of < 0.20 were then fitted, and a backward model selection approach was taken where the variable with the highest *P* value was sequentially selected until all remaining variables in the model had a *P* value of <0.05. An assessment of interaction terms was then performed, and interactions were retained if they had a *P* value of <0.05. Hazard ratios (HR) with 95% confidence interval (CI) are presented for factors where a HR of < 1 indicated that a factor was associated with a reduced probability for achieving the outcome and a HR of > 1 indicated that a factor was associated with an increased probability for achieving the outcome.

Study sponsor
Janssen provided funding for statistical support to analyze the data and scientific input on data interpretation. Janssen and associated employees did not have access to any of the data, and all data analyses were performed at the University of California, San Diego, by SUCCESS Consortium substudy investigators or statisticians.

RESULTS

Demographics
A total of 1,113 patients with CD treated with UST were included in this analysis, with a median follow-up duration of 386 days (IQR, 204–562) (Table 1). Five hundred seventy-six patients were female (51.8%), with a median age of 38 years (IQR, 28–52) and median disease duration of 11 years (IQR, 5–20). Nine hundred eighty-seven patients (88.7%) had previously been exposed to anti-TNF-α therapy. Seven hundred eighteen patients (65%) had a prior exposure to 2 or more biologics in the past. A history of stricturing or penetrating intestinal complications was present in 678 patients (61%), and 413 patients (37%) had a history of perianal disease. A total of 658 patients (59%) had previously required intestinal surgery for their CD. Most patients (82%) had documented ulcerations on baseline endoscopy before initiating UST. The patients without documented ulceration on baseline endoscopy before initiating UST started therapy for active symptoms with elevated C-reactive protein (CRP). At the time of UST initiation, 374 patients (33.6%) were on combination therapy with an immunomodulator (azathioprine, 6-mercaptopurine, or methotrexate), and 437 patients (39.3%) were on concomitant corticosteroids.

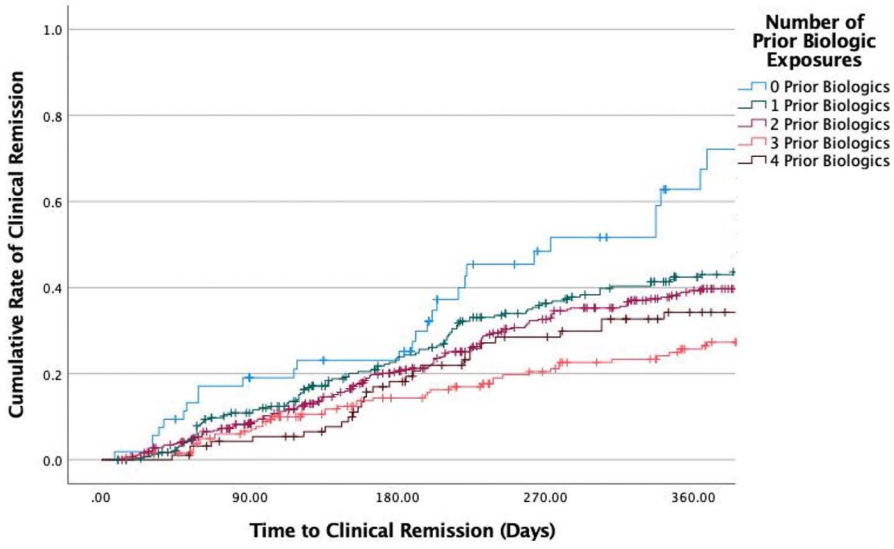
Treatment response
At 6 and 12 months, cumulative rates of clinical remission for the entire cohort were 21% and 40%, respectively (Table 2). Cumulative rates of steroid-free remission at 6 and 12 months were 15% and 32%, respectively. In patients with documented baseline ulcerations, overall cumulative rates of endoscopic remission at 6 and 12 months were 17% and 39%, respectively. Radiographic remission was achieved in 19% and 30% of patients at 6 and 12 months, respectively. Overall proportional event rates for outcomes of interest are given in Table 3. Biologic-naive patients experienced the highest cumulative rates of both clinical and endoscopic remissions after 12 months at 63% and 55%, respectively. In general, cumulative rates of clinical and endoscopic remissions were progressively lower with each additional prior biologic exposure (Figure 1). UST treatment also resulted in a significant reduction in CRP. A total of 183 patients had an

Table 3. Overall event rates for outcomes of interest

Outcome of interest	Event rates
Clinical remission	432/1,113 (38.8%)
Steroid-free[a]	259/437 (59.3%)
Steroid-free remission[a]	123/437 (28%)
Endoscopic remission[b]	304/671 (45.2%)
Radiographic remission	61/190 (32.1%)
Dose escalation for nonresponse or incomplete response	152/681 (22.3%)
Loss of remission	102/432 (23.6%)
Surgery	169/1,113 (15.2%)

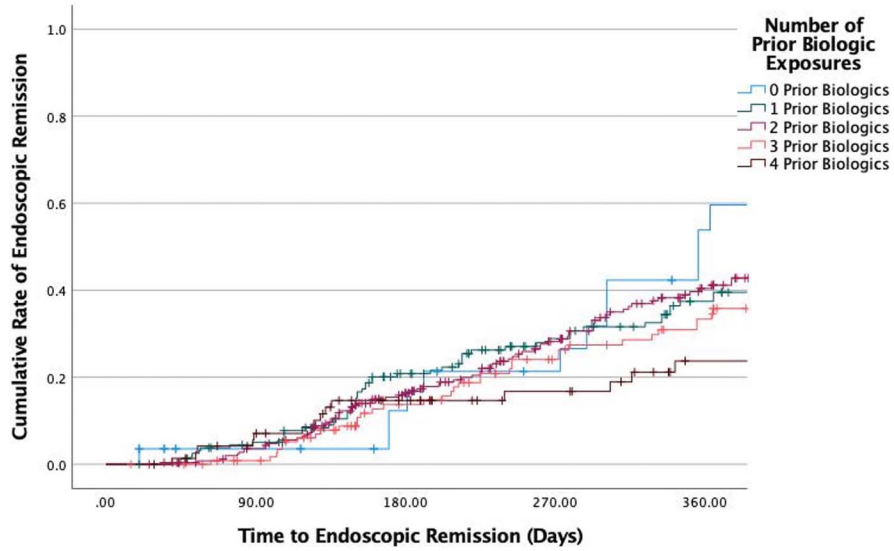
[a]Among those on steroids at baseline, steroid-free—able to taper off steroids with no repeat steroid prescription within 4 weeks of tapering off, but may or may not have achieved clinical remission; steroid-free remission—able to taper off steroids with no repeat steroid prescription within 4 weeks of tapering off and achieved clinical remission.
[b]Endoscopic remission—evaluated in those who had available endoscopy with ulcerations at baseline.

a



0 Prior Biologics	Cumulative Events	20	24	44	54
	Remaining Cases	82	74	32	14
1 Prior Biologic	Cumulative Events	30	62	90	103
	Remaining Cases	234	177	133	96
2 Prior Biologics	Cumulative Events	36	82	121	141
	Remaining Cases	372	279	206	152
3 Prior Biologics	Cumulative Events	13	25	34	42
	Remaining Cases	165	132	111	91
4 Prior Biologics	Cumulative Events	4	16	24	28
	Remaining Cases	87	68	53	39

b



0 Prior Biologics	Cumulative Events	2	7	11	24
	Remaining Cases	48	39	29	14
1 Prior Biologic	Cumulative Events	8	31	41	50
	Remaining Cases	148	106	79	60
2 Prior Biologics	Cumulative Events	9	39	61	81
	Remaining Cases	240	174	123	76
3 Prior Biologics	Cumulative Events	1	15	25	35
	Remaining Cases	114	86	68	52
4 Prior Biologics	Cumulative Events	5	10	11	14
	Remaining Cases	63	50	40	29

Figure 1. Cumulative rates of clinical and endoscopic remissions based on prior biologic exposure.

Table 4. Predictors of clinical and endoscopic remission

	Univariate Cox proportional hazard ratio		Multivariate Cox proportional hazard ratio (with backward model selection)	
	HR	95% CI	aHR	95% CI
Clinical remission				
Disease duration	0.985	0.976–0.994	0.993	0.983–1.002
Sex	0.877	0.726–1.059		
Prior hospitalization	0.710	0.577–0.872		
Albumin	1.323	1.098–1.595	**1.226**	**1.018–1.476**
Stricturing or penetrating disease	0.679	0.562–0.821	0.828	0.662–1.037
Perianal disease	0.738	0.602–0.904	0.836	0.654–1.068
Prior surgery	0.631	0.522–0.763	0.820	0.644–1.045
Prior anti-TNF	0.538	0.412–0.703	**0.553**	**0.415–0.737**
Prior vedolizumab	0.817	0.650–1.027	0.849	0.658–1.097
Concomitant IM	0.752	0.613–0.922		
Endoscopic remission				
Disease duration	0.991	0.981–1.001	0.991	0.980–1.001
Sex	1.195	0.953–1.499		
Ever smoker	1.271	0.960–1.685		
Prior hospitalization	0.838	0.646–1.087		
Albumin	1.410	1.123–1.770	**1.301**	**1.037–1.632**
Stricturing or penetrating disease	0.825	0.657–1.037		
Perianal disease	0.666	0.522–0.850		
Prior surgery	0.803	0.635–1.014		
Prior anti-TNF	0.670	0.472–0.952	**0.744**	**0.617–0.907**
Prior vedolizumab	0.671	0.510–0.882	**0.683**	**0.505–0.922**
Concomitant IM	0.512	0.402–0.653		

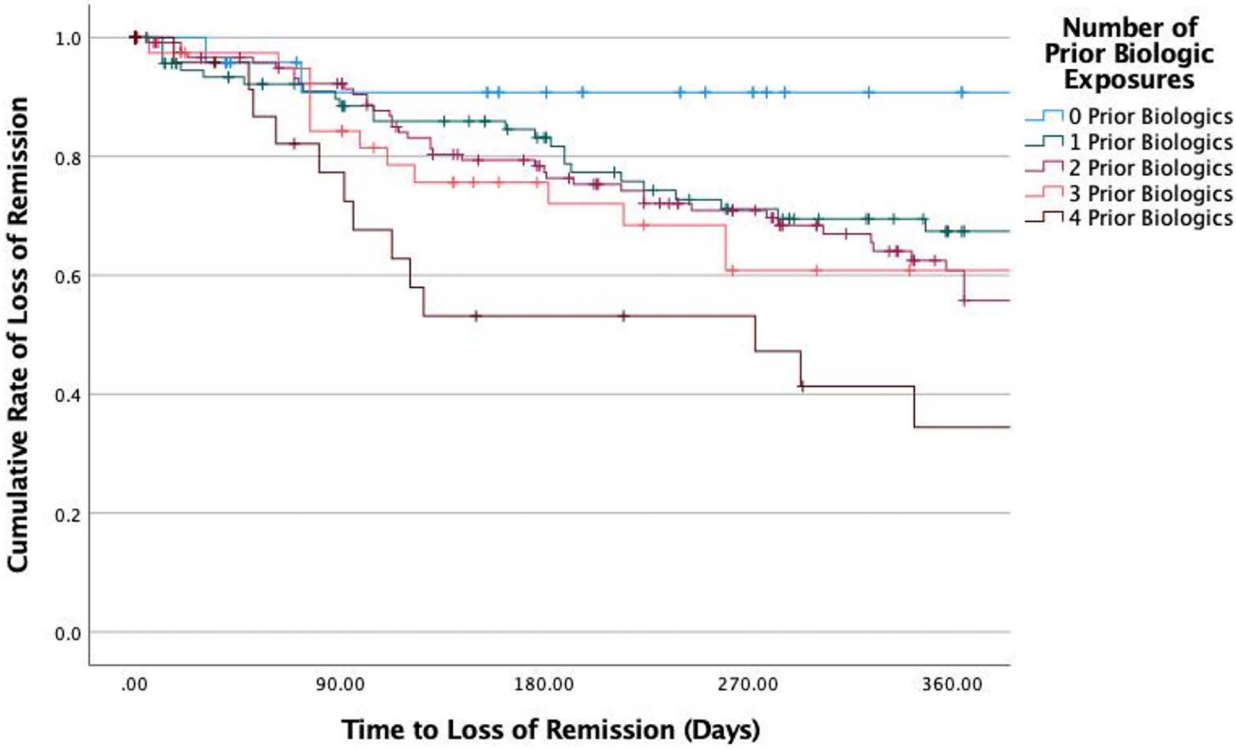
aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; IM, immunomodulator; TNF, tumor necrosis factor. Bold values are statistically significant after adjustment.

elevated baseline CRP level to >5 mg/L (median, 12.8), with 59 (32%) of them achieving normalization in CRP by the time of their first follow-up assessment.

Clinical predictors of treatment response

Previous exposure to TNF-α antagonist therapy was associated with a lower probability of achieving clinical remission (HR, 0.54; 95% CI, 0.41–0.70), steroid-free remission (HR, 0.36; 95% CI, 0.22–0.58), endoscopic remission (HR, 0.67; 95% CI, 0.47–0.95), and radiographic remission (HR, 0.53, 95% CI, 0.30–0.94) on univariable analysis (Table 4). On multivariable analysis, prior TNF-α antagonist exposure remained significantly associated with a reduced probability of achieving clinical remission (adjusted hazard ratio [aHR] 0.55; 95% CI, 0.42–0.74), steroid-free remission (aHR, 0.45; 95% CI, 0.20–0.59), and radiographic remission (aHR, 0.35; 95% CI, 0.16–0.74) (Table 4), after adjusting for disease duration, albumin, history of stricturing or penetrating disease, perianal disease history, prior surgery, and prior vedolizumab use. Previous exposure to a TNF-α antagonist was also significantly inversely associated with endoscopic remission in the multivariate analysis (aHR, 0.74; 95% CI, 0.62–0.91) after adjusting for disease duration and albumin. Prior vedolizumab exposure was significantly associated with a lower probability of endoscopic remission (aHR, 0.65; 95% CI, 0.48–0.88) in multivariate models, but the same was not true for clinical remission, steroid-free remission, or radiographic remission. The few patients (n = 50) who were completely naive to all immunosuppressive therapies (including thiopurines, methotrexate, anti-TNF-α, and vedolizumab) were significantly more likely to achieve clinical remission (HR, 2.25; 95% CI, 1.60–3.17), but not steroid-free (HR, 1.73; 95% CI, 0.90–3.31) or endoscopic (HR, 1.56; 95% CI, 0.97–2.52) remission.

The probability of achieving clinical remission (HR per biologic used, 0.77; 95% CI, 0.71–0.85), endoscopic remission (HR per biologic used, 0.81; 95% CI, 0.73–0.90), and steroid-free remission (HR per biologic used, 0.74; 95% CI, 0.63–0.87) was all significantly reduced with each additional prior biologic exposure. The indication for previous anti-TNF-α discontinuation was also associated with the likelihood of future response to UST. In patients who discontinued TNF-α antagonists because of primary nonresponse, the probability of clinical remission with UST was reduced (HR, 0.72; 95% CI, 0.57–0.91), whereas those who discontinued TNF-α antagonist because of intolerance experienced higher probability of clinical remission (HR, 1.45; 95% CI 1.14–1.84). The indication for prior TNF-α antagonist discontinuation did not significantly affect rates of steroid-free or endoscopic remission with UST.



0 Prior Biologics	Cumulative Events	4	4	4	4
	Remaining Cases	36	32	23	16
1 Prior Biologic	Cumulative Events	10	14	22	24
	Remaining Cases	72	58	43	28
2 Prior Biologics	Cumulative Events	9	25	31	40
	Remaining Cases	104	76	58	34
3 Prior Biologics	Cumulative Events	6	10	13	13
	Remaining Cases	32	20	15	13
4 Prior Biologics	Cumulative Events	5	10	11	13
	Remaining Cases	16	10	8	5

Figure 2. Durable remission with UST based on prior biologic exposure. UST, ustekinumab.

Outcomes for dose optimization

Rates of durable remission, defined as achieving and maintaining clinical remission without loss of remission throughout the duration of follow-up, were significantly reduced based on the number of prior biologic exposures, even after adjusting for disease duration, albumin, history of stricturing or penetrating disease, prior perianal disease, and history of bowel surgery (aHR per biologic exposure, 0.829; 95% CI, 0.74–0.94) (Figure 2).

Cumulative rates of loss of remission were progressively higher in patients with each successive prior biologic exposure, such that those who were biologic-naive experienced only a 9% cumulative loss of remission rate over 6 months while rates rose to 18%, 24%, 28%, and 47% in patients who had exposure to 1, 2, 3, or 4 prior biologics, respectively ($P < 0.001$ for linear trend). Of the 681 patients who experienced either primary nonresponse or incomplete response (<50% reduction in symptom activity), 152 (22.3%) underwent dose optimization with UST, which produced a clinical response (>50% reduction in symptom activity) in 61 patients (40.1%). Strategies for dose optimization included IV reintroduction alone (41.2% response), IV reintroduction plus every 4-week dosing interval (47.5% response), and increasing the interval to every 4-week dosing without IV reintroduction (36.8% response) (Table 5). For the 102 patients who lost remission during the follow-up period, 77 (76%) pursued dose optimization, yielding a response in 44 patients (57%). Dose optimization strategies with IV reintroduction alone, IV reintroduction plus increase to every 4-week dosing interval, or increased dose interval to every 4 weeks without IV reintroduction were similarly successful with 72.7%, 65%, and 50% achieving response, respectively (Table 5).

Safety outcomes

Therapy was well tolerated in most of the patients. Infectious complications (defined as requiring antibiotic therapy, hospitalization, or therapy discontinuation or interruption) were documented in 85 patients (7.6%) (Table 6), with serious infections occurring in only 3.4%. The most common infection (n = 28) was *Clostridiodes*

Table 5. Outcomes for UST dose optimization

	Patients with primary nonresponse or incomplete response, n = 681		Patients with loss of remission, n = 102	
	Dose optimization		Dose optimization	
	Pursued	Responded	Pursued	Responded
Dose optimization, n (%)	152/681 (22.3)	61/152 (40.1)	77/102 (75.5)	44/77 (57.1)
IV reintroduction alone	17 (11.2)	7/17 (41.2)	11 (14.3)	8/11 (72.7)
IV reintroduction + every 4 wk UST	40 (26.3)	19/40 (47.5)	20 (26.0)	13/20 (65.0)
Every 4 wk UST alone	95 (62.5)	35/95 (36.8)	46 (59.7)	23/46 (50.0)

UST, ustekinumab.

difficile colitis, with nearly half (46%) of these patients having had a previous episode of C. difficile infection before UST treatment. A single patient developed lymphoma while on UST, although this patient had a documented history of lymphoma before initiating UST. Additional serious adverse events included joint pain (n = 6), rash (n = 6), headache (n = 3), hepatitis (n = 3), hair loss (n = 3), neuropathy (n = 1), and vasculitis (n = 1) (Table 6).

DISCUSSION

The efficacy of UST for induction and maintenance in CD has been well documented in RCTs (11,12). This large, multicenter consortium illustrated several key findings for UST in routine practice. First, within a highly refractory population of patients with CD, of whom 90% had at least one biologic exposure (65% with ≥2 biologic exposures), UST was effective in a considerable number of patients. Second, prior TNF antagonist exposure was found to significantly reduce the probability of achieving clinical, steroid-free, endoscopic, and radiographic remissions. Vedolizumab exposure was associated with a reduced likelihood of endoscopic remission, but not clinical remission. Third, dose optimization of UST in those with nonresponse or incomplete response and secondary loss of response was successful in capturing clinical response for a substantial number of patients. Finally, UST seemed to be safe and well-tolerated.

Efficacy data from IM-UNITI illustrated clinical remission rates of 53% up to week 44 (6). The lower clinical remission rates in our cohort as compared with IM-UNITI may be partially explained by the fact that a much larger proportion of patients in the IM-UNITI trial (50%) were biologic-naive, as compared with only 10% of our cohort. In addition, the aforementioned week 44 remission rates included an enriched population of patients who responded to induction. Clinical remission rates for the biologic-naive patients in our cohort were similar to those reported in the recent SEAVUE study, which compared UST with adalimumab for induction and maintenance therapy of CD, where 65% of UST-treated patients achieved clinical remission at 52 weeks (13). Real-world effectiveness data for UST-treated CD patients have documented clinical remission rates between 25% and 57% at 6 months and 28% and 64% at 12 months (14–19). Not surprisingly, clinical response rates are higher, approximating 46%–76% at 6 months and 42%–72% at 12 months (14,17,20–23). Clinical remission rates are quite variable between observational cohorts, with some of the highest rates documented at 57% and 64% at 26 and 52 weeks, respectively (18). Notably, in this same cohort, endoscopic remission rates were considerably lower at 16%. The variability in effectiveness data may reflect heterogeneous study populations for multiple factors including prior biologic exposure status, suboptimal correlation between clinical and endoscopic disease activity, use of different clinical disease activity indices between studies, definitions for remission, and the fact that most existing data were derived from smaller studies assessing off-label UST before its US FDA approval.

In addition to clinical remission, we documented objective parameters including cumulative rates of endoscopic and radiographic remission at 39% and 30% by 12 months, respectively. In a substudy of phase 3 RCTs for UST in CD, endoscopic remission (Simple Endoscopic Score Crohn's Disease ≤ 2) was achieved in 10.9% of subjects at week 44, with rates of mucosal healing (absence of mucosal ulceration) around 17% (24). In a head-to-head trial of UST vs adalimumab in biologic-naive patients with CD, endoscopic remission (Simple Endoscopic Score Crohn's Disease ≤ 3) was achieved in 28.5% of UST-treated patients at 52 weeks (13). Real-world cohorts have suggested endoscopic remission rates around 24% after 90 days and 27% at a median of 46 weeks of follow-up (14,25). In the absence of any widely accepted definition for endoscopic remission, variable definitions for endoscopic end points are often applied, making comparisons between studies difficult. The inclusion of cumulative rates of radiographic remission is unique to our study, which was achieved in approximately one-third of patients at 12 months. Another available report suggested that 26.7% of UST-treated patients achieved some form of objective remission (endoscopic or radiographic) at 12 months (14).

Although predictors of clinical response to TNF antagonists have been extensively reviewed, less is known of factors that may influence response to UST (6,7,26). In this study, we describe that prior TNF antagonist exposure was associated with a reduced probability of achieving clinical, steroid-free, endoscopic, and radiographic remissions. Multivariate models also suggested that prior vedolizumab exposure was associated with a lower likelihood of endoscopic remission, but not clinical, steroid-free, or radiographic remission. While these findings corroborate those of several additional observational cohorts (18,23,27–30), others have reported UST response as independent of any prior TNF antagonist exposure (21,22,25). Prior analysis of patients from the UNITI trials identified baseline factors associated with a higher probability of clinical remission with UST by week 16, including baseline albumin, absence of prior intestinal surgery, no prior TNF antagonist use, lack of actively draining fistula, and no smoking history (28). As a result, a clinical decision support tool was created with a goal of better positioning biologic therapy (28).

We also identified that remission rates were significantly associated with the *number* of previous biologics used. Biologic-naive patients achieved cumulative rates of clinical and endoscopic remissions of 63% and 55% at 12 months, respectively, with

Table 6. Rates of adverse events

Adverse event	No. of patients (n = 1,113)
Any infection[a]	85 (7.6%)
Clostridioides difficile colitis	28 (2.5%)
Community-acquired pneumonia	12 (1.1%)
Bacteremia	6 (0.5%)
Cellulitis	5 (0.4%)
Pharyngitis	5 (0.4%)
Abscess	4 (0.4%)
Urinary tract infection	3 (0.3%)
Aspergillus	3 (0.3%)
CMV colitis	2 (0.2%)
Dental infection	2 (0.2%)
Sepsis and ARDS	2 (0.2%)
Shingles	2 (0.2%)
Sinusitis	2 (0.2%)
Candida esophagitis	2 (0.2%)
Orchitis	1 (0.1%)
Otitis media	1 (0.1%)
Tuberculosis	1 (0.1%)
PJP pneumonia	1 (0.1%)
Vaginal candidiasis	1 (0.1%)
Viral enteritis	1 (0.1%)
Diverticulitis	1 (0.1%)
Lymphoma	1 (0.1%)
Hair loss	3 (0.3%)
Headache	3 (0.3%)
Hepatitis	3 (0.3%)
Hypersensitivity reaction	2 (0.2%)
Joint pain	6 (0.5%)
Neuropathy	1 (0.1%)
Rash	6 (0.5%)
Vasculitis	1 (0.1%)

ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; PJP, pneumocystis jirovecii.
[a]Defined as requiring antibiotics, hospitalization, or therapy discontinuation/interruption.

progressively lower rates of clinical (HR, 0.773), endoscopic (HR, 0.809), and steroid-free (HR, 0.737) remissions with each subsequent biologic exposure. We also discovered that the *reason* for prior TNF antagonist discontinuation may be associated with the probability of achieving clinical remission because those who discontinued TNF antagonists for intolerance responded to UST more favorably as compared with those with primary nonresponse. This is consistent with another review reporting a higher likelihood of response to UST when anti-TNF therapy was discontinued for intolerance as opposed to lack of or loss of response (OR, 2.59; 95% CI 1.13–6.30) (27). However, others yet have found that primary nonresponse to anti-TNF predicted a higher probability for short-term response, hypothesizing that the main driver of inflammation in these patients was not TNF-mediated and may benefit from some other mechanism of action (23).

Although outcomes of dose escalation have been described for TNF antagonist and vedolizumab-treated patients (31–33), experience with UST remains scarce. In this study, we identified that dose optimization of UST was effective in attaining clinical response for 40% of patients with primary nonresponse or incomplete response and 57% of those with secondary loss of response, supporting the results of other reviews documenting effectiveness of dose escalation in recapturing response or remission in 40%–73% and 28%–53% of patients, respectively (20–22,34–36). Altogether, these findings suggest that patients who experience either primary nonresponse or secondary loss of response to UST at the US FDA-approved dose may benefit from dose optimization by increasing the interval to every 4 or 6 weeks and, in some cases, by repeating IV induction.

In addition to demonstrating effectiveness in this large real-world cohort, UST also seemed to have a favorable safety profile consistent with findings from available clinical trial data (6,11,12,37). A pooled analysis of 6 phase 2/3 CD and ulcerative colitis studies (n = 2,574) described rates of serious infections and malignancies at 5.02 (95% CI, 4.02–6.19) and 0.40 (95% CI, 0.16–0.83) per 100 patient-years, respectively, both of which were similar to placebo (37). Further supporting the safety of UST in the longer term, the IM-UNITI long-term extension reported on safety outcomes through 5 years of follow-up (38). Overall, the results again demonstrated adverse event rates similar to placebo, with rates of SAEs at 19.3 vs 17.5, serious infections at 3.9 vs 3.4, and malignancies at 1.7 vs 1.06 per 100 person-years when comparing placebo with UST, respectively. Our rates of serious infection and adverse events are, therefore, in line with long-term safety registration studies. *Clostridiodes difficile* infection was noted in 28 patients (2.5%), although it is important to highlight that many patients with IBD may have an inherently increased genetic susceptibility to *Clostridiodes difficile* infection (39).

This study has several strengths. With the inclusion of 1,113 patients, this is the largest observational cohort published to date. Inclusion of patients from multiple centers spanning a broad geographic distribution and region provides broader representation, improving generalizability of results. In addition, only patients with CD initiating UST after US FDA approval were included, which helps to standardize treatment because most other effectiveness data originate from off-label experiences, leading to variable induction and maintenance dosing schemes. In addition, we reported objective outcomes including endoscopic remission, which is an increasingly recognized therapeutic target given its correlation with more favorable long-term outcomes, and radiographic remission, for which there are currently limited data. Finally, these results provide valuable information on outcomes for dose optimization with UST, which were previously sparse.

There are some limitations to note. The biologic-naive subgroup is a smaller subset of the overall population, and demographics would suggest that it is a group of patients with less complicated disease. Our estimates for effectiveness in this subgroup are supported by the SEAVUE trial, but differences in demographics should be considered when interpreting data. With the retrospective nature of this study and practice-based differences in reporting patterns, validated scoring systems for endoscopic and radiographic outcomes could not be applied in the assessment of objective response. Although this may be a perceived limitation, it is more reflective of routine clinical practice. The subjectivity of individual providers performing endoscopic measurements of

disease activity at variable time points may bias endoscopic outcomes data and, thus, may also present a limitation. In addition, retrospective analysis impairs our ability to assess clinical response in a more rigorous fashion at predefined time points and rely on a chart review to apply clinical disease indices. The fact that most of the data were procured from academic centers potentially weakens generalizability, and although there is representation from multiple geographic regions, there is some inherent referral bias.

In conclusion, this large multicenter retrospective cohort illustrated that UST was effective in achieving clinical, steroid-free, endoscopic, and radiographic remissions in a highly refractory population of patients with CD after 12 months of follow-up. Prior TNF antagonist exposure was associated with a reduced likelihood of achieving clinical, endoscopic, steroid-free, or radiographic remission while previous vedolizumab exposure was associated with a reduced probability of achieving endoscopic remission. Dose optimization of UST recaptured clinical response in a significant number of patients with primary nonresponse or secondary loss of response. Although this seems to support the concept of dose optimization to achieve maximal response, additional study is needed to confirm these findings. The favorable safety profile of UST was also supported in this cohort. These data provide important insight into the real-world effectiveness and safety of UST in CD and enhance our understanding of how best to position various biologic therapies.

CONFLICTS OF INTEREST

Guarantor of the article: Parambir S. Dulai, MD.

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Study Highlights

WHAT IS KNOWN

- ✓ Ustekinumab (UST) represents an effective treatment option for moderately to severely active Crohn's disease.
- ✓ Data on the effectiveness and safety of UST in the real-world clinical setting are limited by small cohort sizes and focus on off-label experiences.

WHAT IS NEW HERE

- ✓ In the largest available cohort of UST-treated patients (n = 1,113), of whom 90% had prior biologic exposure, cumulative rates of clinical, endoscopic, steroid-free, and radiographic remissions were documented at 40%, 39%, 32%, and 30%, respectively, after 12 months of treatment.
- ✓ Biologic-naive patients experienced significantly higher rates of both clinical (63%) and endoscopic (55%) remissions at 12 months compared with those with prior biologic exposure.
- ✓ Dose optimization of UST successfully captured clinical response in 40% of patients with primary nonresponse or incomplete response and 57% of those with secondary loss of response.
- ✓ Serious infections requiring hospitalization or treatment discontinuation occurred in 3.4% of patients, with noninfectious serious adverse events occurring in 2.3% of patients.

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