

ORIGINAL ARTICLE

Treatment patterns, persistence with therapy, and outcomes of ustekinumab in Crohn's disease: Real-world data analysis

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Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic gastrointestinal disorders affecting an estimated 1.5 million Americans, 2.2 million people in Europe, and several hundred thousand more worldwide.¹ In Israel, IBD incidence was reported to be 18.2 per 100 000 persons in 2016 and the prevalence of CD was 312.84 per 100 000 persons in the country's Jewish population.² In general, treatment of CD is complex and may include the use of 5-aminosalicylates (5-ASA), corticosteroids (CS), methotrexate, and other immunomodulators (IM), as well as biologic therapies. Treatment for this disease often requires patients to undergo dose changes, switching, and discontinuation.³

In Israel, innovative biologic therapies are available for patients with moderately to severely active CD. The available treatments include ustekinumab (UST), which has been available since 2017. UST was first approved for CD patients who previously

Abstract

Background and Aim: In 2017, ustekinumab (UST) was included in Israel's National Basket of Health Services for treatment of biologic-experienced Crohn's disease (CD) patients with moderately to severely active disease. This study aims to provide real-world evidence on persistence and clinical outcomes among early users of UST.

Methods: This retrospective cohort study was conducted using data from Maccabi Healthcare Services (MHS; 2.5-million-member state-mandated health provider, Israel). Adult patients with a CD diagnosis code who had ≥ 1 dispensed UST prescription in 2017–2018 and at least 12 months of prior continuous health plan enrollment were included. Outcomes, including treatment discontinuation, dose-escalation (based on shortened intervals between purchases), CD-related surgery, CD-related hospitalization, corticosteroid (CS) discontinuation, and use of opioids were evaluated from the date of first dispensed UST through the end of 2019 using Kaplan–Meier analysis.

Results: A total of 162 eligible patients (81 [49.4%] female; median age 34.4 years [IQR 23.2–46.3]; median years since CD diagnosis 8.6 [IQR 4.8–16.0]) were enrolled in the study. Discontinuation rate after 365 and 540 days of follow-up was 27.8% and 35.6%. Dose escalation was estimated at 15.4% and 28.6%, respectively. The first-year cumulative rate of CD-related surgery and CD-related hospitalization were estimated at 4.7% and 9.8%, respectively.

Conclusion: In this real-world CD cohort of UST users, results suggest persistence is relatively high as compared to other biologics for CD. Comparative effectiveness of different biologic treatments for CD in this population should be further explored.

received both anti-TNF and vedolizumab (VDZ) treatments. As of 2018, the Israeli National Basket of Health Services criteria expanded to include UST as second-line treatment after anti-TNF use (irrespective of prior VDZ use). UST is available to patients as an intravenous (IV) infusion for induction and as a subcutaneous injection for maintenance treatment every 8- or 12-week dosing.⁴

This study aims to provide real-world evidence research in Israel on biologic-experienced patients initiating UST treatment in 2017 and 2018. In particular, to analyze treatments patterns and outcomes, including treatment discontinuation, dose-escalation, CD-related surgery, CD-related hospitalization, and CS discontinuation since the introduction of UST therapy for treatment of CD.

Materials and methods

Data source. This study was conducted using data from the Maccabi Healthcare Services (MHS) central computerized

database, the second-largest state-mandated healthcare provider in Israel, containing more than 2.5 million (25% of the population) members and is a representative sample of the Israeli population. This fully computerized database captures all information on patient interaction (including demographics, inpatient and outpatient visits, diagnoses, procedures, imaging, medications prescriptions, medication dispenses, and laboratory measurements).

Study population and design. The study cohort included adult (age ≥ 18 years) patients with a CD diagnosis code who

initiated treatment with UST in 2017 and 2018 (index period). The cohort included patients with at least one dispensed prescription of UST during the index period, where the patients' UST initiation date (i.e. first administration date) was recorded as their index date. All patients were required to have at least 12 months of pre-index health plan enrollment in MHS. UST administration and outcomes were analyzed during a follow-up period beginning at index and ending on 31/12/2019. For analyses of treatment patterns, patients were required to have a record of UST induction (130 mg vial) as their treatment initiation.

Table 1 Baseline characteristics of CD patients initiating UST from 2017 to 2018

Baseline characteristics at biologic index date		All UST initiators	UST initiators (by number of prior biologics)		
			≤ 1	2	≥ 3
N		162	40	65	57
Age at drug initiation in years	Median (IQR)	34.41 (23.2–46.3)	36.09 (23.1–47.5)	31.86 (20.9–42.4)	39.6 (26.7–48.9)
	Mean (SD)	36.23 (15.6)	37.6 (17.0)	32.7 (14.0)	39.3 (15.8)
Years to UST initiation since the earliest IBD diagnosis, median (IQR)		8.57 (4.8–16.0)	7.35 (4.2–16.0)	7.9 (3.7–14.8)	11.2 (7.0–15.9)
Birth Country/region	Israel	14 (8.6%)	1 (2.5%)	2 (3.1%)	11 (19.3%)
	Central/East Europe/FSU	143 (88.3%)	37 (92.5%)	63 (96.9%)	43 (75.4%)
	North/West/South Europe	3 (1.9%)	2 (5%)	34 (52.3%)	1 (1.8%)
	Other or unknown	2 (1.2%)	19 (47.5%)	31 (47.7%)	2 (3.5%)
Sex	Female	80 (49.4%)	21 (52.5%)	11 (16.9%)	27 (47.4%)
	Male	82 (50.6%)	4 (10%)	24 (36.9%)	30 (52.6%)
SES	Low (1–4)	22 (13.6%)	10 (25%)	30 (46.2%)	7 (12.3%)
	Med (5, 6)	56 (34.6%)	26 (65%)	0 (0%)	22 (38.6%)
	High (7–10)	84 (51.9%)	0 (0%)	47 (72.3%)	28 (49.1%)
	Missing	0 (0%)	30 (75%)	5 (7.7%)	0 (0%)
Region of residence	Central	117 (72.2%)	5 (12.5%)	13 (20%)	40 (70.2%)
	North	20 (12.3%)	5 (12.5%)	2 (3.1%)	10 (17.5%)
	South	25 (15.4%)	1 (2.5%)	63 (96.9%)	7 (12.3%)
Smoking	Never	139 (85.8%)	37 (92.5%)	57 (87.7%)	45 (78.9%)
	Ever	17 (10.5%)	2 (5%)	5 (7.7%)	10 (17.5%)
	Missing	6 (3.7%)	1 (2.5%)	3 (4.6%)	2 (3.5%)
BMI [†]	Underweight	31 (19.1%)	6 (15%)	10 (15.4%)	15 (26.3%)
	Normal weight	88 (54.3%)	20 (50%)	38 (58.5%)	30 (52.6%)
	Overweight	27 (16.7%)	11 (27.5%)	8 (12.3%)	8 (14%)
	Obesity	12 (7.4%)	3 (7.5%)	6 (9.2%)	3 (5.3%)
	Missing	4 (2.5%)	0 (0%)	3 (4.6%)	1 (1.8%)
Chronic comorbidities	Diabetes	6 (3.7%)	1 (2.5%)	2 (3.1%)	3 (5.3%)
	CVD	7 (4.3%)	2 (5%)	3 (4.6%)	2 (3.5%)
	CKD	17 (10.5%)	3 (7.5%)	6 (9.2%)	8 (14%)
	Hypertension	19 (11.7%)	7 (17.5%)	3 (4.6%)	9 (15.8%)
	Cancer	13 (8%)	2 (5%)	4 (6.2%)	7 (12.3%)
	Colorectal cancer	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CCI	Mean (SD)	0.8 (1.3)	0.6 (1.0)	0.8 (1.3)	1.0 (1.4)
	0	88 (54.3%)	25 (62.5%)	35 (53.8%)	28 (49.1%)
	1	46 (28.4%)	10 (25%)	22 (33.8%)	14 (24.6%)
	2	16 (9.9%)	2 (5%)	4 (6.2%)	10 (17.5%)
	≥ 3	12 (7.4%)	3 (7.5%)	4 (6.1%)	5 (8.8%)
HCRU 12 months before	Hospitalizations	11 (6.8%)	4 (10%)	5 (7.7%)	2 (3.5%)
	CD-related surgery	16 (9.9%)	3 (7.5%)	7 (10.8%)	6 (10.5%)
Opioid use	Ever	19 (11.7%)	3 (7.5%)	7 (10.8%)	9 (15.8%)
	12 months before	12 (7.4%)	2 (5%)	4 (6.2%)	6 (10.5%)

[†]Most recent BMI measurement to biologic initiation date (within 5 years prior).

FSU, Former Soviet Union.

Study variables and definitions

Baseline characteristics. At UST initiation, patients were characterized according to demographic data (age, sex, residence area, and birth country). Socioeconomic status (SES) of patients' residential area was based on a score ranked with 1 (lowest) to 10 built for commercial purposes by Points Location Intelligence using geographic information systems and data such as expenditures related to retail chains, credit cards, and housing. This score is highly correlated with SES measured by the Israel Central Bureau of Statistics.⁵ SES was categorized into low (1–4), medium, (5, 6) and high (7–10). Body mass index (BMI) was categorized using standard cut-points.⁶ Comorbidities were assessed ever since 1998 unless otherwise specified. Baseline chronic diseases were identified using previously validated MHS automated chronic disease registries for diabetes,⁷ cardiovascular disease (CVD),⁸ chronic kidney disease (CKD),⁹ and hypertension.¹⁰ Cancer history was obtained from National Cancer Registry.¹¹ A modified Deyo-Charlson Comorbidity Index (CCI)¹² was calculated based on ICD-9-CM diagnoses and augmented, where available, using MHS chronic disease registries. Data were obtained on patients' medication use up to 12 months before index date, including 5-ASA and IM. Prior biologic use was also described at baseline and presented in three categories: ≤ 1 , 2, or ≥ 3 biologic treatments before initiating UST. This stratification will allow for comparison of various outcomes between less severe CD patients (likely ≤ 1 or 2 prior biologics) to more severe CD patients (likely ≥ 3 prior biologics). Patients initiating UST with no prior biologic history were also included in this study, as there were only three patients, assuming their first biologic purchase was not recorded in the MHS database.

Biologic treatment patterns. Switching treatment was defined as initiation of another biologic after UST index date, including cycling back to a biologic that was previously used in the baseline period. Treatment discontinuation was defined as switching biologic or a treatment gap of at least 90 days (treatment gap was defined as 90 days after the calculated UST runout date), whichever occurred first. Persistence was defined as the time to UST discontinuation date (censored at the end of follow-

up, leaving the health plan, or death), accounting for the 90-day grace periods.

In Israel, the standard UST treatment for CD patients is every 8 weeks, but this may vary depending on their prescription and disease severity. In this study, dose escalation was estimated according to interval shortening by half, which we defined as an interval between two doses (interval 1) followed by at least two consecutive shorter intervals (intervals 2–3). For instance, interval 1 was at least twice as long as intervals 2 and 3. Only patients with at least four UST maintenance treatments (i.e. three doses) were eligible for this analysis. Additionally, in Israel, interval shortening less than twice as long is considered a dose adjustment period (for example, 12 to 8 weeks). Few patients in this cohort demonstrated dose adjustment events. In addition, post-dose adjustment, some patients proceeded with dose escalations, such as 8 to 4-week intervals.

Healthcare resource utilization (HCRU) outcomes. CD-related overnight hospitalizations were defined by an inpatient diagnosis of CD linked to the hospitalization dates and CD-related surgeries were defined by Current Procedural Terminology (CPT) codes, including colectomy, colostomy/ileostomy, and fistula/abscess repair.

CS treatment patterns. Discontinuation of CS, with UST therapy being continued, was described among baseline CS-dependent patients. Only patients with a history of dispensed CS medication, up to 90 days before index date (UST initiation) were considered for this analysis. CS discontinuation was defined here as stopping CS purchases for at least 120 days after the UST initiation date.

Statistical analyses. Descriptive statistics were presented as frequencies (*n*, %), mean (standard deviation [SD]), or median (interquartile range [IQR]). Time-to-event outcomes, including treatment discontinuation, dose-escalation, CD-related surgery, CD-related hospitalization, and CS discontinuation were evaluated using Kaplan Meier, and cumulative % events were reported at 180 and 365 days. In the time-to-event outcomes, results were

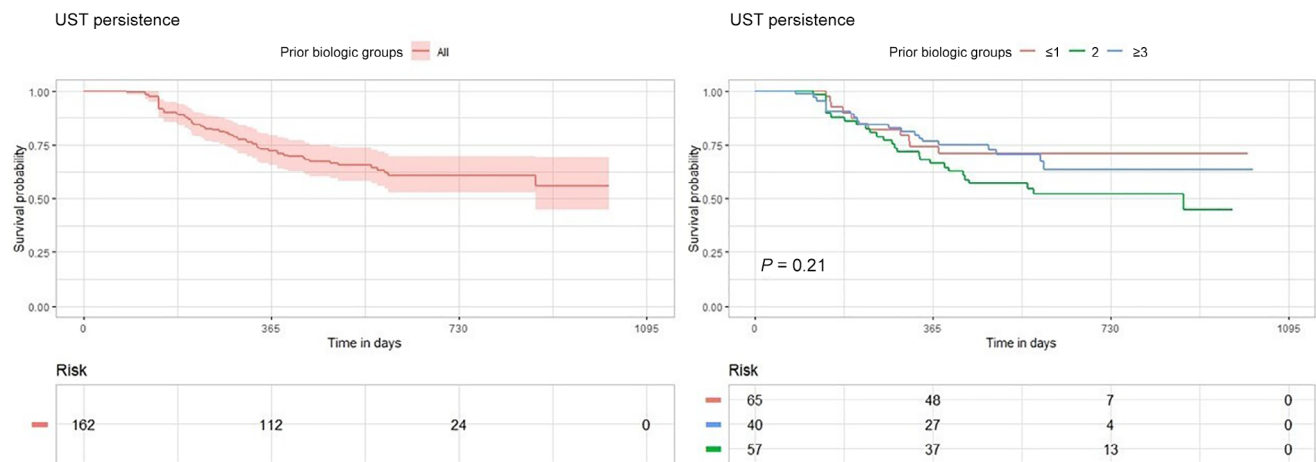


Figure 1 Kaplan–Meier survival curve of CD patient's (*n* = 162) time to UST discontinuation by a number of prior biologics.

compared by number of prior biologic (log-rank test). All analyses were conducted in IBM SPSS version 25.

Ethical considerations. The study was approved by the Institutional Review Board of MHS.

Table 2 Study outcomes for patients who persisted on UST treatment versus patients that discontinued UST treatment during the study period

Study outcomes	UST persistence	
	Persisted (<i>n</i> = 104)	Discontinued (<i>n</i> = 58)
Surgery	1 (1.0%)	8 (8.6%)
Hospitalization	8 (7.7%)	11 (19.0%)
CS discontinuation	0	11 (19.0%)

Data availability. Data sharing is not applicable in this research article due to privacy matters, and therefore, it was not approved by the MHS internal review board.

Results

A total of 162 patients were included in the study, where 47 initiated UST in 2017 and 115 initiated in 2018. Among these patients, 40 (24.7%) had up to 1 prior biologic use, 65 (40.1%) had used 2 prior biologics, and 57 (35.2%) had used 3 or more biologics at baseline. Three patients had no record of prior biologic purchases and three patients had records of four prior biologic lines before UST index date. The median age at UST initiation was 34.4 (IQR = 23.2–46.3) years, with 49.4% female patients and a median of 8.6 (IQR = 4.8–16.0) years since CD diagnosis. For prior IBD treatments, 91.4% of patients used IM and 74.6% used 5-ASA in the past year. At baseline, 30.7% had a history of CD-related surgery. Within 12 months prior to UST

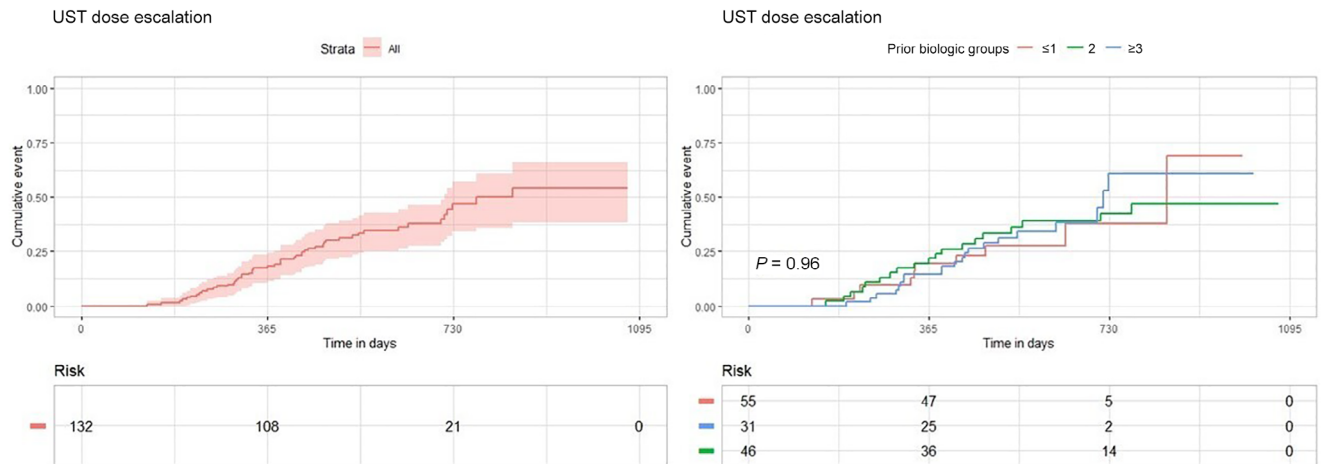


Figure 2 Kaplan–Meier survival curve of CD patient’s (*n* = 132) time UST dose escalation by a number of prior biologics.

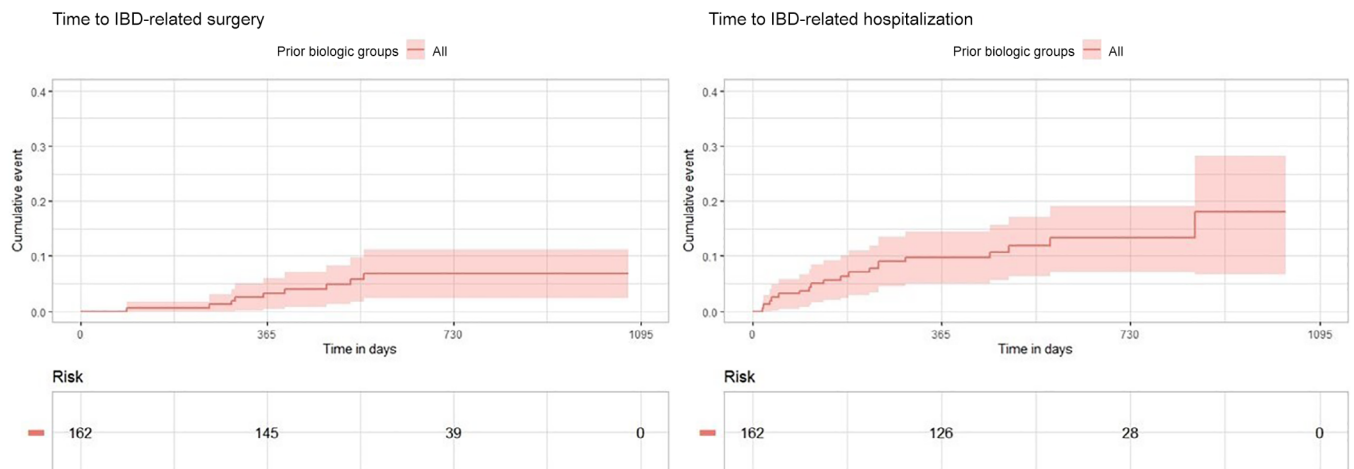


Figure 3 Kaplan–Meier survival curve of CD patient’s (*n* = 162) time to CD-related surgery and CD-related hospitalization during UST treatment.

initiation, 6.8% had a CD-related hospitalization, 9.9% had a CD-related surgery and 13.0% were CS-dependent (Table 1).

By the end of the follow-up, a total of 58 patients discontinued UST. Among those who discontinued UST, 16 patients switched to a different biologic treatment (7 to certolizumab, 4 to adalimumab, 3 to VDZ, and 2 to infliximab). At 180, 365, and 540 days after UST induction, 10.6%, 27.8%, and 35.6% of patients discontinued therapy, respectively (Fig. 1). There was no statistically significant difference in time to discontinuation by number of prior biologics (Fig. 1; $P = 0.215$). Study outcomes among patients that persisted in UST treatment and patients that discontinued UST are presented in Table 2.

Among patients eligible for the analysis of dose escalation ($n = 132$), 50 patients had an event by the end of follow-up, with estimated rates at 180, 365, and 540 days of 1.5%, 18.2%, and 28.6%, respectively (Fig. 2). There were no significant differences in rates of dose escalation- by number of prior biologic groups (Fig. 2; $P = 0.962$).

By the end of follow-up, 9 patients had a CD-related surgery and 19 patients had a CD-related hospitalization. The estimated cumulative surgery rates at 180 days and at 365 days after UST induction were 1.3% and 4.7%, respectively; for hospitalization, the corresponding rates were 6.4% and 9.8% (Fig. 3). For CDD-related surgery and hospitalization, there was no statistical significance by number of prior biologics ($P = 0.660$ and $P = 0.224$). Among patients who were CS-dependent at baseline ($n = 21$), 11 patients discontinued CS use during follow-up and at 180 days 42.9% had discontinued CS purchases.

Discussion

The results suggest that UST adherence is high, as only about a third of patients discontinued treatment during follow-up until the end of 2019. Our results suggest there is no statistically significant difference for UST discontinuation and UST dose escalation ($P = 0.210$ and $P = 0.960$, respectively) between less and more severe CD patients (based on ≤ 1 , 2, or ≥ 3 prior biologic treatments). This study's result is comparable to a recent study with real-world data from 12 hospitals in Finland. Researchers explored UST therapy for CD patients initiating the treatment in 2017; results from the study suggest that 40 out of 48 patients (83.3%) persisted on UST treatment until end of follow-up (April 30th, 2018).¹³ In the Finnish study, 96% of patients had been treated with at least one prior biologic therapy before initiating UST, in comparison to 24.7% in this study. In addition, the Finnish study had 14 patients (29.2%) with three prior biologics compared to this study with 57 patients (35.2%) who had three or more prior biologics. The lower proportion of biologic-experienced patients from the Finnish study may explain the cohort's higher adherence to UST.

Another real-world study explored UST persistence, switching, and dose escalation among CD patients in the United States, where persistence to UST was 83.6%, 8.6% switched biologic treatments among patients who discontinued UST, and 17.9% had dose escalation during a 12-month follow-up period.¹⁴ Their study used data pooled from various databases between the years 2015 and 2018 and all patients had 12 months of follow-up. Out of the 214 patients, 74.8% were biologic experienced, where 59.3% had one prior biologic and 15.4% had two

prior biologics. The higher UST persistence and lower dose escalation in the American cohort may be due to differences in the proportion of patients who had previously used more than one biologic therapy; 15.4% had two prior biologics compared to this study with 40.1%, and 35.1% having two and three or more prior biologic therapies, respectively.

The present study had several strengths, including describing a real-world cohort of the first CD patients eligible for UST treatment in Israel since its inclusion in the national basket of health services. This study includes systematic data collection of UST administration for up to 2 years and multiple data sources to capture HCRU-related outcomes, availability of rich longitudinal data since 1998 to characterize patients, and a high retention rate in the health fund (>98%/year).

Nonetheless, several methodological limitations should be considered. First, patients' prior biologic use may not have been captured if they were treated prior to joining the MHS health plan. Therefore, the prior biologic use may have been underestimated, as most medication history from prior healthcare providers is not available. In addition, UST dosage was not directly available and the study used a conservative "dose escalation" definition, based on interval shortening of at least half (e.g. from two 12-week intervals to 6-week intervals twice). By doing so, we may not have captured all dose escalations for patients (particularly those with shorter follow-up times). Reasons for UST switching, discontinuation, and dose escalation were not available for this analysis and additional research should be done to analyze other factors that may affect UST persistence. This study may inform further research on the comparative effect of UST compared to other biologics.

Conclusions

In this real-world CD cohort of UST users, results suggest persistence is relatively high. Comparative effectiveness of different biologic treatments for CD in this population should be further explored.

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