Real-world Effectiveness of Advanced Therapies Among Patients With Moderate to Severe Ulcerative Colitis in the United States

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Background: Ulcerative colitis (UC) treatment aims to induce response and maintain steroid-free remission. For patients with moderate to severe UC and/or nonresponse to conventional treatment, advanced therapies (immunosuppressants and biologics) are available. We assessed real-world effectiveness of advanced UC therapies.

Methods: This retrospective analysis of claims data included adult patients with UC initiating immunosuppressant or biologic therapy, with 12 months' continuous enrollment pre- and postinitiation. Patients had no prescription for biologic therapy (and/or immunosuppressant if initiating immunosuppressant) in the previous 12 months. Proportion of patients remaining steroid-free (excluding 14-week tapering period), hospitalizations, and costs in the 12 months postinitiation were assessed.

Results: In total, 3562 patients were included in the analysis. Most patients (83.0%) used steroids in the 12 months before initiating advanced therapy. Overall, 47.8% remained steroid-free after 12 months (excluding tapering). After adjusting for patient characteristics, remaining steroid-free was significantly more likely with infliximab (43.9%) than with adalimumab (39.4%; $P < 0.05$); golimumab (38.2%) and vedolizumab (41.4%) were not significantly different vs adalimumab. Overall, 12.2% of patients had a UC-related hospitalization within 12 months of initiation, with a mean (SD) total length of stay of 8.2 (8.9) days and no significant differences between biologic therapies. Mean, unadjusted, UC-related costs in the 12 months postinitiation were $42,579 and were similar between therapies.

Conclusions: Patients with UC initiating advanced therapy frequently continued using steroids for at least a year. Some patients experienced extended UC-related hospitalizations, with high UC-related costs overall. This suggests an ongoing challenge in managing patients with moderate to severe UC.

Key Words: biologic therapy, immunosuppressant, real-world effectiveness, ulcerative colitis

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory disease of the colon characterized by intermittent periods of disease flaring and remission.[1, 2] It affects approximately 900,000 people in the United States.[3] Although the primary clinical symptom is the presence of bloody diarrhea, patients can also experience a range of additional symptoms including urgency and abdominal pain.[2, 4] Individuals can also have more systemic symptoms, such as fever and weight loss.[2, 4, 5]

The goal of treatment in UC is to induce and maintain remission of symptoms and allow for healing of inflammation.[5] For patients with mild to moderate disease severity, conventional treatment typically consists of oral or topical aminosalicylates (5-ASAs) or topical steroids for induction of remission and oral and/or topical 5-ASAs for maintenance.[5, 6] For patients who are refractory to 5-ASA therapy or topical steroids, oral steroids can be used to induce remission.[5, 6] However, steroids are not indicated for maintenance therapy in UC.[5, 6] Despite this, 22% of patients develop steroid dependency, and only half achieve steroid-free remission within a year of their first course of systemic steroids.[7] Inability to taper off steroids is suggestive of a need to switch to advanced therapies.[5, 6, 8]

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Approximately half of newly diagnosed patients progress to moderate or severe disease, either continuously or intermittently.[9] In addition, many patients with UC do not respond to conventional therapies, either failing to respond to induction therapy (primary nonresponse) or initially achieving remission but not maintaining it with long-term treatment (secondary nonresponse). For example, 42% of patients fail to achieve clinical improvement with oral 5-ASA induction treatment,[10] and a further subset fail to maintain remission at ≥6 months.[11] For patients with moderate to severe disease, advanced therapies available at the time of this study (March 31, 2017) included immunosuppressants (eg, azathioprine and 6-mercaptopurine) and biologic therapies (adalimumab, infliximab, golimumab, and vedolizumab),[6, 12] although clinical practice guidelines have recently been updated to include tofacitinib, an oral small molecule Janus kinase inhibitor for the treatment of UC.[5] In patients with primary nonresponse to one of the tumor necrosis factor inhibitor (TNFi) biologic therapies, an alternative mechanism of disease control (eg, a different class of therapy) is recommended over switching to a different TNFi.[5]

The broad aim of the present study was to understand health outcomes in patients initiating advanced therapies (immunosuppressants and biologic therapies). Specifically, the objective was to assess the real-world effectiveness of advanced therapies by evaluating the proportion of patients who remained steroid-free, the proportion of patients who were hospitalized, the number of hospitalizations, total hospitalization length of stay, and total UC-related costs in the 12 months following initiation.

METHODS

Data Source

A retrospective cohort study was conducted using data from IBM MarketScan Research Databases. The MarketScan Research Databases consist of fully adjudicated medical (inpatient and outpatient diagnoses and procedures) and pharmacy (retail and mail order prescriptions) claims for over 250 million patients across the United States and are generally representative of the US population with employer-provided health insurance.

Sample

The study included individuals who were commercially insured and/or had Medicare Supplemental Insurance paid for by their employers, were treated with at least 1 immunosuppressant (azathioprine or 6-mercaptopurine) or biologic therapy (for the purposes of this study, the term "biologic therapy" referred specifically to biologic therapies indicated for the treatment of ulcerative colitis: adalimumab, infliximab, golimumab, or vedolizumab) between January 1, 2012, and March 31, 2017, as well as at least 1 diagnosis code for UC (International Classification of Diseases, 9th Revision [ICD-9] 556.X [as done in previous claims research studies][13] or International Classification of Diseases, 10th Revision [ICD-10] K51.X),[14, 15] on or within 12 months before the initial claim for biologic therapy. Medication exposures were defined with all available coding (including J-codes and now-obsolete C-codes). To be included in the final study sample, patients were required to have at least 12 months' continuous medical and pharmacy enrollment both before and after the date of their first use of that therapy (index date) and to be between 18 and 89 years old at the index date.

The index date for patients who used a biologic therapy was the date of the first prescription for or administration of that biologic therapy (even if an immunosuppressant was administered previously). For patients without a biologic therapy (ie, patients who only used an immunosuppressant), the index date was the date of the first prescription for or administration of that immunosuppressant. Patients were included if they had no prescription for an immunosuppressant or a biologic therapy (for patients whose index therapy was an immunosuppressant) or no prescription for a biologic therapy (for patients whose index therapy was a biologic) in the 12-month pre-index period. Therefore, patients initiating advanced therapy in this study were either naïve to immunosuppressant and/or biologic therapy for UC or had not received these therapies for at least 1 year before the index date.

Patients who had any prescription for or administration of a biologic therapy in the 12-month pre-index period, a second biologic therapy on the index date, or a diagnosis of Crohn's disease (CD; diagnosis code of ICD-9 555.X or ICD-10 K50.X) in the 12-month pre-index period were excluded from the study. Patients were categorized into mutually exclusive treatment cohorts based on their index therapy: adalimumab, infliximab, golimumab, vedolizumab, or immunosuppressant (azathioprine or 6-mercaptopurine).

Demographic and Clinical Characteristics

Demographic characteristics at index, including the month and year of the index date, age, sex, and geographic region, were collected. Clinical characteristics were also assessed, including disease duration (calculated based on the time since the earliest claim); Quan-Charlson Comorbidity Index score (calculated based on the presence of diagnosis codes in medical claims data); and specific comorbidities of special interest (defined a priori as hypertension, hyperlipidemia, myocardial infarction, stroke/transient ischemic attack [TIA], anxiety, depression, cytomegalovirus [CMV] colitis, *Clostridium difficile* [now reclassified as *Clostridioides difficile* (*C. difficile*)[16]], herpes zoster, lymphoma, and nonmelanoma skin cancer [NMSC]; documented history was identified using the relevant ICD-9 and ICD-10 diagnosis codes).

Steroid Use and Proportion of Patients Remaining Steroid-free

Steroid use was identified based on the generic drug name, and all forms were included; it was not possible to differentiate between systemic and topical or locally active treatments. To evaluate effectiveness, the proportion of patients who did not use any steroids in the 12-month postindex period (as a surrogate outcome indicative of increased inflammatory burden) was assessed. A tapering period of up to 14 weeks after initiation of the index advanced therapy (immunosuppressant or biologic therapy) was allowed. Use of steroids within this time window was not considered for the purposes of either "steroid-free" outcome.

Hospitalizations and Costs

Effectiveness was also evaluated using the percentage of patients who did not have any UC-related hospitalizations in the follow-up period. In addition, the number of UC-related hospitalizations, mean UC-related hospitalization rate, and total UC-related hospitalization length of stay during the 12-month postindex period were calculated. Total unadjusted per-patient UC-related costs are also reported. The UC-related costs were defined as inpatient and outpatient encounters with a diagnosis of UC and prescriptions or physician-administered UC-related drugs including steroids, immunomodulators, and biologics. The UC-related drug costs were calculated using the allowed cost and mean dose.

Statistical Analyses

Data analyses were conducted in SAS v9.4 (Cary, NC). Demographic and clinical characteristics and steroid use are reported descriptively. Frequencies and percentages are reported for categorical variables; means and standard deviations, or medians and interquartile ranges, are reported for continuous variables.

Differences across treatment cohorts were examined using χ^2 tests and analysis of variance (ANOVA) F-tests for categorical and continuous variables, respectively. Variables thought to influence the dependent variables were compiled as a single set of confounding variables applied in all the subsequent multivariable models. The models controlled for age, sex, region, insurance type, health plan, Quan-Charlson Comorbidity Index score, disease duration, disease extent, total pre-index costs, number of pre-index gastroenterology visits, number of pre-index hospitalizations, and concomitant immunosuppressant. As no direct measures of disease severity were available in the database, we relied upon pre-index costs, gastroenterology visits, and hospitalizations as proxies to control for baseline severity.

Effectiveness outcomes (proportion of patients who remained steroid-free and hospitalization rates) for biologic therapies were examined using a generalized linear model specifying the appropriate distribution and link function (ie, binomial distribution and logit link function for binary outcomes and negative binomial distribution and log link function for count data with limited number of categories). The primary predictor was index treatment cohort (excluding immunosuppressant cohort). Covariates included the patient characteristic variables noted above. The interaction of index medication with combination therapy was included in the model; if it was not significant ($P > 0.20$), the term was removed and the model refit. Adalimumab was selected as the reference cohort due to a large sample size. Parameters, 95% confidence intervals (CIs), standard errors, and *P* values are reported. Probability (adjusted for confounding variables) of remaining steroid-free (along with 95% CIs) is also reported. Total unadjusted per-patient UC-related costs are reported descriptively, as the combination of small sample sizes and a large proportion of patients with zero hospitalization costs made some of the model-fitting not meaningful.

Ethical Considerations

In compliance with the Health Insurance Portability and Accountability Act (HIPAA), patient data included in the analysis were de-identified. Because this study was a retrospective analysis of de-identified data, Institutional Review Board review was not required or sought.

RESULTS

Patient Characteristics

The sample attrition figure is displayed in Figure 1. A total of 3562 patients, each with 1 year of data both before and after their index date, was included in the study sample.

A total of 2331 (65.4%) patients (who had not received a UC biologic therapy for at least 12 months) initiated a biologic therapy at index (adalimumab [N = 1291; 36.2%], infliximab [N = 810; 22.7%], golimumab [N = 127, 3.6%], or vedolizumab [N = 103, 2.9%]). The remaining 1231 (34.6%) patients (who had not received a UC immunosuppressant or biologic therapy for at least 12 months) initiated an immunosuppressant without an accompanying biologic therapy at index (Table 1). Combination therapy was common, with 27.9% of adalimumab, 29.6% of infliximab, 26.0% of golimumab, and 21.4% of vedolizumab patients adding on an immunosuppressant during the 12-month postindex period (Table 1).

Differences in demographic and clinical characteristics across the treatment cohorts are shown in Table 2. Overall, the sample was 51.4% male with a mean (SD) age of 45.0 (15.1) years. Patients initiating advanced therapies had been diagnosed with UC for a mean (SD) of 1.3 (1.0) years. The mean (SD) Quan-Charlson Comorbidity Index score was 0.6 (1.1). Both hypertension (25.7%) and hyperlipidemia (21.2%) were common comorbidities (based on documented history), as were anxiety (13.3%) and depression (10.9%). Also present were *C. difficile* (4.4%), NMSC (3.4%), and herpes zoster (1.3%).

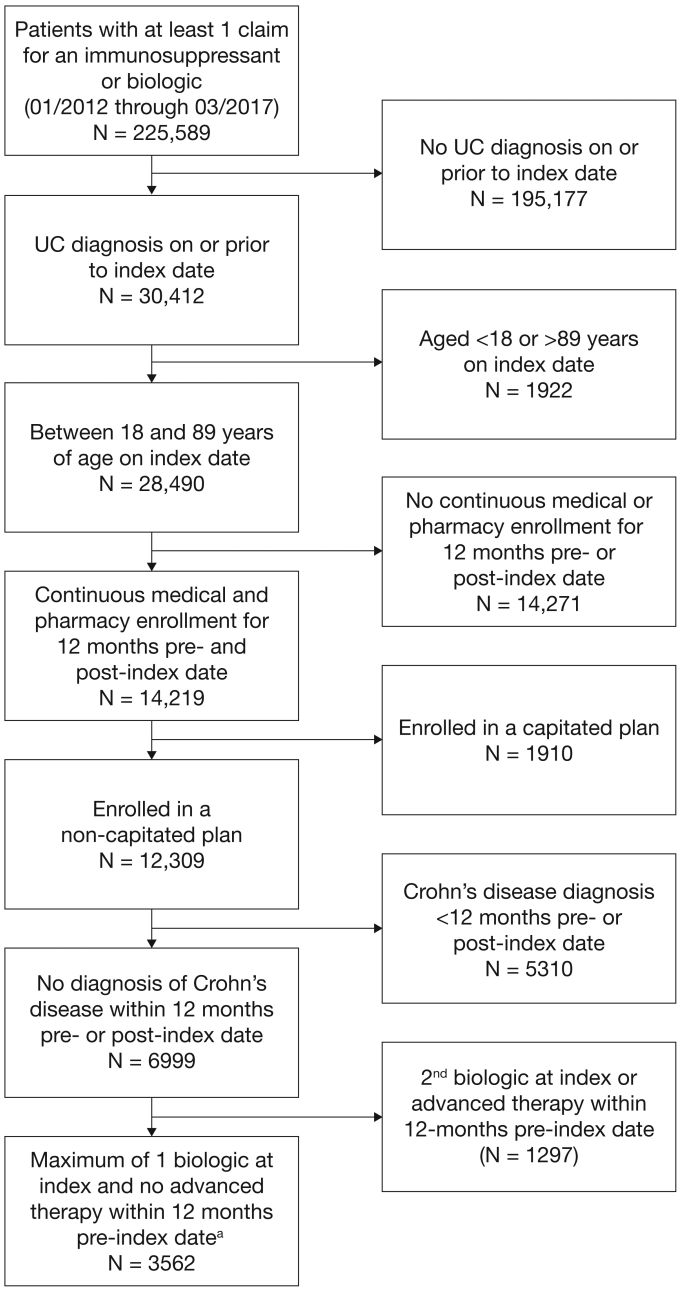

FIGURE 1. Attrition figure. For patients who initiated a biologic therapy at index, the use of an immunosuppressant during the pre-index period was not an exclusion criterion. However, for patients who initiated an immunosuppressant at index, immunosuppressant use during the pre-index period was an exclusion criterion. For either group, use of a biologic during the pre-index period was an exclusion criterion. Abbreviations: N, number of patients; UC, ulcerative colitis.

Cytomegalovirus colitis, myocardial infarction, stroke/TIA, and lymphoma were uncommon (all <1.0%).

During the 12-month pre-index period, patients frequently used 5-ASA treatments (eg, mesalamine [74.4%]) and steroids (83.0% used some form of steroid; Table 3). Pain-related treatments were also common (eg, acetaminophen/hydrocodone [21.9%]; Table 3). Additionally, 5-ASA treatments and pain medications were frequently used in the 12-month postindex period (mesalamine, 2053 patients [57.6%]; acetaminophen/hydrocodone bitartrate, 756 patients [21.2%]; acetaminophen/oxycodone hydrochloride, 322 patients [9.0%]).

Proportion of Patients Remaining Steroid-free

After initiating an advanced therapy, 53.1% of patients used steroids during the 14-week tapering period, and 52.2% of patients used steroids during the post-tapering period up to 1 year from the index date. In other words, before any confounder adjustment, 47.8% of patients met the definition of being steroid-free in the 12-month postindex period, excluding the 14-week tapering period. By treatment cohort, the unadjusted proportions of patients remaining steroid-free in the post-tapering period were 43.6% (adalimumab), 48.3% (infliximab), 41.7% (golimumab), 46.6% (vedolizumab), and 52.7% (immunosuppressant [azathioprine or 6-mercaptopurine]).

After adjusting for differences in patient characteristics across treatment cohorts for patients initiating a biologic therapy, the probability of remaining steroid-free during the post-tapering period (12-month maintenance period, excluding the initial 14-week tapering period) was significantly higher for patients initiating infliximab (43.9%) than for those initiating adalimumab (39.4%; $P < 0.05$). The probabilities of remaining steroid-free for patients initiating golimumab (38.2%) and vedolizumab (41.4%) were not significantly different compared with adalimumab (Fig. 2).

Hospitalizations and Costs

Overall, 12.2% of patients had a UC-related hospitalization during the 12-month postindex period. Among patients with at least 1 hospitalization, the mean (SD) number of hospitalizations was 1.6 (1.0) with a mean (SD) total (cumulative) length of stay of 8.2 (8.9) days. Unadjusted hospitalization outcomes by index therapy during the 12-month postindex period are reported in Table 4. No significant differences between the biologic treatment cohorts in unadjusted or adjusted hospitalization variables (probability of a hospitalization, number of hospitalization visits, and total length of stay) were observed, with the exception of the adjusted probability of a hospitalization being significantly higher with infliximab (20.4%) compared with adalimumab (16.3%; $P < 0.05$). No significant differences in this variable vs adalimumab were observed for the golimumab (10.5%) or vedolizumab (15.6%) treatment cohorts.

Mean (95% CI) total unadjusted per-patient UC-related costs in the 12-month postindex period across all treatments were $42,579 ($1110; $108,923). Total unadjusted per-patient UC-related costs were similar regardless of index therapy (mean [95% CI]: adalimumab, $57,590 [$13,906; $112,097]; infliximab,

TABLE 1. Use of Initial Biologic Therapies With and Without Concomitant Immunosuppressant Therapy

	Total	No Concomitant Immunosuppressant[a]	Concomitant Immunosuppressant[a]
	N	n (%)	n (%)
Adalimumab	1291	931 (72.1%)	360 (27.9%)
Infliximab	810	570 (70.4%)	240 (29.6%)
Golimumab	127	94 (74.0%)	33 (26.0%)
Vedolizumab	103	81 (78.6%)	22 (21.4%)

[a]Immunosuppressant therapy was defined as azathioprine or 6-mercaptopurine.
Abbreviations: N, number of patients; n, number of patients within the given category.

TABLE 2. Demographic and Clinical Characteristics at Index, by Index Therapy

	Total	Adalimumab	Infliximab	Golimumab	Vedolizumab	Immunosuppressant[a]	
	N = 3562	N = 1291	N = 810	N = 127	N = 103	N = 1231	*P* value
Male, n (%)	1831 (51.4)	659 (51.0)	417 (51.5)	64 (50.4)	60 (58.3)	631 (51.3)	0.724
Age (years), mean (SD)	45.0 (15.1)	44.8 (14.4)	43.8 (15.8)	45.3 (15.2)	44.4 (15.7)	46.1 (15.2)	0.016
Region, n (%)							0.007
Northeast	639 (17.9)	229 (17.7)	132 (16.3)	30 (23.6)	16 (15.5)	232 (18.8)	
North Central	878 (24.6)	278 (21.5)	240 (29.6)	20 (15.7)	22 (21.4)	318 (25.8)	
South	1438 (40.4)	555 (43.0)	312 (38.5)	58 (45.7)	44 (42.7)	469 (38.1)	
West	583 (16.4)	218 (16.9)	120 (14.8)	18 (14.2)	21 (20.4)	206 (16.7)	
Unknown	24 (0.7)	11 (0.9)	6 (0.7)	1 (0.8)	0 (0.0)	6 (0.5)	
Disease duration (years), mean (SD)	1.3 (1.0)	1.4 (1.0)	1.3 (1.1)	1.5 (0.9)	1.9 (1.1)	1.2 (0.9)	<0.001
Quan-Charlson comorbidity score, mean (SD)	0.6 (1.1)	0.6 (1.1)	0.6 (1.1)	0.6 (1.3)	0.4 (0.9)	0.7 (1.3)	0.123
Comorbid conditions, n (%)[b]							
CMV colitis	10 (0.3)	4 (0.3)	3 (0.4)	0 (0.0)	0 (0.0)	3 (0.2)	0.913
C. difficile	155 (4.4)	63 (4.9)	42 (5.2)	0 (0.0)	5 (4.9)	45 (3.7)	0.050
Hypertension	917 (25.7)	341 (26.4)	207 (25.6)	28 (22.0)	22 (21.4)	319 (25.9)	0.684
Hyperlipidemia	756 (21.2)	282 (21.8)	171 (21.1)	28 (22.0)	17 (16.5)	258 (21.0)	0.777
Myocardial infarction	20 (0.6)	2 (0.2)	4 (0.5)	0 (0.0)	2 (1.9)	12 (1.0)	0.018
Stroke/TIA	18 (0.5)	9 (0.7)	2 (0.2)	0 (0.0)	0 (0.0)	7 (0.6)	0.511
Herpes zoster	48 (1.3)	17 (1.3)	9 (1.1)	2 (1.6)	0 (0.0)	20 (1.6)	0.642
Depression	387 (10.9)	159 (12.3)	90 (11.1)	9 (7.1)	5 (4.9)	124 (10.1)	0.053
Anxiety	472 (13.3)	185 (14.3)	113 (14.0)	13 (10.2)	11 (10.7)	150 (12.2)	0.347
NMSC	122 (3.4)	46 (3.6)	24 (3.0)	7 (5.5)	6 (5.8)	39 (3.2)	0.366
Lymphoma	12 (0.3)	4 (0.3)	0 (0.0)	1 (0.8)	1 (1.0)	6 (0.5)	0.231

P values are from χ^2 tests for the rates of the categorical variables, or an F-test for the means of continuous variables, comparing all six therapies.
[a]Immunosuppressant therapy was defined as azathioprine or 6-mercaptopurine.
[b]Documented history identified using the relevant ICD-9 and ICD-10 diagnosis codes.
Abbreviations: *C. difficile*, *Clostridioides/Clostridium difficile*; CMV, cytomegalovirus; ICD, International Classification of Diseases; N, number of patients; n, number of patients within the given category; NMSC, nonmelanoma skin cancer; SD, standard deviation; TIA, transient ischemic attack.

$59,898 [$11,352; $135,440]; golimumab, $62,088 [$21,071; $107,437]; vedolizumab, $59,400 [$8168; $123,756]; $P = 0.35$).

DISCUSSION

In this retrospective cohort study of real-world effectiveness of advanced therapies for UC, many patients continued to use steroids after initiating immunosuppressant or biologic therapies, with 53.1% of patients using steroids immediately after initiating (during the 14-week tapering period) and 52.2% using steroids in the post-tapering period up to 12 months postindex. Steroid use is common among patients with moderate to severe UC[17] (eg, as rescue therapy during flares or due to suboptimal control[5, 6]), and these findings may reflect the fact that onset of efficacy with advanced therapies is somewhat

TABLE 3. Medications During the 12-Month, Pre-index Period, by Index Therapy

	Total	Adalimumab	Golimumab	Infliximab	Vedolizumab	Immunosuppressant[a]	
	N = 3562	N = 1291	N = 127	N = 810	N = 103	N = 1231	*P* value
5-ASAs, n (%)							
Mesalamine	2651 (74.4)	983 (76.1)	95 (74.8)	578 (71.4)	72 (69.9)	923 (75.0)	0.120
Sulfasalazine	265 (7.4)	115 (8.9)	11 (8.7)	50 (6.2)	3 (2.9)	86 (7.0)	0.047
Pain medications, n (%)							
Acetaminophen/hydrocodone bitartrate	781 (21.9)	309 (23.9)	25 (19.7)	182 (22.5)	17 (16.5)	248 (20.1)	0.107
Acetaminophen/oxycodone hydrochloride	293 (8.2)	100 (7.7)	10 (7.9)	70 (8.6)	8 (7.8)	105 (8.5)	0.941
Steroids, n (%)[b]							
Any	2956 (83.0)	1112 (86.1)	108 (85.0)	674 (83.2)	73 (70.9)	989 (80.3)	<0.001
Beclomethasone	25 (0.7)	10 (0.8)	0 (0.0)	4 (0.5)	0 (0.0)	11 (0.9)	0.579
Budesonide	944 (26.5)	372 (28.8)	45 (35.4)	216 (26.7)	32 (31.1)	279 (22.7)	<0.001
Hydrocortisone	796 (22.3)	291 (22.5)	43 (33.9)	188 (23.2)	16 (15.5)	258 (21.0)	0.007
Methylprednisolone	594 (16.7)	259 (20.1)	24 (18.9)	133 (16.4)	14 (13.6)	164 (13.3)	<0.001
Prednisone	2433 (68.3)	929 (72.0)	83 (65.4)	584 (72.1)	51 (49.5)	786 (63.9)	<0.001
Prednisolone	86 (2.4)	45 (3.5)	3 (2.4)	13 (1.6)	1 (1.0)	24 (1.9)	0.032

P values are from χ^2 tests, comparing all six therapies.
[a]Immunosuppressant therapy was defined as azathioprine or 6-mercaptopurine.
[b]Steroid use was identified based on the generic drug name, and all forms were included; it was not possible to differentiate between systemic and topical/locally active treatments.
Abbreviations: ASA, aminosalicylate; N, number of patients; n, number of patients within the given category.

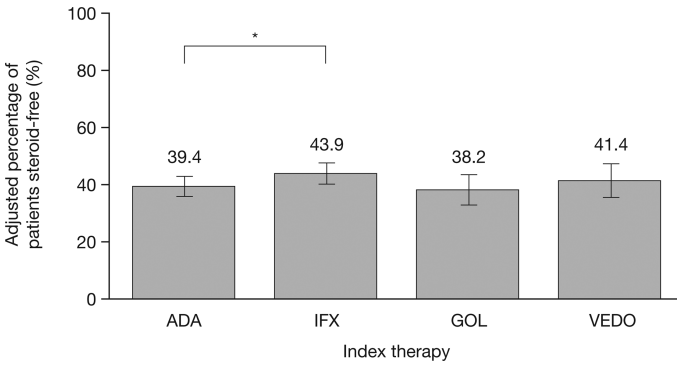

FIGURE 2. Adjusted probability of patients being steroid-free during the post-tapering period, by index therapy. Values shown are least squares mean +/- standard error. The model controlled for age, sex, region, insurance type, health plan, Quan-Charlson Comorbidity Index score, disease duration, disease extent, total pre-index costs, number of pre-index gastroenterology visits, number of pre-index hospitalizations, and concomitant immunosuppressant. Results are independent of patient remission status. ADA was selected as the reference cohort. *$P < 0.05$ vs ADA. Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; VEDO, vedolizumab.

delayed, and steroids are still required for symptom control in the meantime. However, excluding a 14-week tapering period, the proportion of patients remaining steroid-free after 1 year was still less than 50%. In addition, combination therapy was common, with 21%–30% of patients who initiated a biologic using concomitant immunosuppressant therapies within the first year. Together, these results suggest that patients initiating biologic therapies frequently require combination therapy with immunosuppressants and/or steroids to maintain remission and/or continue to control symptoms.

Previous studies have shown that in patients with inflammatory bowel disease (IBD), steroid use can increase the risk of several adverse events related to immunosuppression, including serious and opportunistic infections and malignancies. In a population-based cohort of patients with IBD, initiating steroids significantly increased the risk of *C. difficile* compared with immunosuppressive drugs (azathioprine, 6-mercaptopurine or methotrexate) and infliximab,[18] and in case-control studies, use of steroids was significantly associated with increased risk of herpes zoster[19] and opportunistic infection.[20] However, TNFi biologic therapies and immunosuppressants have also been associated with increased risk of infections. For example, Long et al demonstrated that thiopurine and TNFi biologic therapies were significant risk factors for herpes zoster,[21] and Toruner et al showed that patients receiving combinations of thiopurine plus steroid or triple thiopurine/infliximab/steroid therapy had higher opportunistic infection risk than those receiving any of these therapies alone.[20] In a retrospective analysis of the Truven database, use of steroids—but not immunosuppressants or biologic therapies—was significantly associated with the risk of malignancy among patients with IBD.[22] In addition to an increased risk of adverse events, steroid use has been shown to be independently associated with the risk of colectomy.[23]

In addition to the findings on real-world effectiveness of advanced therapies for UC based on recurrent need for steroid use, these analyses showed that many patients used

TABLE 4. Unadjusted UC-related Hospitalization Outcomes During the 12-Month, Postindex Period, by Index Therapy

	Adalimumab	Golimumab	Infliximab	Vedolizumab
	N = 1291	N = 127	N = 810	N = 103
Any hospitalization, n (%)	166 (12.9)	11 (8.7)	148 (18.3)	10 (9.7)
Number of hospitalizations, mean (SD)	1.61 (1.05)	1.82 (1.08)	1.68 (1.08)	1.30 (0.67)
Total (cumulative) length of stay (days), mean (SD)	8.39 (9.46)	10.82 (9.18)	8.89 (9.00)	5.20 (4.52)

Abbreviations: SD, standard deviation; UC, ulcerative colitis.

narcotic-containing pain medications both before and after initiating an advanced therapy (although 12-month postindex data did not account for any delay in the onset of efficacy of the advanced therapies). This use of steroids and/or narcotics indicates a significant disease burden on patients before initiating an advanced therapy. Prior data from the TREAT registry have shown that narcotics are an independent predictor of mortality in IBD (specifically Crohn's disease), thereby demonstrating a need to alter the use of narcotics in these patients.[24] Of note, this real-world study found that >10% of patients with UC were experiencing comorbid depression and anxiety, factors that are known to be associated with impaired quality of life in patients with UC,[25] before initiating advanced therapies. This finding highlights the substantial burden of disease on these patients. Moreover, approximately 4% of patients had evidence of *C. difficile*, and 1% had herpes zoster in their medical history based on ICD-9 billing codes. This suggests that in the real-world setting, infectious complications should be considered and managed, for example, by assessing whether vaccination may be necessary.[26]

Hospitalizations for UC are associated with an increased risk of adverse outcomes, such as subsequent colectomy.[27] Our analyses of UC-related hospitalizations and costs in the 12-month postindex period showed that 12.2% of patients experienced at least 1 UC-related hospitalization within 12 months of initiating an advanced therapy, with lengthy hospital stays of 8.2 days within a 1-year period, and total UC-related costs in excess of $40,000. This demonstrates that UC continues to exert a substantial burden after a patient initiates advanced therapy, suggesting that up to 20% of patients initiating an advanced therapy will go on to be hospitalized within the following 12 months. No significant differences between the biologic treatment cohorts in hospitalization characteristics (probability of a hospitalization, number of hospitalization visits, and total length of stay) were observed, except that the adjusted probability of a hospitalization was significantly higher with infliximab vs adalimumab. This finding may reflect the recommended use of infliximab as a treatment for acute severe UC,[28] resulting in a higher proportion of patients with severe UC in the infliximab cohort than in the adalimumab cohort.

The strengths of this study include the large sample size and the inclusion criterion of continuous medical and pharmacy coverage for at least 12 months pre- and postindex, which ensured an accurate representation of steroid and other concomitant medication use, hospitalizations, and costs both before and after initiation of advanced therapy. Furthermore, the real-world nature of this study offers a perspective on effectiveness outside of a clinical trial setting.

In this study, effectiveness was measured using the proportion of patients remaining steroid-free, hospitalizations, and costs. Clinical measures of effectiveness, such as endoscopic results and symptom experience (ie, stool frequency and rectal bleeding) were not available due to the nature of a study of administrative claims data. Furthermore, because direct measures of disease severity were not available in the database, assumptions regarding baseline severity were made based on various indirect measures (ie, patients with more severe disease were more likely to have a hospitalization, visit their gastroenterologist, and incur greater health care costs). Steroid use was identified based on the generic drug name without differentiating between systemic and topical or locally active forms, meaning steroid dose could not be accurately extracted from the records. In addition, steroid dose and duration were unlikely to have been recorded in sufficient detail in claims data to provide meaningful data. Therefore, our analysis was limited to determining the proportion of patients remaining steroid-free in the 12-month postindex period, and additional detail on steroid treatment patterns could not be reported. Drug costs related to UC (which were part of the reported total UC-related costs) were calculated using the allowed cost and mean dose, rather than the paid amount on the pharmacy claim, so out-of-pocket costs and health plan-specific price discounts and contracting are not included in the costs. In the multivariable modeling for hospitalizations outcomes, although observed differences between cohort groups were controlled for, there may be other variables not included in the data that may explain some of the variation between treatment outcomes.

The population in this study comprised UC patients initiating treatment with an immunosuppressant or biologic therapy who were continuously enrolled in a US commercial health insurance plan. The study findings may not be

generalizable to other populations such as uninsured patients. Additionally, although the study aimed to assess treatment patterns among patients initiating their first immunosuppressant or biologic therapy, patients were only required to have a minimum of 12 months' coverage before initiating their index therapy and may have previously received advanced therapy before this pre-index period. Therefore, immunosuppressant or biologic exposure more than 12 months before the index date could not be accounted for and could represent an unmeasured confounder in this study.

CONCLUSIONS

Patients with UC frequently continue using steroids during the first year after initiating advanced therapies, and those initiating biologic therapies often require combination therapy with an immunosuppressant. A subset of patients also experience extended UC-related hospitalization stays. These results suggest that optimization of current therapies and/or therapies with alternative mechanisms of action are needed to achieve steroid-free goals of treatment.

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