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Observations and Research

Real-World Patterns and Economic Burden Associated With Treatment Failure With Advanced Therapies in Patients With Moderate-to-Severe Ulcerative Colitis

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Background: Some patients lose response during treatment for moderate-to-severe ulcerative colitis (UC). We aimed to characterize real-world treatment failure patterns and associated economic burdens during use of first-line advanced therapies for UC.

Methods: IBM MarketScan Commercial and Medicare Supplemental Databases were used to identify adults initiating ≥ 1 advanced therapy for UC (January 1, 2010–September 30, 2019). Treatment failure was defined as augmentation with non-advanced therapy, discontinuation, dose escalation/interval shortening, failure to taper corticosteroids, UC-related surgery, or UC-related urgent care ≤ 12 months after treatment initiation. The index date was the date of treatment failure (treatment failure cohort) or 12 months after treatment initiation (persistent cohort). Treatment failure rates were assessed using Kaplan–Meier analyses. All-cause and UC-related healthcare resource utilization (HCRU) and costs 12 months post-index were also assessed.

Results: Analysis of treatment failure patterns included data from 6745 patients; HCRU and cost analyses included data from 5302 patients (treatment failure cohort, $n = 4295$; persistent cohort, $n = 1007$). In the overall population, 75% experienced treatment failure within the first 12 months (median: 5.1 months). Augmentation with non-advanced therapy (39%) was the most common first treatment failure event. The treatment failure cohort had significantly ($P < .001$) higher mean costs than the persistent cohort (all-cause, $74 995 vs $56 169; UC-related, $57 096 vs $47 347) mainly attributed to inpatient admissions and outpatient visits. Dose escalation/interval shortening accounted for the highest total costs ($101 668) across treatment failure events.

Conclusions: Advanced therapies for moderate-to-severe UC are associated with high rates of treatment failure and significant economic burden. More efficacious and durable treatments are needed.

Lay Summary

As a chronic disease with potentially debilitating symptoms, ulcerative colitis is associated with high costs. Current treatments stop working for most patients with moderate-to-severe disease, further increasing medical costs and underscoring the need for better treatment options.

Key Words: Ulcerative colitis, biologic therapy, health care costs, outcomes research

Introduction

Ulcerative colitis (UC) is a chronic immune-mediated condition characterized by recurring episodes of inflammation of the mucosal layer of the colon, commonly involving the rectum and extending to other parts of the colon.[1] The primary symptom of UC is diarrhea, which may include blood, and associated relapsing and remitting symptoms include abdominal pain, incontinence, fatigue, fever, and weight loss.[2] Most patients with UC present with mild symptoms, while approximately 28% have moderate or severe disease.[3] The incidence of UC in North America and northern Europe varies between 9 and 20 cases per 100 000 person-years, and the prevalence ranges from 156 to 291 cases per 100 000 people.[1] Both the incidence and prevalence of UC are increasing worldwide.[4]

The overall goal of UC therapy is corticosteroid-free remission and, ideally, complete mucosal healing.[5] Treatment typically consists of 2 phases: induction of remission and maintenance of remission. For moderate-to-severe UC, conventional therapies include aminosalicylates, immunomodulators or immunosuppressants, and systemic and non-systemic corticosteroids. The first anti–tumor necrosis factor alpha (anti-TNF) agent infliximab was approved in 2005 for moderate-to-severe UC by the US Food and Drug Administration (FDA), and since then, the use of advanced therapies for UC has become common in

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clinical practice.[6] Several advanced therapies are currently available in the United States, including anti-TNF agents (infliximab, adalimumab, and golimumab), an anti-integrin antibody (vedolizumab), an anti–interleukin-12/23 antibody (ustekinumab), a Janus kinase inhibitor (tofacitinib), and a sphingosine 1-phosphate receptor modulator (ozanimod). The American Gastroenterological Association and the American College of Gastroenterology recommend both conventional and advanced therapies for UC.[5,7]

UC is a lifelong disease that is associated with high clinical, functional, and quality-of-life burdens. Patients with UC often experience substantial morbidity and elevated mortality.[8] The alternating periods of symptom exacerbation and remission significantly affect quality-of-life and functional status,[9] including social interactions and career progression.[10] Furthermore, UC is associated with a substantial economic burden and high healthcare resource utilization (HCRU), with about 50% of patients requiring hospitalization at some point during the disease course.[11] In 2017, the average UC-related healthcare cost in the first year after initiation of advanced therapy was estimated at $42 579 among patients with moderate-to-severe UC in the United States.[12]

This high economic burden may be partially attributed to the fact that, despite the broadening treatment landscape, patients with UC frequently experience treatment failure and are unable to achieve durable disease control.[13] For example, a 2017 systematic review and network meta-analysis estimated that 68% to 84% of patients with moderate-to-severe UC failed to achieve clinical remission after receiving first-line advanced therapies. The failure rate exceeds 75% among patients receiving second-line advanced therapies.[14] Another real-world study using claims data showed that the proportion of patients remaining corticosteroid-free 1 year after the initiation of advanced therapies was less than 50%.[12] Treatment failure may lead to poor symptom control and disease progression, which could, in turn, result in life-threatening complications, surgery, additional hospitalizations and healthcare costs, and further morbidity.[13,15]

Few studies have assessed the economic burden associated with UC treatment failure using a comprehensive definition and accounting for the most commonly used advanced therapies currently approved in the United States. Rubin et al evaluated the healthcare costs associated with discontinuation, dose escalation, switching, and augmentation of first-line conventional and advanced UC therapies.[16] However, during the time from which study data were taken (2006–2010), infliximab was the only advanced therapy approved by the FDA for moderate-to-severe UC.[16] More recent studies evaluated economic outcomes associated with some aspects of treatment failure, particularly treatment switching. For example, Null et al (2017) assessed costs associated with anti-TNF discontinuation and cycling and Chiorean et al (2020) studied the economic outcomes of anti-TNF cycling and switching from anti-TNF to vedolizumab.[17,18]

With the increasing number of advanced therapies for UC, it is important for healthcare practitioners and payers to understand the clinical and economic burden associated with treatment failure to make informed treatment decisions. Therefore, the primary objective of the study is to both characterize the real-world patterns of treatment failure and assess HCRU and healthcare costs associated with UC treatment failure.

Materials and Methods

Data Source

This retrospective analysis used data from the IBM MarketScan Commercial Claims and Encounters Databases and the Medicare Supplemental and Coordination of Benefits Database from January 1, 2010, to September 30, 2019. These databases collect data from approximately 100 insurance companies representing approximately 25 million beneficiaries annually from all census regions in the United States. The database contains patient demographics, healthcare plan enrollment history, and claims for inpatient, outpatient, and pharmacy services. As de-identified claims data were used, no institutional board review was required.

Sample Selection

To be included in the study, patients were required to (1) have ≥ 2 UC diagnoses (International Classification of Diseases-9-CM code: 556.xx; International Classification of Diseases-10-CM code: K51.xx) ≥ 90 days apart; (2) have ≥ 2 claims on different dates for an advanced UC treatment (adalimumab, golimumab, infliximab, tofacitinib, and vedolizumab) on or after the initial UC diagnosis with the initiation date on or after January 1, 2010, and on or after the FDA approval dates for the therapy (as ustekinumab was approved to treat UC shortly after the period of data capture, patients receiving ustekinumab were not included in this study); (3) have continuous enrollment for 6 months before and 12 months after initiation of the first-line advanced therapy; and (4) be aged ≥ 18 years at the initial UC diagnosis. Patients were excluded if they had ≥ 1 of the following: (1) diagnosis of other autoimmune condition for which the advanced therapy can be used (ie, rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, noninfectious uveitis, and hidradenitis suppurativa) in the 6 months before the first-line advanced therapy; (2) diagnoses of any type of malignancy, including primary and secondary malignant neoplasms, in the 6 months before the first-line advanced therapy; and (3) ≥ 2 Crohn's disease diagnoses on different dates at any time from the initial UC diagnosis or 6 months before initiation of the first-line advanced therapy, whichever occurred earlier, to the initiation date of the first-line advanced therapy.

Cohorts

The analysis to characterize treatment failure included patients fulfilling the criteria dictating sample selection (overall cohort). The overall cohort was divided into the *treatment failure cohort* and the *persistent cohort*. The treatment failure cohort included patients who experienced a treatment failure event (defined in the "Treatment Failure" subsection) within the 12 months after initiation of the first-line advanced therapy. The persistent cohort included patients who did not experience treatment failure within the 12 months after initiation of the first-line advanced therapy. The *index date* was the date of the first treatment failure event for the treatment failure cohort and 12 months after initiation of the first-line advanced therapy for the persistent cohort.

For the analyses of HCRU and healthcare costs, treatment failure and persistent cohort patients were further required to have ≥ 12 months of continuous enrollment after the index date (*study period*).

Study Variables

Treatment Failure

The definition of treatment failure was based on the medical literature,[17,19] particularly Patel et al,[19] and modified per input from clinical experts. Treatment failure was defined as dose escalation,[19] discontinuation,[19] augmentation,[19] failure to taper corticosteroids (remaining on corticosteroids with the first-line advanced therapy for > 12 months), UC-related surgery (rectosigmoid, rectum, perineum, and anal surgeries),[19] and UC-related urgent care (emergency department [ED] visit or inpatient admission with a UC diagnosis).[19]

Dose escalation included increases in doses in each dosing interval or interval shortening during the maintenance phase that resulted in an increase in daily dose of ≥ 50% compared with the daily dose recommended by the FDA. The threshold of 50% was selected based on discussions with clinicians to reflect clinical practice patterns.

Discontinuation was defined as a treatment gap after the last day of supply, greater than the allowable gap, or as initiation of a new treatment. For medical claims for infusion treatments, the days of supply were set equal to the interval for the maintenance regimen recommended by the FDA. Allowable gaps were identified as the interval length of the maintenance regimen plus 30 days, which was rounded to the nearest 45, 60, or 90 days, per Brady et al.[20] The last day of supply before discontinuation was defined as the discontinuation date. Discontinuation events were further classified into 3 categories: (1) switching to a new advanced therapy, defined as initiation of the new advanced therapy after discontinuing the first-line therapy; (2) restarting the same first-line advanced therapy after a treatment gap greater than the allowable gap; and (3) discontinuation of the first-line advanced therapy completely without initiating a new advanced therapy during the follow-up time.

Augmentation was defined as the use of non-advanced systemic therapy (ie, corticosteroids, immunomodulators, and aminosalicylates) as adjunct (add-on) treatment with the first-line advanced therapy; ≥ 28 days of overlapping use were required. Non-advanced systemic therapy initiated within ± 30 days of the initiation of the first-line advanced therapy was considered concurrent treatment(s), not augmentation. Concurrent treatments that were re-initiated after being discontinued for 60 days were considered as augmentation.

HCRU and costs

All-cause and UC-related HCRU and costs were evaluated from a commercial payer's perspective during the 12-month study period in both cohorts. HCRU included inpatient admissions, ED visits, outpatient visits, and gastroenterologist visits. Healthcare costs (in 2020 USD) included medical costs, drug costs, and total costs (the sum of medical and drug costs). Medical costs were further classified into inpatient costs, outpatient costs, ED costs, and other costs. Drug costs included costs from pharmacy claims for all drugs and outpatient claims for injections/infusions of advanced therapies. UC-related HCRU and medical costs were identified from claims with a UC diagnosis. UC-related drug costs were estimated using pharmacy and medical claims for advanced therapies.

Statistical Analysis

Baseline characteristics were described by cohort, as well as by type of first treatment failure event, using counts and proportions. Data collected included age at index date, sex, index year, Charlson Comorbidity Index (CCI) and selected comorbidities (based on discussions with clinical experts) in the 6 months before the index date, first-line advanced therapy received, and treatments given concurrently with the first-line advanced therapy.

The proportions of patients in the overall cohort with any treatment failure and each type of treatment failure at 6, 12, 24, and 36 months after initiation of the first-line advanced therapy were evaluated using Kaplan–Meier analyses. For time to discontinuation, patients were censored at the earlier of the end of continuous enrollment or end of data availability. For all other types of treatment failure, patients were censored at the first occurrence of discontinuation, end of continuous enrollment, or end of data availability. The distributions of the first treatment failure events were described overall and by first-line advanced therapy.

HCRU, all-cause, and UC-related healthcare costs were compared between cohorts using Wilcoxon rank sum tests for continuous variables and chi-squared tests for categorical variables. Furthermore, HCRU and healthcare costs for the subgroups of patients using FDA-approved anti-TNF agents as first-line therapy for moderate-to-severe UC (ie, infliximab, adalimumab, and golimumab) were described by the type of first treatment failure event: anti-TNF dose escalation, anti-TNF cycling (switching to a different anti-TNF agent), and switching from anti-TNF agents to vedolizumab.

Analyses were conducted in SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA). A *P* value of .05 was used to determine statistical significance.

Results

Sample Selection

Of the 6745 patients who met the sample selection criteria and were included in the overall cohort, 5086 experienced a treatment failure event within 12 months after initiation of a first-line advanced therapy for UC and 1659 did not (Supplementary Figure 1). After applying the requirement of 12 months of continuous enrollment after the index date to the overall cohort, 4295 patients were included in the treatment failure cohort and 1007 were included in the persistent cohort (Supplementary Figure 1).

Treatment Failure in the Overall Population

Proportions of patients with treatment failure and time to treatment failure

The median follow-up time for the overall population (*N* = 6745) from initiation of first-line advanced therapy was 28.5 months. The proportions of patients with ≥ 1 treatment failure event at 6, 12, 24, and 36 months were 55.1%, 75.4%, 87.7%, and 91.9%, respectively (Figure 1). The median time to first treatment failure event was 5.1 months.

In the first 12 months after initiating first-line advanced therapy, 48.1% of the overall population augmented their treatment with non-advanced therapies, 22.7% switched to a new advanced therapy, 10.1% restarted the same advanced therapy, 14.6% discontinued advanced therapy completely, 19.8% had UC-related urgent care, 18.4% escalated doses, 5.5% failed to taper corticosteroids, and 1.2% had UC-related surgeries (Figure 1).

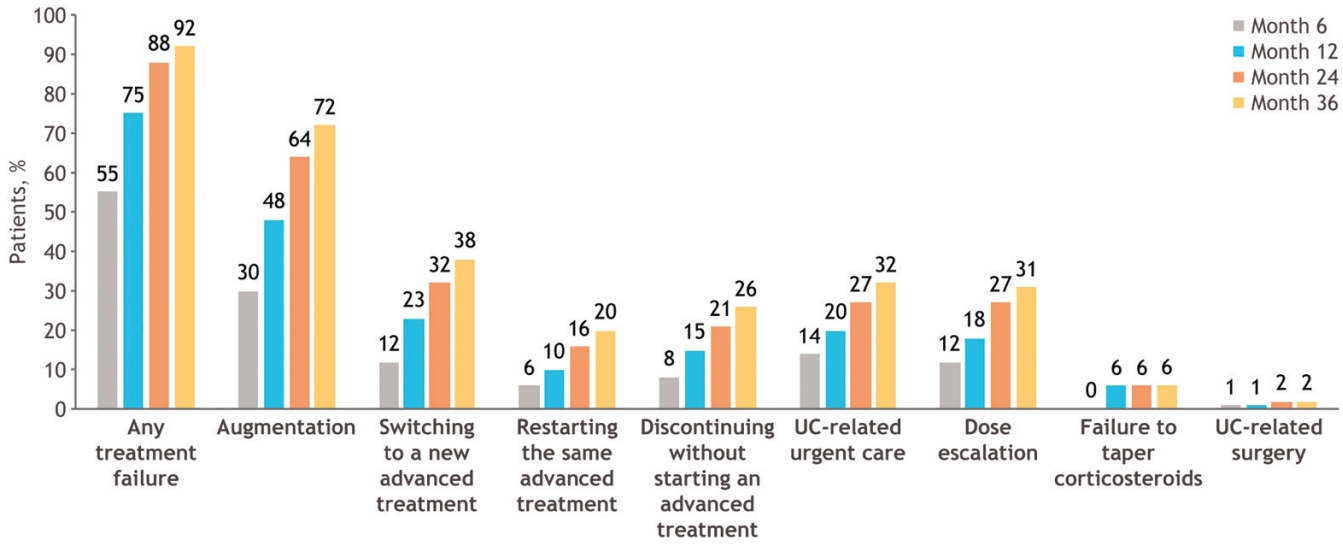

Figure 1. Proportions of the overall cohort ($N = 6745$) with treatment failure events at 6, 12, 24, and 36 months. UC, ulcerative colitis.

Distribution of first treatment failure events, overall and by treatment

The most common first treatment failure event in the overall population was augmentation (39.0%; 19.3% with corticosteroids, 12.3% with aminosalicylates, and 7.4% with immunomodulators), followed by UC-related urgent care (14.6%), dose escalation (9.8%), and switching to a new advanced therapy (9.6%) (Table 1). The most common first treatment failure events were augmentation (35.4%) and dose escalation (13.3%) among the 2998 patients prescribed adalimumab, augmentation (42.2%) and UC-related urgent care (17.9%) among the 2971 patients prescribed infliximab, and augmentation (39.4%) among the 551 patients prescribed vedolizumab. More patients had no treatment failure events during follow-up in the vedolizumab group (21.2%) than in the adalimumab (10.6%) or infliximab (10.4%) group. UC-related surgery was rare (0.2%–0.6% across the 3 advanced therapies).

Baseline Characteristics

Among patients with continuous enrollment for 12 months after the index date in the treatment failure and persistent cohorts ($N = 5302$), the mean age was 43.3 (standard deviation [SD]: 14.4) years and 47.4% were female (Table 2). More than 70% of patients had their first treatment failure events in or after 2014. Infliximab (45.1%) and adalimumab (45.0%) were the most commonly used first-line advanced therapies for UC, accounting for 90% of advanced therapy use, followed by vedolizumab (6.8%). Use of concurrent treatments along with the first-line advanced therapies was common, especially corticosteroids (60.3%) and aminosalicylates (53.3%). The mean CCI in the 6 months before the index date was 0.25 (SD: 0.68), and the most common comorbidity was anemia (22.4%), followed by hypertension (17.4%) and hyperlipidemia (11.6%).

The mean age and sex distributions were similar between the treatment failure and persistent cohorts (Table 2). More patients in the treatment failure cohort than in the persistent cohort used concurrent corticosteroids (63.1% vs 48.3%). Patients in the treatment failure cohort also had a higher mean CCI compared with persistent patients (0.27 [SD: 0.70]) vs 0.18 [0.56]), as well as higher rates of comorbidities, including anemia (25.2% vs 10.4%), anxiety (9.5% vs 6.9%), depression (9.6% vs 7.7%), chronic pulmonary disease (7.7% vs 4.4%), mild liver disease (4.6% vs 2.7%), and asthma (5.0% vs 2.7%).

Baseline characteristics by first treatment failure event in the treatment failure cohort

The baseline characteristics were generally similar between patients with different first treatment failure events in the treatment failure cohort (Table 2). Patients with UC-related urgent care or who switched to a new advanced therapy had higher rates of concurrent corticosteroid use (75.7% and 70.7%, respectively) than patients with other treatment failure events (range: 42.9%–66.4%). Patients experiencing UC-related urgent care also had the highest average CCI (0.37 [SD: 0.87]) and slightly higher proportions of comorbidities.

Healthcare Costs and HCRU

All-cause and UC-related healthcare costs

During the 12-month study period, the treatment failure cohort had significantly higher mean all-cause ($74 995 vs $56 169; $P < 0.001$) and UC-related healthcare costs ($57 096 vs $47 347; $P < 0.001$) than the persistent cohort, with per-patient cost differences of $18 827 and $9749, respectively (Figure 2). The main driver of all-cause and UC-related costs in both cohorts was drug costs, comprising 62.6% to 89.5% of total costs. While drug costs were statistically significantly different for the treatment failure cohort compared with the persistent cohort, the numerical differences were modest (ie, the treatment failure cohort had $818 higher all-cause drug costs [$P < .05$] and $1978 lower UC-related costs [$P < .001$]). In contrast, the differences between the 2 cohorts in medical cost components were much larger. The treatment failure cohort incurred significantly higher all-cause medical costs ($28 104 vs $10 095; difference: $18 009; $P < .001$) and higher UC-related medical costs ($16 706 vs $4979; difference: $11 727; $P < .001$) than the persistent cohort. A higher proportion of the all-cause medical costs were UC-related costs in the treatment failure cohort than in the persistent cohort (59.4% vs 49.3%). In

Table 1. Distribution of first treatment failure events in the overall population and by first-line advanced therapy.

First treatment failure event	All patients (N = 6745)		Adalimumab (n = 2998)		Infliximab (n = 2971)		Vedolizumab (n = 551)		Other therapies[a] (n = 225)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Augmentation	2633	39.0	1062	35.4	1254	42.2	217	39.4	100	44.4
Switching to a new advanced treatment	647	9.6	321	10.7	267	9.0	30	5.4	29	12.9
Restarting the same advanced treatment	504	7.5	300	10.0	150	5.0	34	6.2	20	8.9
Discontinuing advanced treatment completely	433	6.4	200	6.7	200	6.7	21	3.8	12	5.3
Dose escalation	660	9.8	399	13.3	198	6.7	54	9.8	9	4.0
Failure to taper corticosteroids	72	1.1	17	0.6	43	1.4	8	1.5	4	1.8
UC surgery	36	0.5	16	0.5	19	0.6	1	0.2	0	0
UC-related urgent care	984	14.6	366	12.2	531	17.9	69	12.5	18	8.0
No event	776	11.5	317	10.6	309	10.4	117	21.2	33	14.7

[a]Other therapies included golimumab (n = 213) and tofacitinib (n = 12).
UC, ulcerative colitis.

addition, patients in the treatment failure cohort had significantly higher inpatient (all-cause: $14 964 vs $3237; UC-related: $9984 vs $1777), outpatient (all-cause: $11 470 vs $6275; UC-related: $6128 vs $3112), and ED (all-cause: $1591 vs $529; UC-related: $583 vs $88) costs (all $P < .001$) (**Figure 2**).

All-cause and UC-related HCRU

Patients experiencing treatment failure (treatment failure cohort) had significantly more all-cause and UC-related HCRU than those in the persistent cohort (**Table 3**), which is consistent with the differences in healthcare costs between cohorts. Specifically, the treatment failure cohort had significantly higher proportions of inpatient admissions (all-cause: 28.1% vs 7.9%; UC-related: 25.2% vs 6.1%) and ED visits (all-cause: 40.4% vs 27.9%; UC-related: 17.6% vs 4.7%; all $P < .001$). The proportions of patients with outpatient or gastroenterologist visits were similar between cohorts; however, the treatment failure cohort had significantly more outpatient visits (all-cause: 23.1 vs 17.0; UC-related: 9.5 vs 6.8) and gastroenterologist visits (all-cause: 4.8 vs 3.5; UC-related: 4.0 vs 3.1; all $P < .001$).

Healthcare costs and resource use by type of first treatment failure event

All-cause healthcare costs were lower for patients who discontinued first-line therapy without starting another advanced therapy or who restarted the same first-line therapy ($31 688 and $42 409, respectively) compared with costs incurred by patients in the persistent cohort ($56 169), including lower drug costs ($6907 and $27 624 vs $46 073, respectively) during the study period (**Figure 3**). For the remaining treatment failure events, the treatment failure cohort had higher mean all-cause total healthcare costs (range: $70 267–$101 668) than the persistent cohort ($56 169). Patients with dose escalations or UC-related urgent care had the highest all-cause total costs ($101 668 and $101 355, respectively). Patients with dose escalation or failure to taper corticosteroids had the highest drug costs ($80 983 and $63 418, respectively), while drug costs among patients in the treatment failure cohort who did not discontinue an advanced therapy without starting another or restarted the same advanced therapy were close to that of the persistent cohort ($46 073).

Inpatient and outpatient costs were higher among patients experiencing any type of treatment failure, including those who discontinued or restarted therapy, compared with the persistent cohort (inpatient cost: $5134–$39 475 vs $3237; outpatient cost: $8600–$15 127 vs $6275) (Figure 3). Inpatient costs were highest among patients with UC-related urgent care ($39 475), followed by UC-related surgery ($15 813). Outpatient costs were also highest among patients with UC-related urgent care ($15 127) and UC-related surgery ($12 884), as well as those switching to a new advanced therapy ($12 864). UC-related healthcare costs showed a similar pattern across treatment failure event types as all-cause healthcare costs (Supplementary Figure 2), and the all-cause and UC-related HCRU were also consistent with the pattern of healthcare costs (Supplementary Table 1).

Healthcare costs and resource use with first-line anti-TNF therapies in the treatment failure cohort

Among patients in the treatment failure cohort who were prescribed first-line anti-TNF therapies for UC, those experiencing dose escalation had higher total all-cause healthcare costs ($101 058) than those switching to vedolizumab ($75 096) or cycling anti-TNF therapies ($68 847) (**Figure 4**). These higher overall costs were primarily driven by the high drug costs among patients with dose escalation ($81 125). Patients switching from first-line anti-TNF therapies to second-line vedolizumab incurred higher total costs than those cycling anti-TNF therapies ($75 096 vs $68 847) because of higher inpatient ($14 159 vs $11 890) and outpatient ($14 857 vs $11 237) costs, with associated increased inpatient and outpatient resource use (Supplementary Table 2). Similar trends were observed for UC-related healthcare costs and HCRU (Supplementary Figure 3 and Supplementary Table 2).

Discussion

As a chronic disorder with potentially debilitating symptoms, UC often requires lifelong treatment and therefore is associated with high HCRU and healthcare costs.[11,12] Additionally,

Table 2. Baseline characteristics among patients with 12 months of enrollment post-index, by cohort and by type of first treatment failure.

	All patients[a] (*N* = 5302)	Persistent cohort (*n* = 1007)	Treatment failure cohort (*n* = 4295)	Type of first treatment failure event in the treatment failure cohort							
				Augmentation (*n* = 1845)	UC-related urgent care (*n* = 790)	Dose escalation (*n* = 473)	Switch to a new advanced therapy (*n* = 460)	Restart the same advanced therapy (n = 366)	Discontinue without starting an advanced therapy (*n* = 287)	Failure to taper cortico-steroids (*n* = 42)	UC surgery (*n* = 32)
Age at index year, mean (SD)	43.3 (14.4)	44.0 (13.8)	43.2 (14.6)	43.6 (14.2)	42.3 (15.6)	42.1 (14.5)	43.6 (14.0)	41.9 (14.3)	45.1 (14.9)	46.5 (14.6)	42.2 (13.6)
Female, *n* (%)	2515 (47.4)	465 (46.2)	2050 (47.7)	898 (48.7)	369 (46.7)	223 (47.1)	222 (48.3)	166 (45.4)	142 (49.5)	21 (50.0)	9 (28.1)
Index year ≥ 2014, *n* (%)	3781 (71.3)	762 (75.7)	3019 (70.3)	1277 (69.2)	535 (67.7)	360 (76.1)	373 (81.1)	247 (67.5)	178 (62)	27 (64.3)	22 (68.8)
First-line advanced therapy, n (%)											
Adalimumab	2384 (45.0)	395 (39.2)	1989 (46.3)	771 (41.8)	294 (37.2)	314 (66.4)	245 (53.3)	206 (56.3)	132 (46.0)	12 (28.6)	15 (46.9)
Infliximab	2390 (45.1)	486 (48.3)	1904 (44.3)	883 (47.9)	431 (54.6)	118 (24.9)	180 (39.1)	122 (33.3)	131 (45.6)	23 (54.8)	16 (50.0)
Vedolizumab	361 (6.8)	90 (8.9)	271 (6.3)	124 (6.7)	50 (6.3)	34 (7.2)	15 (3.3)	27 (7.4)	16 (5.6)	4 (9.5)	1 (3.1)
Golimumab	166 (3.1)	36 (3.6)	130 (3.0)	67 (3.6)	15 (1.9)	7 (1.5)	20 (4.3)	10 (2.7)	8 (2.8)	3 (7.1)	0 (0)
Tofacitinib	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)
Concurrent treatment with first-line advanced therapy, n (%)											
Corticosteroids	3196 (60.3)	486 (48.3)	2710 (63.1)	1092 (59.2)	598 (75.7)	314 (66.4)	325 (70.7)	157 (42.9)	165 (57.5)	42 (100)	17 (53.1)
Immunomodulators	1176 (22.2)	243 (24.1)	933 (21.7)	409 (22.2)	180 (22.8)	102 (21.6)	107 (23.3)	64 (17.5)	55 (19.2)	12 (28.6)	4 (12.5)
Aminosalicylates	2826 (53.3)	514 (51.0)	2312 (53.8)	1000 (54.2)	456 (57.7)	263 (55.6)	249 (54.1)	158 (43.2)	141 (49.1)	28 (66.7)	17 (53.1)
CCI, mean (SD)[b]	0.25 (0.68)	0.18 (0.56)	0.27 (0.70)	0.23 (0.63)	0.37 (0.87)	0.30 (0.71)	0.26 (0.63)	0.23 (0.64)	0.25 (0.82)	0.26 (0.73)	0.16 (0.45)
Comorbidities, n (%)[b]											
Anemia	1187 (22.4)	105 (10.4)	1082 (25.2)	420 (22.8)	287 (36.3)	123 (26.0)	105 (22.8)	76 (20.8)	62 (21.6)	1 (2.4)	8 (25.0)
Hypertension	923 (17.4)	162 (16.1)	761 (17.7)	342 (18.5)	150 (19.0)	78 (16.5)	57 (12.4)	69 (18.9)	55 (19.2)	4 (9.5)	6 (18.8)
Hyperlipidemia	615 (11.6)	111 (11.0)	504 (11.7)	229 (12.4)	107 (13.5)	49 (10.4)	47 (10.2)	35 (9.6)	32 (11.1)	3 (7.1)	2 (6.3)
Anxiety	479 (9.0)	69 (6.9)	410 (9.5)	169 (9.2)	94 (11.9)	47 (9.9)	44 (9.6)	21 (5.7)	28 (9.8)	4 (9.5)	3 (9.4)
Depression	489 (9.2)	78 (7.7)	411 (9.6)	156 (8.5)	98 (12.4)	41 (8.7)	40 (8.7)	34 (9.3)	33 (11.5)	3 (7.1)	6 (18.8)
Chronic pulmonary disease	374 (7.1)	44 (4.4)	330 (7.7)	124 (6.7)	85 (10.8)	38 (8.0)	36 (7.8)	24 (6.6)	16 (5.6)	4 (9.5)	3 (9.4)
Diabetes without chronic complications	341 (6.4)	53 (5.3)	288 (6.7)	129 (7.0)	53 (6.7)	23 (4.9)	25 (5.4)	30 (8.2)	23 (8.0)	1 (2.4)	4 (12.5)
Liver disease, mild	224 (4.2)	27 (2.7)	197 (4.6)	71 (3.8)	56 (7.1)	26 (5.5)	22 (4.8)	12 (3.3)	9 (3.1)	1 (2.4)	0 (0)
Asthma	241 (4.5)	27 (2.7)	214 (5.0)	84 (4.6)	54 (6.8)	21 (4.4)	24 (5.2)	17 (4.6)	8 (2.8)	3 (7.1)	3 (9.4)

[a]All patients in the overall sample who met the 12-month database enrollment criteria.
[b]CCI and comorbidities were measured during the 6 months before the index date.
CCI, Charlson Comorbidity Index; SD, standard deviation; UC, ulcerative colitis.

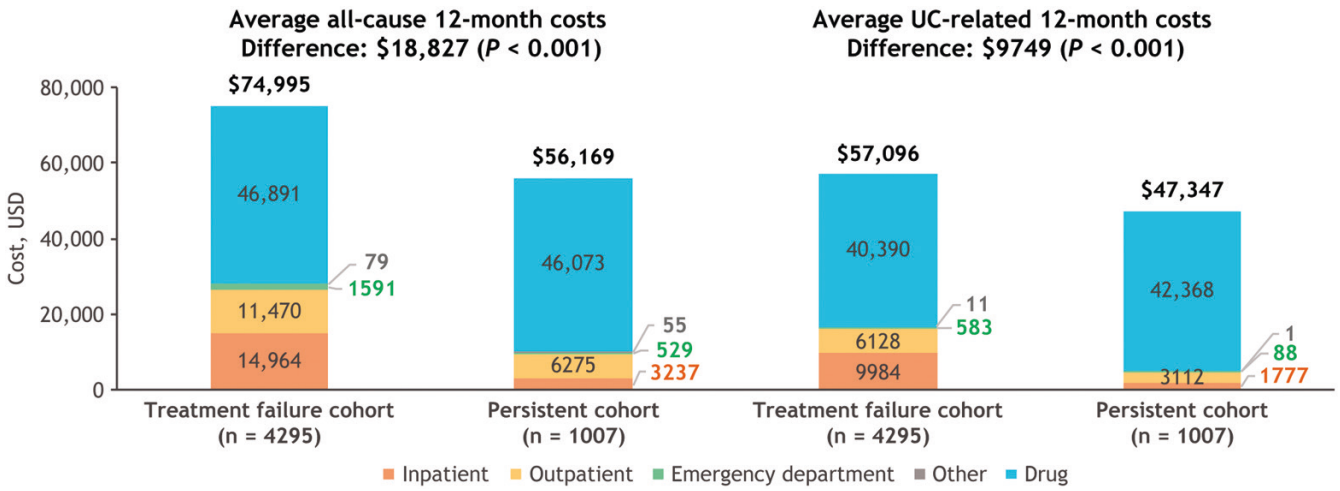

Figure 2. Average all-cause and UC-related healthcare costs in the 12-month study period for the treatment failure and the persistent cohort (2020 USD). Total costs are rounded to the nearest dollar. UC, ulcerative colitis.

Table 3. Average all-cause and UC-related HCRU in the 12-month study period for the treatment failure and persistent cohorts.

	Treatment failure cohort (n = 4295)	Persistent cohort (n = 1007)	Difference	P
All-cause HCRU				
Inpatient admissions				
% patients	28.1	7.9	20.2	<.001*
Average number	0.5	0.1	0.4	<.001*
Emergency department visits				
% of patients	40.4	27.9	12.5	<.001*
Average number	0.9	0.5	0.4	<.001*
Outpatient visits				
% patients	99.4	99.1	0.3	.423
Average number	23.1	17.0	6.1	<.001*
Gastroenterologist visits				
% patients	80.0	79.9	0.1	1.000
Average number	4.8	3.5	1.3	<.001*
UC-related HCRU				
Inpatient admissions				
% patients	25.2	6.1	19.1	<.001*
Average number	0.5	0.1	0.4	<.001*
Emergency department visits				
% patients	17.6	4.7	12.9	<.001*
Average number	0.3	0.1	0.2	<.001*
Outpatient visits				
% patients	95.0	94.2	0.8	.371
Average number	9.5	6.8	2.7	<.001*
Gastroenterologist visits				
% patients	74.3	74.1	0.2	.920
Average number	4.0	3.1	0.9	<.001*

*P < 0.05.
HCRU, healthcare resource utilization; UC, ulcerative colitis.

clinical trials have shown that advanced therapies for UC have been only modestly effective at inducing clinical remission.[21–24] Treatment failure is a frequent occurrence and its consequences are not well documented.[19] This real-world study of treatment failure among patients with UC receiving first-line advanced therapies is one of the first to assess HCRU and healthcare costs associated with treatment failure. The results of this study showed that within 12 months of initiating first-line advanced therapies for UC, 75% of patients experienced ≥1 type of treatment failure event, with augmentation

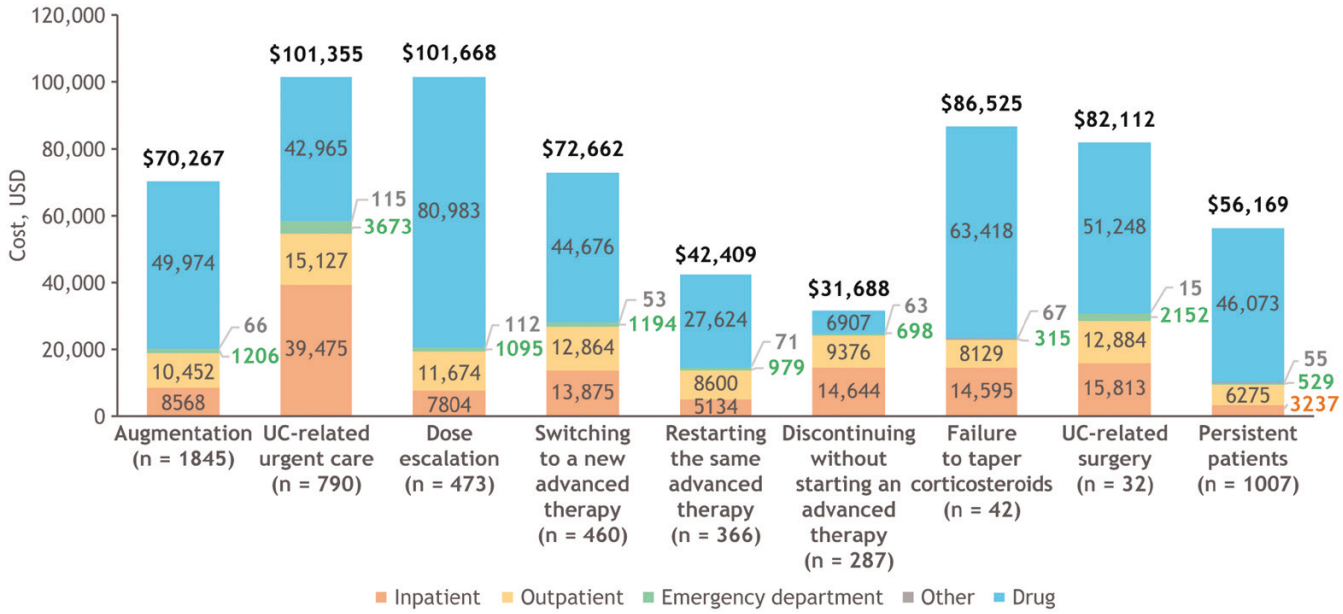

Figure 3. Average all-cause healthcare costs among patients in the treatment failure cohort during the 12-month study period, by type of first treatment failure (2020 USD). Total costs are rounded to the nearest dollar. UC, ulcerative colitis.

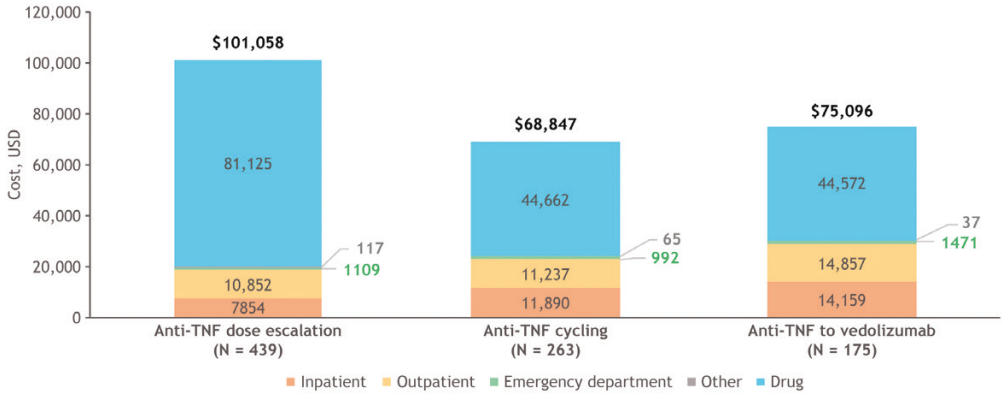

Figure 4. Average all-cause healthcare costs in the 12-month study period for the treatment failure cohort with anti-TNF dose escalation, anti-TNF cycling, or first-line anti-TNF switching to vedolizumab (2020 USD). Total costs are rounded to the nearest dollar. TNF, tumor necrosis factor.

and UC-related urgent care accounting for 54% of the first events and treatment failure occurring within a median of 5.1 months after initiation of therapy.

The overall rates of treatment failure observed in this study are largely consistent with those reported in the few previously conducted studies, including a study by Patel et al (2017), which used claims data from 2005 to 2013.[19] However, the current estimates for the specific types of treatment failure differed from those reported by Patel et al, mainly owing to the different years of data evaluated.

The consequences of treatment failure were reflected in significantly higher HCRU and healthcare costs, primarily inpatient and outpatient costs, incurred by patients experiencing treatment failure compared with those who did not during the first year after treatment failure. In particular, patients experiencing dose escalation and UC-related urgent care incurred the highest healthcare costs. At the therapy level, first-line treatment with adalimumab was associated with higher likelihood of dose escalation, while infliximab was associated with higher likelihood of augmentation and UC-related urgent care. These latter patterns associated with infliximab may be related to variations in clinical practice and patient disease characteristics rather than inherent to the therapy itself. The former finding, concerning a high rate of adalimumab dose escalation, has been noted in other real-world studies, suggesting a discrepancy between real-world and clinical trial populations.[25,26]

The different types of treatment failure observed in this study have been associated with clinical consequences in prior research studies. For example, studies report that approximately 10% to 20% of the patients treated with increased doses of infliximab or adalimumab still require colectomy within 12 to 38 months; escalated doses are also associated with higher rates of adverse events.[27–30] Furthermore, 11% to 22% of the patients cycling between anti-TNF treatments have undergone colectomy within 1 year.[30,31] These findings, together with the economic burden demonstrated in this study, suggest that more efficacious treatments with durable effectiveness are needed for patients with moderate-to-severe UC. Such treatments could reduce both the clinical and

economic burden associated with treatment failure. Payers, when making formulary decisions, should take into consideration the costs of treatment failure in addition to the costs of the drugs alone.

Finally, the healthcare costs after 1 year of dose escalation are more than $25 000 higher than that of treatment switching (including cycling between anti-TNF treatments and switching to a treatment with a different mechanism of action), primarily because of the high drug costs associated with escalated doses. Therefore, dose escalation may be a less favorable option than treatment switching from the cost perspective. Future research is needed to fully evaluate the benefits and risks of dose escalation and treatment-switching strategies.

This study has several limitations, some of which are common among retrospective claims database analyses. First, due to the lack of clinical information in the claims data, such as endoscopy data, we were unable to assess the impact of the disease characteristics and severity on treatment failure. The advanced therapies were used as a proxy for moderate-to-severe UC, which may not reflect the actual treatment paradigm for patients with moderate-to-severe UC in the real world. Second, because the data in this study were taken only from patients with employer-sponsored insurance or Medicare supplemental plans, the results may not be generalizable to the overall UC patient population in the United States. Third, because of the lack of information in claims data, we were unable to verify that each identified event was a result of treatment failure and therefore, may have misclassified some patients. For example, discontinuing and restarting advanced therapies or concurrent non-advanced treatments could indicate treatment failure (ie, discontinuation and augmentation, respectively), but they could also indicate patients' personal choices, change of insurance, or other reasons not captured in the administrative data. Fourth, because medical claims do not contain adequate information to infer dosage in each administration, interval shortening was identified using medical claims. This may lead to an underestimation of dose escalation, especially for drugs such as infliximab, which is administered through intravenous infusions and results in more medical than pharmacy claims. Finally, ustekinumab was approved by the FDA in October 2019, after the dates of data collection, and was therefore not included as an advanced treatment for UC in this study. However, the rich data on the other advanced treatments for UC still allowed a comprehensive overview of treatment failure in the past 10 years. Additionally, since the completion of this study, there has been an increase in the use of biosimilar versions of infliximab and adalimumab, which may reduce the drug costs but still impose an economic burden on patients experiencing treatment failure.

Conclusion

In conclusion, existing advanced therapies for moderate-to-severe UC are associated with high rates of treatment failure, which, in turn, can lead to substantial healthcare costs and resource utilization. Thus, there is an unmet need for more efficacious and durable treatments for UC that could help to mitigate or avoid the high economic burden associated with treatment failure.

Supplementary Material

Supplementary data are available at *Crohn's & Colitis 360* online.

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Author Contributions

Scott Lee, Keith A. Betts, Komal Gupte-Singh, and Timothy Ritter were involved in the conception or design of the study; Xiaoyu Nie and Ella Xiaoyan Du were involved in data acquisition; Keith Betts, Xiaoyu Nie, and Ella Xiaoyan Du were involved in data analysis; and Scott Lee, Keith A. Betts, Komal Gupte-Singh, and Timothy Ritter were involved in data interpretation. All authors were involved in writing and revision of the manuscript draft, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Conflicts of Interest

Komal Gupte-Singh is an employee of Bristol Myers Squibb and holds stock/options in the company. Keith A. Betts, Ella Xiaoyan Du, and Xiaoyu Nie are employees of Analysis Group, Inc., which has received consulting fees from Bristol Myers Squibb. Scott D. Lee has served as a consultant for and/or received research support from Bristol Myers Squibb, Takeda, AbbVie, Janssen, Pfizer, Protagonist, AMT, and TLL Pharmaceutical. Timothy Ritter has nothing to disclose.

Data Availability

Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html. Data are not publicly available.

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