Economic Outcomes of Inflammatory Bowel Disease Patients Switching to a Second Anti-Tumor Necrosis Factor or Vedolizumab

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Background: Anti-tumor necrosis factor (TNF) therapies have been the mainstay of inflammatory bowel disease (IBD) treatment for nearly 2 decades. Therapies with novel mechanisms of action have been recently developed. This study compared healthcare resource utilization (HRU) and costs incurred while switching from an initial anti-TNF to another anti-TNF versus switching to vedolizumab.

Methods: Adults with IBD who switched from initial anti-TNF to another anti-TNF or vedolizumab were identified from Truven MarketScan claims database (January 1, 2000–September 30, 2017). Patient characteristics were assessed during the 6-month period before the initiation date of the switched-to treatment (index date). Adjusted analyses of all-cause and disease-related HRU and costs during the 6-month period after the index date (study period) were performed. Anti-TNF and vedolizumab switchers with Crohn's disease (CD) and ulcerative colitis (UC) were separately compared.

Results: A total of 502 vedolizumab, 1708 adalimumab, 755 infliximab, and 703 other switchers with CD and 461, 428, 311, and 148 with UC, respectively, were identified. Patient demographics were similar across cohorts. Total all-cause costs were significantly higher for vedolizumab than adalimumab, infliximab, and certolizumab switchers in the CD cohort and adalimumab and infliximab in the UC cohort. In both cohorts, adalimumab and other switchers had fewer all-cause and IBD-related outpatient visits than vedolizumab switchers.

Conclusions: CD/UC patients who switched to vedolizumab from initial anti-TNF had higher total and treatment costs than patients who switched to another anti-TNF, except for UC patients who switched to golimumab. Prospective studies should be conducted to confirm these findings.

Lay Summary

Adults with inflammatory bowel disease who switched to vedolizumab from an initial anti-tumor necrosis factor (TNF) had higher healthcare resource utilization (HRU) and cost burden than patients who switched to another anti-TNF. Switching to a different anti-TNF agent is a potentially more cost-effective option than switching to vedolizumab.

Key Words: inflammatory bowel disease, anti-TNF therapy, vedolizumab, switching, healthcare resource use

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are the 2 most prevalent forms of inflammatory bowel disease (IBD). The main goals in the treatment of CD and UC are to reduce inflammation and, ultimately, induce and maintain remission.[1, 2] To this end, biologic therapies—particularly anti-tumor necrosis factor (TNF) agents—have significantly improved the management of both CD and UC by ameliorating symptoms, inducing disease remission, promoting mucosal healing, and facilitating corticosteroid tapering.[1, 3–5] While 60%–70% of patients experience early clinical response to anti-TNFs, about one-third of patients with CD or UC do not respond to anti-TNFs and some lose response over time, frequently leading to treatment changes or discontinuation.[6–10]

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Vedolizumab, a humanized α4β7-integrin monoclonal antibody, has been approved in the United States for use in patients with moderate-to-severe CD or UC who lose response, are intolerant to anti-TNFs or conventional therapy, or have a demonstrated dependence on corticosteroids.[11] Given that vedolizumab is the first widely used non-anti-TNF biologic therapy, it is important to study how to sequence therapies with different mechanisms of action optimally. In the most recent UC clinical care pathway published by the American Gastroenterological Association (AGA),[12] vedolizumab was included as a switch-to therapeutic option after loss of response to anti-TNF under therapeutic levels of the anti-TNF. Similarly, the CD clinical care pathway suggests switching to another drug class for patients who fail to respond to an anti-TNF at optimal therapeutic drug concentration and absent antidrug antibodies.[13] In addition, both guidelines suggest switching to a different drug within the same anti-TNF class in patients with high antidrug antibody levels and low levels of the current anti-TNF. The switch from one anti-TNF to another has been the focus of a recent systematic review and meta-analysis.[10] It reported that among patients with CD who received an anti-TNF after failing treatment with a previous one, the clinical remission and response rates were 43% and 63%, respectively. On the other hand, in a clinical trial of vedolizumab for CD, 27% of patients receiving vedolizumab after failure with an anti-TNF experienced clinical remission at week 10 based on the Crohn's Disease Activity Index (CDAI ≤150 points), versus 12% of placebo-treated patients.[14] In a recent head-to-head clinical trial in UC, 31% of patients receiving vedolizumab achieved clinical remission at week 52 compared to 23% of patients receiving adalimumab (an anti-TNF); however, corticosteroid-free remission rates at week 52 showed numerical but nonsignificant difference in favor for adalimumab.[15, 16]

No real-world study has compared the economic outcomes of use of vedolizumab versus that of anti-TNF drugs in patients with CD or UC after treatment of an initial anti-TNF agent. To address this gap, this study aimed to assess and compare healthcare resource utilization (HRU) and costs associated with the switch (for any reason) from one anti-TNF to another versus those associated with the switch (for any reason) from an anti-TNF to vedolizumab among patients with CD or UC in clinical practice.

METHODS

Data Source

This retrospective analysis used data from the IBM MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases (January 1, 2000–September 30, 2017; *observation period*), a nationally representative administrative claims database which reflects the healthcare experience of employees and dependents covered by the health benefit programs of more than 260 US employers. Data are collected from more than 40 health plans and represent nearly 240 million covered lives. The databases contain patient demographics, enrollment history, claims for inpatient and outpatient medical services, and claims for pharmacy services.

Ethical Considerations

No ethics review was required for the use of the retrospective de-identified claims data used in this study.

Sample Selection

To be included in the study, patients were required to have (1) at least 2 entries with a diagnosis of CD (International Classification of Diseases Ninth/Tenth Revision, Clinical Modification [ICD-9-CM]: 555.xx or [ICD-10-CM]: K50.xx) or UC (ICD-9-CM: 556.xx or ICD-10-CM: K51.xx), (2) at least 2 claims for an anti-TNF after the relevant US Food and Drug Administration approval date, and (3) a switch to a relevant treatment (*index treatment*) for any reason. The initiation date of the index treatment was defined as the *index date*. Patients were additionally required to (1) be at least 18 years of age as of the *index date*, (2) have at least 6 months of continuous eligibility before (*baseline period*) and after (*study period*) the index date, and (3) have at least 1 CD or UC diagnosis in the baseline period. Two sample subgroups were selected separately for CD and UC: (1) vedolizumab switchers, which included patients who were treated with an initial anti-TNF and switched to vedolizumab and (2) anti-TNF switchers, which included patients who were treated with an initial anti-TNF and switched to another anti-TNF. Anti-TNF switchers were further split into 3 groups for each cohort: patients who switched to adalimumab, infliximab, or certolizumab pegol for the CD cohort, and patients who switched to adalimumab, infliximab, or golimumab for the UC cohort. The results and comparisons to vedolizumab switchers are presented separately for each of these anti-TNF subgroups.

Vedolizumab switchers were identified as patients with at least 2 claims for vedolizumab, use of an anti-TNF in the 6-month period before vedolizumab initiation and use of no more than one anti-TNF at any time before vedolizumab initiation. Vedolizumab claims were identified by the following methods: (1) a prescription claim for vedolizumab identified in outpatient prescription claims via a National Drug Code of 64764030020; or (2) an office-administered medication claim for vedolizumab with a Healthcare Common Procedure Coding System (HCPCS) code of C9026 or J3380. The vedolizumab-specific HCPCS code was issued on January 1, 2016, so claims before this date were also identified by unclassified codes of J3590, J3490, or C9399 with a diagnosis code of CD or UC on the claim, and with a payment amount on the claim of at

least $4500. Vedolizumab was defined as the *index treatment* for vedolizumab switchers.

Anti-TNF switchers were identified as patients with at least 2 claims for each of at least 2 different anti-TNFs, use of an anti-TNF in the 6-month period before switch-to anti-TNF initiation and use of no more than one anti-TNF at any time before the switch-to anti-TNF initiation. The switched-to anti-TNF was defined as the *index treatment* for the anti-TNF switchers.

Patients were excluded from the study if they had a prescription for the initial anti-TNF in the 30 days after the index date, if they had a liver transplant or malignancy at any time during the observation period, or if they had claims for the treatment that was switched to (second anti-TNF or vedolizumab) before the index date.

Study Variables

Baseline characteristics

Patients' age and sex were measured at the index date. Characteristics measured during the baseline period included Charlson Comorbidity Index (CCI) score,[17] use of CD or UC therapies (corticosteroids, immunomodulators, or narcotics), all-cause HRU, and total all-cause healthcare costs (adjusted to 2017 US dollars [USD] using the Consumer Price Index, medical component[18]).

In addition, loss of response to the initial anti-TNF was estimated during the baseline period. As clinical data are not present in a claims dataset, loss of response was defined by the presence of a CD- or UC-related urgent care (defined as any emergency room [ER] visit or inpatient admission with a CD or UC diagnosis code) or surgery, an increase in frequency of the treatment during maintenance phase or the addition of a CD or UC treatment (ie, azathioprine, 6-mercaptopurine, methotrexate, or corticosteroids), use of parenteral nutrition therapy, or a newly diagnosed fistula, intestinal abscess, or stricture.[19]

Outcome measures

All-cause HRU and CD- or UC-related HRU (defined as medical services associated with a diagnosis code of CD or UC) were measured during the 6-month study period and included the number of inpatient admissions, hospitalization days, ER visits, and outpatient visits. All-cause healthcare costs and CD- or UC- related healthcare costs (defined as costs for medical services associated with a diagnosis code of CD or UC) assessed from the payer's perspective were measured during the study period. These included medical service costs (hospitalization, ER, and outpatient costs excluding outpatient medical claims associated with index treatment injections), treatment costs (index treatment costs and other pharmacy costs), and total costs (the sum of medical service and treatment costs).

Statistical Analysis

Categorical variables were compared between vedolizumab switchers and each of the anti-TNF switcher subgroups within the CD and UC cohorts using chi-squared tests (or Fisher's exact tests if frequencies were <5). Continuous variables were compared using Wilcoxon rank-sum tests. For HRU outcomes, unadjusted and adjusted incidence rate ratios (IRRs) were estimated using negative binomial regression models. Adjusted cost differences were estimated using a generalized linear model with a gamma distribution; for outcomes with at least 5% zeros, a Tweedie distribution was used. For all the adjusted analyses, age, sex, CCI, use of immunomodulators, use of systemic corticosteroids, use of narcotics, baseline loss of response, baseline number of inpatient admissions, baseline number of ER visits, baseline number of outpatient visits, and baseline all-cause medical and treatment costs were included in the models. A $P < 0.05$ was used to determine significance. Statistical analyses were performed using SAS Enterprise Guide 7.1.

RESULTS

Sample Selection

A total of 3668 patients with CD and 1348 patients with UC met the sample selection criteria and were included in the analysis (Supplementary Figure S1). In the CD cohort, 502 patients were classified as vedolizumab switchers, 1708 patients as adalimumab switchers, 755 patients as infliximab switchers, and 703 patients as certolizumab switchers. In the UC cohort, 461 patients were classified as vedolizumab switchers, 428 patients as adalimumab switchers, 311 patients as infliximab switchers, and 148 patients as golimumab switchers.

Baseline Characteristics

Among all switchers in both CD and UC cohorts, the mean age of patients at the index date ranged between 38 and 42 years, with adalimumab switchers and infliximab switchers being younger than vedolizumab switchers in the CD cohort (both $P < 0.01$); the proportion of males ranged from 39% to 54% across both cohorts (Tables 1 and 2). Mean baseline CCI was not significantly different between vedolizumab switchers and adalimumab, infliximab, or other switchers in either CD or UC cohort. However, adalimumab switchers and other switchers had less severe baseline disease than vedolizumab switchers, as shown by a significantly lower prevalence of select findings associated with IBD in both the CD and UC cohorts (eg, symptoms of the abdomen and pelvis, intestinal disorders, or diarrhea). Vedolizumab switchers had more baseline use of systemic corticosteroids than adalimumab switchers in the CD cohort (72% vs 66%, respectively; $P = 0.0113$) and in the UC cohort (84% vs 74%; $P = 0.0003$). In the CD cohort, vedolizumab switchers had less baseline use of narcotics than

infliximab switchers (44% vs 50%; $P = 0.0283$), as well as less baseline use of immunomodulators (28% vs 34%; $P = 0.0227$).

Vedolizumab switchers had a larger proportion of patients with loss of response to the initial anti-TNF than adalimumab switchers (92% vs 84%; $P < 0.0001$) and certolizumab pegol switchers in the CD cohort (92% vs 86%; $P = 0.0019$) and adalimumab switchers in the UC cohort (95% vs 90%; $P = 0.0088$) (Tables 1 and 2).

In the UC cohort, vedolizumab switchers incurred significantly higher baseline all-cause outpatient visits than infliximab switchers (14 vs 12 visits; $P = 0.0003$) and golimumab switchers (14 vs 11; $P = 0.0005$) and significantly higher baseline all-cause inpatient admissions than golimumab switchers (0.32 vs 0.16 admissions; $P = 0.0130$) (Table 2). Vedolizumab switchers incurred significantly higher baseline all-cause total costs than adalimumab, infliximab, and certolizumab pegol switchers in the CD cohort (all $P < 0.0001$) and adalimumab and golimumab switchers in the UC cohort (both $P < 0.0001$) (Tables 1 and 2).

HRU and Healthcare Costs

All-cause and IBD-related outpatient visits after the index date were significantly higher among vedolizumab switchers than among adalimumab switchers (all $P < 0.0001$; Tables 3 and 4) in both the UC and CD cohorts. Among patients with CD, vedolizumab switchers had a 1.5- to 2-fold increase in all-cause (adjusted IRR [95% CI] = 1.52 [1.20–1.93]) and CD-related (adjusted IRR [95% CI] = 2.08 [1.47–2.96]) ER visits and significantly more all-cause inpatient admissions (adjusted IRR [95% CI] = 1.33 [1.01–1.75]) than adalimumab switchers (Table 3). There were no significant differences between vedolizumab and infliximab switchers in the CD cohort (Table 3), but vedolizumab switchers had significantly more UC-related outpatient visits (adjusted IRR [95% CI] = 1.20 [1.07–1.33]) than infliximab switchers in the UC cohort (Table 4). All-cause and IBD-related outpatient visits were significantly higher among vedolizumab switchers than among other switchers (all $P < 0.0001$; Tables 3 and 4) in both the UC and CD cohorts.

For patients with CD (Table 5), the all-cause (adjusted mean difference: $5917; $P < 0.0001$) and CD-related ($3980; $P < 0.0001$) medical costs were significantly higher among vedolizumab switchers than adalimumab switchers, primarily driven by higher outpatient and ER costs; vedolizumab switchers also incurred higher all-cause ER costs than infliximab switchers and higher all-cause outpatient and ER costs than certolizumab pegol switchers. Additionally, vedolizumab switchers incurred higher treatment costs compared to adalimumab ($11,173; $P < 0.0001$), infliximab ($9009; $P < 0.0001$), and certolizumab pegol switchers ($15,825; $P < 0.0001$); these differences were driven by the higher costs for vedolizumab. Vedolizumab switchers incurred higher total costs compared to adalimumab ($16,562; $P < 0.0001$), infliximab ($7785; $P < 0.0001$), and other switchers ($16,736; $P < 0.0001$).

For patients with UC (Table 6), the all-cause ($3687; $P = 0.0014$) and UC-related ($2855; $P = 0.0158$) medical costs were also significantly higher among vedolizumab switchers than adalimumab switchers, primarily driven by higher outpatient costs; all-cause medical costs were also significantly higher among vedolizumab than golimumab switchers. Additionally, vedolizumab switchers incurred higher treatment costs compared to adalimumab switchers ($5851; $P < 0.0001$), which were driven by the higher costs of vedolizumab, and compared to infliximab switchers ($4388; $P = 0.0025$), which were driven by higher non-index treatment costs. Vedolizumab switchers incurred higher total costs than adalimumab ($9524; $P < 0.0001$) and infliximab switchers ($4249; $P = 0.0396$).

DISCUSSION

To the best of our knowledge, the current study is the first to compare the real-world economic outcomes of patients who switched from an initial anti-TNF to a second anti-TNF (ie, adalimumab, infliximab, certolizumab, pegol, or golimumab) or to vedolizumab. The results showed that, after adjusting for baseline characteristics, vedolizumab switchers incurred a higher HRU burden than the anti-TNF switchers. IBD costs have shifted from inpatient to outpatient care since the introduction of biologic therapies as the standard of care. However, in both the CD and UC cohorts, all-cause and IBD-related outpatient visits were significantly higher among vedolizumab switchers than adalimumab and other switchers, and no statistical differences were observed with infliximab switchers. These differences impact outpatient costs and reflect that vedolizumab and infliximab incur higher outpatient costs because they require outpatient intravenous infusions for their administration.

The results also showed that, for patients with CD or UC, the all-cause total costs were significantly higher among patients switching to vedolizumab compared with patients who switched to other anti-TNF agents including adalimumab, infliximab, or certolizumab. In most cases this was driven mainly by higher vedolizumab treatment costs.

There are many studies that assess the clinical effectiveness of subsequent anti-TNF treatment among patients with IBD who have failed a previous anti-TNF; these studies show that a second anti-TNF is still effective for patients with CD. For example, Gisbert et al[10] conducted a systematic review and meta-analysis evaluating the efficacy and safety of a subsequent anti-TNF treatment among patients with IBD who had failed a previous anti-TNF; the response rate after primary nonresponse reported in that study was 53% for adalimumab as the second anti-TNF among patients with CD. Ma et al[20] conducted a systematic review to determine the efficacy of adalimumab in CD patients who discontinued infliximab; the reported response at 4 weeks ranged from 41% to 83%.

TABLE 1. Baseline Characteristics for CD Patients

Baseline Characteristics	Vedolizumab Switchers [A] N = 502	Adalimumab Switchers [B] N = 1708	*P* [A] vs [B]	Infliximab Switchers [C] N = 755	*P* [A] vs [C]	Certolizumab Pegol Switchers [D] N = 703	*P* [A] vs [D]
Demographics							
Age as of the index date, mean (SD)	41.6 (14.8)	39.5 (14.7)	0.0066*	38.2 (13.8)	<0.0001*	40.6 (14.0)	0.2591
Male, n (%)	216 (43.0%)	749 (43.9%)	0.7433	294 (38.9%)	0.1483	274 (39.0%)	0.1580
Comorbidities							
CCI, mean (SD)	0.43 (0.86)	0.37 (0.81)	0.0695	0.38 (0.83)	0.2869	0.41 (0.92)	0.3878
Select additional findings, n (%)							
Symptoms of the abdomen and pelvis	257 (51.2%)	612 (35.8%)	<0.0001*	395 (52.3%)	0.6964	294 (41.8%)	0.0013*
Intestinal disorders	253 (50.4%)	546 (32.0%)	<0.0001*	352 (46.6%)	0.1894	249 (35.4%)	<0.0001*
Abdominal pain	218 (43.4%)	587 (34.4%)	0.0002*	370 (49.0%)	0.0521	287 (40.8%)	0.3669
Diarrhea	200 (39.8%)	361 (21.1%)	<0.0001*	273 (36.2%)	0.1870	173 (24.6%)	<0.0001*
Noninfectious gastroenteritis and colitis	175 (34.9%)	435 (25.5%)	<0.0001*	275 (36.4%)	0.5712	204 (29.0%)	0.0313*
Anemia	147 (29.3%)	355 (20.8%)	<0.0001*	201 (26.6%)	0.3019	159 (22.6%)	0.0088*
Respiratory or other chest symptoms	103 (20.5%)	308 (18.0%)	0.2084	144 (19.1%)	0.5277	122 (17.4%)	0.1647
Hypertension	99 (19.7%)	251 (14.7%)	0.0067*	112 (14.8%)	0.0232*	110 (15.6%)	0.0656
Treatment pattern							
Baseline therapies, n (%)							
Systemic corticosteroids	359 (71.5%)	1118 (65.5%)	0.0113*	569 (75.4%)	0.1283	481 (68.4%)	0.2494
Immunomodulators	139 (27.7%)	426 (24.9%)	0.2147	255 (33.8%)	0.0227*	164 (23.3%)	0.0854
Narcotics	221 (44.0%)	805 (47.1%)	0.2197	380 (50.3%)	0.0283*	349 (49.6%)	0.0540
All-cause HRU at baseline							
Number of inpatient admissions, mean (SD)	0.33 (0.73)	0.28 (0.65)	0.3033	0.36 (0.75)	0.2580	0.29 (0.68)	0.4869
Number of ER visits, mean (SD)	0.49 (1.16)	0.43 (1.06)	0.2304	0.47 (1.09)	0.5598	0.42 (0.98)	0.3383
Number of outpatient visits, mean (SD)	13.34 (9.40)	13.78 (9.34)	0.2587	13.35 (9.58)	0.6498	13.17 (9.23)	0.5174
All-cause healthcare costs at baseline (2017 USD)							
Total costs, mean (SD)	$42,054 ($31,428)	$34,102 ($32,153)	<0.0001*	$36,679 ($28,284)	<0.0001*	$33,738 ($32,332)	<0.0001*
Medical costs	$24,251 ($31,718)	$29,006 ($27,792)	<0.0001*	$17,189 ($27,068)	<0.0001*	$19,664 ($31,906)	0.0010*
Drug costs	$17,803 ($14,762)	$5096 ($18,875)	<0.0001*	$19,490 ($10,747)	0.0023*	$14,075 ($11,973)	<0.0001*
Patients with loss of response to the initial anti-TNF, n (%)	460 (91.6%)	1431 (83.8%)	<0.0001*	696 (92.2%)	0.7244	603 (85.8%)	0.0019*

*$P < 0.05$.

CCI, Charlson Comorbidity Index; CD, Crohn's disease; SD, standard deviation; TNF, anti-tumor necrosis factor; USD, United States Dollar.

TABLE 2. Baseline Characteristics for UC Patients

Baseline Characteristics	Vedolizumab Switchers [A] N = 461	Adalimumab Switchers [B] N = 428	*P* [A] vs [B]	Infliximab Switchers [C] N = 311	*P* [A] vs [C]	Golimumab Switchers [D] N = 148	*P* [A] vs [D]
Demographics							
Age as of the index date, mean (SD)	42.0 (14.6)	41.5 (14.6)	0.6299	41.4 (14.7)	0.5012	42.7 (14.0)	0.4840
Male, n (%)	241 (52.3%)	206 (48.1%)	0.2166	167 (53.7%)	0.6983	72 (48.6%)	0.4422
Comorbidities							
CCI, mean (SD)	0.44 (0.89)	0.43 (0.78)	0.4996	0.36 (0.71)	0.6368	0.43 (0.95)	0.8905
Select additional findings, n (%)							
Symptoms of the abdomen and pelvis	227 (49.2%)	147 (34.3%)	<0.0001*	149 (47.9%)	0.7167	52 (35.1%)	0.0027*
Intestinal disorders	219 (47.5%)	140 (32.7%)	<0.0001*	155 (49.8%)	0.5245	56 (37.8%)	0.0398*
Abdominal pain	165 (35.8%)	131 (30.6%)	0.1012	124 (39.9%)	0.2506	42 (28.4%)	0.0976
Diarrhea	235 (51.0%)	138 (32.2%)	<0.0001*	157 (50.5%)	0.8929	59 (39.9%)	0.0186*
Noninfectious gastroenteritis and colitis	203 (44.0%)	175 (40.9%)	0.3430	166 (53.4%)	0.0108*	65 (43.9%)	0.9803
Anemia	121 (26.2%)	102 (23.8%)	0.4065	93 (29.9%)	0.2656	29 (19.6%)	0.1022
Respiratory or other chest symptoms	100 (21.7%)	95 (22.2%)	0.8559	62 (19.9%)	0.5567	25 (16.9%)	0.2084
Hypertension	91 (19.7%)	81 (18.9%)	0.7587	55 (17.7%)	0.4746	29 (19.6%)	0.9692
Treatment pattern							
Baseline therapies, n (%)							
Systemic corticosteroids	388 (84.2%)	318 (74.3%)	0.0003*	269 (86.5%)	0.3724	122 (82.4%)	0.6192
Immunomodulators	144 (31.2%)	109 (25.5%)	0.0568	118 (37.9%)	0.0536	38 (25.7%)	0.1985
Narcotics	177 (38.4%)	182 (42.5%)	0.2100	133 (42.8%)	0.2244	63 (42.6%)	0.3661
All-cause HRU at baseline							
Number of inpatient admissions, mean (SD)	0.32 (0.71)	0.31 (0.66)	0.9697	0.39 (0.81)	0.3374	0.16 (0.43)	0.0130*
Number of ER visits, mean (SD)	0.43 (0.95)	0.39 (0.94)	0.7949	0.49 (1.22)	0.9667	0.24 (0.59)	0.1033
Number of outpatient visits, mean (SD)	14.19 (8.80)	14.65 (9.72)	0.7523	12.44 (8.32)	0.0003*	11.35 (6.26)	0.0005*
All-cause healthcare costs at baseline (2017 USD)							
Total costs, mean (SD)	$43,358 ($28,350)	$37,855 ($30,360)	<0.0001*	$40,020 ($26,561)	0.0748	$34,649 ($21,220)	<0.0001*
Medical costs	$25,213 ($29,962)	$32,187 ($29,469)	<0.0001*	$15,831 ($26,203)	<0.0001*	$14,106 ($20,428)	<0.0001*
Drug costs	$18,144 ($15,452)	$5667 ($11,481)	<0.0001*	$24,189 ($10,202)	<0.0001*	$20,543 ($16,135)	0.1698
Patients with loss of response to the initial anti-TNF, n (%)	437 (94.8%)	386 (90.2%)	0.0088*	293 (94.2%)	0.7267	134 (90.5%)	0.0627

*$P < 0.05$.

CCI, Charlson Comorbidity Index; CD, Crohn's disease; SD, standard deviation; TNF, anti-tumor necrosis factor; USD, United States Dollar.

TABLE 3. Healthcare Resource Utilization for CD Patients

	Mean Number of Admissions/Visits		Adjusted Healthcare Resource Utilization	
	Vedolizumab Switchers N = 502	Adalimumab Switchers N = 1708	IRR (95% CI) [Vedo]/[Ada]	*P*
All-cause healthcare resource utilization				
Inpatient admissions	0.28	0.21	1.33 (1.01–1.75)	0.0411*
Total hospitalization days	1.61	1.35	1.48 (0.94–2.32)	0.0894
Outpatient visits	16.57	11.20	1.52 (1.43–1.62)	<0.0001*
ER visits	0.58	0.36	1.52 (1.20–1.93)	0.0005*
CD-related healthcare resource utilization				
Inpatient admissions	0.22	0.17	1.29 (0.95–1.73)	0.1013
Total hospitalization days	1.28	1.11	1.47 (0.90–2.41)	0.1232
Outpatient visits	8.40	4.01	2.16 (1.98–2.36)	<0.0001*
ER visits	0.29	0.13	2.08 (1.47–2.96)	<0.0001*
	Vedolizumab Switchers N = 502	Infliximab Switchers N = 755	IRR (95% CI) [Vedo]/[Ifx]	*P*
All-cause healthcare resource utilization				
Inpatient admissions	0.28	0.28	0.96 (0.72–1.27)	0.7698
Total hospitalization days	1.61	1.82	0.92 (0.58–1.47)	0.7290
Outpatient visits	16.57	15.62	1.03 (0.98–1.09)	0.2383
ER visits	0.58	0.43	1.19 (0.91–1.54)	0.2058
CD-related healthcare resource utilization				
Inpatient admissions	0.22	0.24	0.88 (0.65–1.19)	0.4189
Total hospitalization days	1.28	1.61	0.86 (0.52–1.42)	0.5551
Outpatient visits	8.40	8.26	1.01 (0.94–1.10)	0.7075
ER visits	0.29	0.20	1.07 (0.72–1.59)	0.7330
	Vedolizumab Switchers N = 502	Certolizumab Pegol Switchers N = 703	IRR (95% CI) [Vedo]/[Czp]	*P*
All-cause healthcare resource utilization				
Inpatient admissions	0.28	0.29	0.95 (0.71–1.26)	0.7074
Total hospitalization days	1.61	1.80	1.09 (0.68–1.75)	0.7208
Outpatient visits	16.57	12.70	1.31 (1.23–1.40)	<0.0001*
ER visits	0.58	0.38	1.25 (0.96–1.63)	0.1013
CD-related healthcare resource utilization				
Inpatient admissions	0.22	0.25	0.87 (0.65–1.19)	0.3900
Total hospitalization days	1.28	1.62	1.11 (0.66–1.84)	0.7019
Outpatient visits	8.40	5.15	1.62 (1.48–1.77)	<0.0001*
ER visits	0.29	0.16	1.35 (0.92–2.00)	0.1283

*P <0.05.
Ada, adalimumab; CD, Crohn's disease; CI, confidence interval; Czp, certolizumab pegol; ER, emergency room; Ifx, infliximab; IRR: incidence rate ratio; Vedo, vedolizumab.

In addition, the GAIN (Gauging Adalimumab Efficacy in Infliximab Nonresponders) study demonstrated that CD patients who lost response or developed intolerance to infliximab and then received adalimumab had, at 4 weeks, a 52% response rate (defined as a decrease from baseline in CDAI score of 70 points or more).[21] Real-world studies showed that a large proportion of patients with CD lose response to vedolizumab after 6 months. For example, a retrospective cohort study published in 2016 reported that only 35% of patients with CD receiving vedolizumab achieved clinical remission by 12 months, and that patients with prior anti-TNF exposure were less likely to achieve remission.[22] This in turn may translate into higher medical costs and HRU, as observed in the current study.

The current findings provide initial real-world evidence on direct outcome comparisons between a second anti-TNF and vedolizumab among anti-TNF experienced patients with

CD or UC. These findings provide important insight on comparative effectiveness that can help inform treatment decisions. Among patients who have used an anti-TNF drug but experienced a secondary loss of response, switching within class and the use of a new mechanism of action are both viable options from a clinical standpoint. However, this study found that a second anti-TNF may be a more cost-effective option than vedolizumab. A recent cost-effectiveness study also suggested that using adalimumab as a second-line treatment for UC is a more cost-effective strategy than using vedolizumab.[23] In adults with active IBD treated with anti-TNF agents, the AGA recommends therapeutic drug monitoring to guide treatment changes. For example, the guidelines suggest that in patients with high antidrug antibody levels and low levels of the current drug, switching to a different drug within the same class (or to a different drug class) may be effective.[24] The results of the current

TABLE 4. Healthcare Resource Utilization for UC Patients

	Mean Number of Admissions/Visits		Adjusted Resource Utilization	
	Vedolizumab Switchers N = 461	Adalimumab Switchers N = 428	IRR (95% CI) [Vedo]/[Ada]	*P*
All-cause healthcare resource utilization				
Inpatient admissions	0.26	0.25	1.01 (0.68–1.49)	0.9726
Total hospitalization days	1.70	1.84	1.06 (0.53–2.13)	0.8586
Outpatient visits	16.49	11.84	1.47 (1.36–1.59)	<0.0001*
ER visits	0.40	0.37	1.17 (0.82–1.66)	0.3890
UC-related healthcare resource utilization				
Inpatient admissions	0.19	0.17	1.02 (0.66–1.58)	0.9275
Total hospitalization days	1.29	1.29	0.98 (0.46–2.10)	0.9624
Outpatient visits	8.04	3.58	2.10 (1.88–2.34)	<0.0001*
ER visits	0.09	0.08	1.13 (0.58–2.18)	0.7169
	Vedolizumab Switchers N = 461	Infliximab Switchers N = 311	IRR (95% CI) [Vedo]/[Ifx]	*P*
All-cause healthcare resource utilization				
Inpatient admissions	0.26	0.27	0.95 (0.63–1.43)	0.8089
Total hospitalization days	1.70	1.93	0.87 (0.44–1.73)	0.6919
Outpatient visits	16.49	14.87	1.04 (0.97–1.12)	0.2860
ER visits	0.40	0.41	0.87 (0.60–1.27)	0.4802
UC-related healthcare resource utilization				
Inpatient admissions	0.19	0.22	1.05 (0.66–1.64)	0.8489
Total hospitalization days	1.29	1.54	1.03 (0.47–2.27)	0.9380
Outpatient visits	8.04	6.93	1.20 (1.07–1.33)	0.0011*
ER visits	0.09	0.14	0.68 (0.35–1.35)	0.2734
	Vedolizumab Switchers N = 461	Golimumab Switchers N = 148	IRR (95% CI) [Vedo]/[Gol]	*P*
All-cause healthcare resource utilization				
Inpatient admissions	0.26	0.18	1.06 (0.61–1.85)	0.8232
Total hospitalization days	1.70	1.46	1.26 (0.51–3.10)	0.6179
Outpatient visits	16.49	9.95	1.50 (1.36–1.65)	<0.0001*
ER visits	0.40	0.28	1.22 (0.74–2.01)	0.4408
UC-related healthcare resource utilization				
Inpatient admissions	0.19	0.15	1.07 (0.59–1.96)	0.8157
Total hospitalization days	1.29	1.34	1.40 (0.50–3.95)	0.5223
Outpatient visits	8.04	4.01	1.88 (1.65–2.14)	<0.0001*
ER visits	0.09	0.08	1.39 (0.47–4.18)	0.5528

*$P < 0.05$.

Ada, adalimumab; CD, Crohn's disease; CI, confidence interval; Czp, certolizumab pegol; ER, emergency room; Gol, golimumab; Ifx, infliximab; IRR: incidence rate ratio; Vedo, vedolizumab.

TABLE 5. Healthcare Costs for CD Patients

	Unadjusted Mean Healthcare Costs (2017 USD)		Adjusted Healthcare Costs (2017 USD)	
	Vedolizumab Switchers N = 502	Adalimumab Switchers N = 1708	Mean Difference [Vedo] −[Ada]	*P*
All-cause healthcare costs				
Total costs	$53,374	$34,957	$16,562	<0.0001*
Medical costs	$16,637	$11,631	$5917	<0.0001*
Hospitalization costs	$6667	$5720	$907	0.3202
Outpatient costs	$8525	$5299	$3786	<0.0001*
ER costs	$1445	$611	$401	<0.0001*
Drug costs	$36,737	$23,326	$11,173	<0.0001*
Treatment costs related to index treatment	$32,728	$20,912	$10,633	<0.0001*
Pharmacy costs excluding index treatment	$4009	$2413	$192	0.2839
CD-related healthcare costs				
Medical costs	$9491	$5567	$3980	<0.0001*
Hospitalization costs	$4372	$3224	$1043	0.0950
Outpatient costs	$4385	$2091	$2503	<0.0001*
ER costs	$735	$253	$249	<0.0001*
	Vedolizumab Switchers N = 502	Infliximab Switchers N = 755	Mean Difference [Vedo] −[Ifx]	*P*
All-cause healthcare costs				
Total costs	$53,374	$44,009	$7785	<0.0001*
Medical costs	$16,637	$16,966	−$1175	0.2366
Hospitalization costs	$6667	$8275	−$1491	0.1797
Outpatient costs	$8525	$7928	−$281	0.4740
ER costs	$1445	$763	$260	0.0153*
Drug costs	$36,737	$27,043	$9009	<0.0001*
Treatment costs related to index treatment	$32,728	$24,525	$7472	<0.0001*
Pharmacy costs excluding index treatment	$4009	$2518	$1486	<0.0001*
CD-related healthcare costs				
Medical costs	$9491	$10,513	−$1134	0.3185
Hospitalization costs	$4372	$5480	−$844	0.3597
Outpatient costs	$4385	$4669	−$512	0.1692
ER costs	$735	$364	$105	0.2212
	Vedolizumab Switchers N = 502	Certolizumab Pegol Switchers N = 703	Mean Difference [Vedo] −[Czp]	*P*
All-cause healthcare costs				
Total costs	$53,374	$35,890	$16,736	<0.0001*
Medical costs	$16,637	$15,636	$1851	0.0939
Hospitalization costs	$6667	$8331	−$1516	0.2406
Outpatient costs	$8525	$6666	$1554	0.0004*
ER costs	$1445	$638	$257	0.0082*
Drug costs	$36,737	$20,255	$15,825	<0.0001*
Treatment costs related to index treatment	$32,728	$17,134	$15,135	<0.0001*
Pharmacy costs excluding index treatment	$4009	$3121	$454	0.1001
CD-related healthcare costs				
Medical costs	$9491	$7735	$1839	0.1129
Hospitalization costs	$4372	$4695	$31	0.9718
Outpatient costs	$4385	$2756	$1453	<0.0001*
ER costs	$735	$284	$128	0.0539

*$P < 0.05$.

Ada, adalimumab; CD, Crohn's disease; Czp, certolizumab pegol; ER, emergency room; Ifx, infliximab; Vedo, vedolizumab; USD, United States Dollar.

TABLE 6. Healthcare Costs for UC Patients

	Unadjusted Mean Healthcare Costs (2017 USD)		Adjusted Healthcare Costs (2017 USD)	
	Vedolizumab Switchers	Adalimumab Switchers	Mean Difference	*P*
	N = 461	N = 428	[Vedo] −[Ada]	
All-cause healthcare costs				
Total costs	$54,528	$43,118	$9524	<0.0001*
Medical costs	$17,839	$13,545	$3687	0.0014*
Hospitalization costs	$9082	$7600	$168	0.8903
Outpatient costs	$7768	$5216	$3129	<0.0001*
ER costs	$989	$729	$206	0.1091
Drug costs	$36,689	$29,573	$5851	<0.0001*
Treatment costs related to index treatment	$32,864	$26,098	$6237	<0.0001*
Pharmacy costs excluding index treatment	$3825	$3475	−$167	0.5443
UC-related healthcare costs				
Medical costs	$9207	$5855	$2855	0.0158*
Hospitalization costs	$5007	$3993	$535	0.5793
Outpatient costs	$3960	$1716	$2235	<0.0001*
ER costs	$240	$146	$69	0.1799
	Vedolizumab Switchers	Infliximab Switchers	Mean Difference	*P*
	N = 461	N = 311	[Vedo] −[Ifx]	
All-cause healthcare costs				
Total costs	$54,528	$47,861	$4249	0.0396*
Medical costs	$17,839	$15,999	−$1731	0.1760
Hospitalization costs	$9082	$8021	$171	0.8888
Outpatient costs	$7768	$7008	−$126	0.7874
ER costs	$989	$970	$56	0.7252
Drug costs	$36,689	$31,862	$4388	0.0025*
Treatment costs related to index treatment	$32,864	$28,948	$3390	0.0524
Pharmacy costs excluding index treatment	$3825	$2914	$953	0.0044*
UC-related healthcare costs				
Medical costs	$9207	$8692	$298	0.8270
Hospitalization costs	$5007	$5080	−$7	0.9940
Outpatient costs	$3960	$3345	$420	0.3457
ER costs	$240	$267	−$51	0.4870
	Vedolizumab Switchers	Golimumab Switchers	Mean Difference	*P*
	N = 461	N = 148	[Vedo] −[Gol]	
All-cause healthcare costs				
Total costs	$54,528	$49,677	−$791	0.7460
Medical costs	$17,839	$11,629	$4314	0.0006*
Hospitalization costs	$9082	$6055	−$1147	0.4569
Outpatient costs	$7768	$5214	$2687	<0.0001*
ER costs	$989	$360	$267	0.0949
Drug costs	$36,689	$38,048	−$2678	0.1202
Treatment costs related to index treatment	$32,864	$32,598	−$843	0.6835
Pharmacy costs excluding index treatment	$3825	$5450	−$1259	0.0138*
UC-related healthcare costs				
Medical costs	$9207	$6405	$1103	0.4587
Hospitalization costs	$5007	$4389	−$923	0.3964
Outpatient costs	$3960	$1959	$1819	0.0010*
ER costs	$240	$56	$80	0.1356

*$P < 0.05$.

Ada, adalimumab; Czp, certolizumab pegol; ER, emergency room; Gol, golimumab; Ifx, infliximab; n, number; Vedo, vedolizumab; UC, ulcerative colitis; USD, United States Dollar.

study favoring switching within the same anti-TNF class over vedolizumab would be most relevant in this setting. On the other hand, patients who are not responding to treatment, despite having optimal drug levels, would be unlikely to respond to other drugs of the same class. Future research is warranted to identify subgroups of patients with IBD who could benefit most from a second anti-TNF or vedolizumab following initial anti-TNF therapy.

Limitations

The claims data used in this analysis represent a large and valid dataset. However, this study was subject to some limitations. First, the baseline disease severity information was not directly available in administrative claims data and is likely different between the patient cohorts. The findings were consistent after adjusting for population characteristics and proxy disease severity variables (ie, age, sex, CCI, use of immunomodulators, use of systemic corticosteroids, use of narcotics, baseline loss of response, baseline number of inpatient admissions, baseline number of ER visits, baseline number of outpatient visits, and baseline all-cause medical and treatment costs) in multivariable models. The variables for adjustment were selected because of observed differences between groups at baseline and because they were identified as potential indicators of severity in prior literature.[25, 26] However, as with any real-world analysis, there could still be residual confounding due to unmeasured confounding variables. Second, the identification of vedolizumab was primarily based on proxy methods before January 1, 2016 because there was no specific HCPCS code for vedolizumab available before that date. However, the sharp increase in these claims at vedolizumab launch and a sharp decrease after the vedolizumab-specific HCPCS code was issued lend credence that our proxy methods were reliable in identifying actual vedolizumab claims. Third, the efficacy of a second treatment often depends on the reason for switching. However, this information is not available in the claims database. In addition, therapeutic drug monitoring information, which could also be used to guide treatment changes, is not available in the claims database either. Fourth, generalization of the current results to populations beyond those covered by the health benefit programs of large employers should be made with caution. Fifth, how the disease behavior (eg, occurrence of fistulas or stricture) factored into the practitioners' selection of the index therapy is not observable in the claims database; however, it is possible that patients with fistulizing disease were more likely to receive a second anti-TNF agent after a first anti-TNF. Even though it is well known that patients with fistulas tend to have worse outcomes, no significant differences in the proportion of patients with fistulas or stricture were observed between the treatment groups. Finally, this study was subject to the limitations of retrospective studies based on healthcare claims data, such as possible errors or omissions of claims; however, these limitations likely affect both cohorts similarly and are unlikely to bias the main findings.

CONCLUSIONS

Patients with IBD who were treated with an initial anti-TNF drug and switched to another anti-TNF agent incurred a lower HRU burden compared to those who switched to vedolizumab. Patients who switched to another anti-TNF agent also incurred significantly lower costs compared with those who switched to vedolizumab. These results suggest that among anti-TNF experienced patients with CD or UC, a second agent within the same class may be a more cost-effective option than vedolizumab.

SUPPLEMENTARY MATERIAL

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

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AUTHOR CONTRIBUTIONS

M.C.: study concept and design; critical revision of the manuscript for important intellectual content. A.A.: study concept and design; critical revision of the manuscript for important intellectual content. R.K.C.: study concept and design; critical revision of the manuscript for important intellectual content. D.M.: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis. J.G.: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. A.W.: study concept and design; critical revision of the manuscript for important intellectual content. V.G.-H.: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis. All authors contributed to the development of the publication and maintained control over the final content.

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