Retrospective Database Analysis: Dose Escalation and Adherence in Patients Initiating Biologics for Ulcerative Colitis

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Keywords

Biologic therapies · Dose escalation · Treatment adherence · Ulcerative colitis

Abstract

Background: Biologic therapies are often used in patients with ulcerative colitis (UC) who are nonresponsive to conventional treatments. However, nonresponse or loss of response to biologics often occurs, leading to dose escalation, combination therapy, and/or treatment switching. We investigated real-world treatment patterns of biologic therapies among patients with UC in the USA. **Methods:** This study analyzed data from the IBM® MarketScan® Commercial and Medicare Supplemental Databases (medical/pharmacy claims for >250 million patients in the USA) to identify patients with UC initiating a biologic therapy (adalimumab, infliximab, golimumab, or vedolizumab) with 12 months of follow-up post-initiation. Key measures were patient baseline characteristics, dose escalation (average maintenance dose >20% higher than label), adherence (proportion of days covered), and ulcerative colitis-related healthcare costs in the 12 months following biologic therapy initiation. **Results:** Of 2,331 patients included in the study (adalimumab [$N = 1,291$], infliximab [$N = 810$], golimumab [$N = 127$], and

vedolizumab [$N = 103$]), 28.1% used concomitant immunosuppressant therapy within 12 months post-initiation. Overall, 23.6% (adalimumab), 34.8% (infliximab), 9.9% (golimumab), and 39.2% (vedolizumab) of patients dose escalated within 12 months. Patients who dose escalated incurred USD 20,106 higher total UC-related healthcare costs over 12 months than those who did not. Adherence (covariate-adjusted proportion of days covered) ranged from 0.63 to 0.73, and 39.3% of patients discontinued within 12 months (median treatment duration = 112 days). **Conclusion:** Dose escalation was common, and incurred higher costs, in patients with UC initiating biologic therapies. Suboptimal adherence and/or discontinuation within 12 months of initiation occurred frequently, highlighting the challenges in managing these patients.

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon that affects an estimated 910,000 people in the USA and is increasing in incidence and prevalence [1]. The primary clinical symptom is the presence of bloody diarrhea, which can be accompanied by a range of

other symptoms, including urgency and abdominal pain [2–5]. Individuals can also have more systemic symptoms such as fatigue, fever, and weight loss [2–4].

Treatment goals in UC focus on inducing clinical response via improvement in patient-reported outcomes, endoscopic improvement of inflammation, and maintenance of long-term, steroid-free remission [5]. For patients with mild to moderate disease severity, treatment typically consists of oral and/or rectal 5-aminosalicylates (5-ASA) for induction and maintenance of remission [5]. Systematic reviews and meta-analyses found that 29–46% of patients with UC who received 5-ASA entered remission [6], with 41–48% of patients then relapsing [7]. Approximately half of newly diagnosed patients progressed to moderately or severely active disease [8].

For patients with moderately to severely active disease who were intolerant to, or did not achieve maintenance of remission with, 5-ASA, the treatment options available at the time of this study (March 31, 2017) were immunosuppressants (e.g., thiopurines) and several biologic therapies (adalimumab, infliximab, golimumab, and vedolizumab) [5, 9]. Although these therapies are effective, not all patients respond, either failing to respond to induction therapy (primary nonresponse) or initially achieving remission but not maintaining it with long-term treatment (secondary loss of response). Among those who respond to biologic therapies, previous studies have indicated that 20–37% of patients lose response over time [10–13], which may at least partially be due to the formation of antidrug antibodies [14–16]. In the event of secondary loss of response, clinicians can choose to switch a patient's therapy to one with a different mechanism of action, or escalate the dose of their current biologic therapy [5, 17–19]. At the time of this analysis, there were 3 approved biologic mechanisms of action for the treatment of moderate to severe UC (tumor necrosis factor inhibition, integrin receptor inhibition, and interleukin-12/23 inhibition) [20]. Investigating real-world treatment patterns could further our understanding of how frequently dose escalation or combination therapy are used with different biologic therapies in clinical practice. In addition, dose escalation has a substantial impact on pharmacy costs, since wholesale cost is proportional to increase in dose [19]. Therefore, real-world research could provide insights into the economic consequences of this practice [21], allowing evaluation of whether dose escalation is a cost-effective strategy.

The aim of this study was to understand the real-world treatment patterns of biologic therapies among patients with UC in the USA. The primary objectives were to as-

sess the frequency of dose escalation (i.e., the use of doses or dosing frequencies higher than the labeled indication) and levels of adherence to therapy. Additional objectives were to assess the frequency of combination therapy (i.e., concomitant immunosuppressant and biologic therapy use) and possible reasons for discontinuation of biologic therapies, as available in administrative data.

Patients and Methods

Data Source

A retrospective cohort study was conducted using data from the IBM® MarketScan® Commercial and Medicare Supplemental Databases. The Commercial and Medicare Supplemental Databases consist of fully adjudicated medical (inpatient and outpatient diagnoses and procedures) and pharmacy (retail and mail order prescriptions) claims for >250 million patients across the USA. This study does not require Ethical Committee approval as it uses de-identified structured data.

Sample

The study included individuals who were commercially insured and/or had Medicare Supplemental insurance paid for by their employers, and who were treated with at least 1 biologic therapy (for the purposes of this study, the term “biologic therapy” referred specifically to biologic therapies indicated for the treatment of UC that were available at the time of the dataset: adalimumab, infliximab, golimumab, or vedolizumab) between January 01, 2012 and March 31, 2017, and who had at least 1 diagnosis code for UC (International Classification of Diseases, 9th revision [ICD-9] 556.X or International Classification of Diseases, 10th revision [ICD-10] K51.X [22, 23]) on or within 12 months prior to the initial claim for biologic therapy. Treatments approved for UC after March 31, 2017, were not included in this analysis. To be included in the final study sample, patients were required to have at least 12 months of continuous medical and pharmacy enrollment with the same insurer both prior to and after the date of their first use of that therapy (index date), and be between 18 and 89 years of age at the index date. Patients were included if they had no prescription for a biologic therapy indicated for UC in the 12-month pre-index period. Therefore, patients were either naïve to biologic therapy, or had not received biologic therapy for UC for at least 12 months prior to the index date. Patients were assumed to have moderately to severely active UC based on their physician's decision to prescribe a biologic therapy.

Patients were excluded from the study if they had any prescription for, or administration of, a second biologic therapy at index, or had a diagnosis of Crohn's disease (ICD-9 555.X or ICD-10 K50.X [22, 23]). Patients were categorized into treatment cohorts based on their index therapy (adalimumab, infliximab, golimumab, or vedolizumab).

Demographic and Clinical Characteristics

Demographic and clinical characteristics at index (age, sex, geographic region [Northeast, Midwest, South, and West] [24], and Quan-Charlson Comorbidity Index scores [calculated based on the presence of diagnosis codes in medical claims data]) [25],

were collected. The 25 most common medications prescribed during the 12-month pre-index period were obtained, and those related to 5-ASA, steroids, or immunosuppressants are reported. Immunosuppressant use in the post-index period is also reported.

Assessment of Dose Escalation

Dose escalation was defined differently for each biologic therapy, although the principle was the same. First, an induction period was calculated for each therapy, based on the labeled induction length, with an extra 1 week added for adalimumab and golimumab, and an extra 2 weeks added for infliximab and vedolizumab, to account for slight delays or variation in administration. Induction doses for adalimumab (160 mg at week 0, then 80 mg at week 2), golimumab (200 mg at week 0, then 100 mg at week 2), and vedolizumab (300 mg at weeks 0, 2, and 6) were ignored for the purpose of calculating dose escalation (because doses, based on product labels, are higher for induction than during maintenance). If the average dose (i.e., accounting for both the dose and the frequency of treatment within this fixed time period) during maintenance (the 12-month post-index period, excluding the induction period) was at least 20% higher than the product label, this was considered dose escalation. For infliximab, since dosing is weight-based and weight was not available from the claims data, the index dose was used to derive an average daily baseline maintenance dose. This was calculated by dividing the total quantity administered at index by 56 (based on the labeled maintenance dose frequency of 8 weeks, or 56 days). If this estimated average dose during maintenance was at least 20% higher than the index dose, this was considered dose escalation. For all medications, dose escalation was evaluated as the only persistent portion of the maintenance period (treatment prior to a gap greater than 60 days) because the gap might signal a treatment interruption.

The proportion of patients with dose escalation during the 12-month post-index period excluding the induction period (maintenance) was assessed. The effect of concomitant immunosuppressants on the proportion of patients with dose escalation was also explored. Additionally, all-cause direct medical costs paid out by insurance companies (inpatient, outpatient, and pharmacy) and UC-related costs paid out by insurance companies (inpatient and outpatient encounters with a diagnosis of UC, as well as physician-administered or prescriptions for UC-related drugs, including steroids, immunosuppressants, and biologic therapies) were calculated. Prescription drugs (self-administered) were found via pharmacy claims, whereas administrations (physician-administered) were found via medical claims. Infusible biologics could have been assigned differently depending on the patients' insurance plan; if they were part of the medical plan, they would comprise medical costs, and if they were part of the pharmacy plan, they would comprise pharmacy costs.

Assessment of Adherence

Adherence, defined as the extent to which a patient takes their medication as prescribed [26], was measured using a proportion of days covered (PDC) approach. This approach calculates the number of days the patient was treated (for prescriptions, days supplied was used; for administrations, treated days were imputed using the standard maintenance dosing schedule, regardless of patients' specific prescriptions) divided by the number of days in the 12-month post-index period (a fixed denominator of 360 days), to arrive at a proportion. In order to prevent early prescription fills

from impacting the calculation of adherence for self-administered biologic therapies, up to 15 days of stockpiling was incorporated by moving the early prescription fill date forward to coincide with the last day supplied by the previous prescription, rather than assuming that the biologic therapies were immediately administered. No stockpiling was used for physician-administered biologic therapies. A PDC ≥ 0.80 , a common threshold for evaluating medication adherence [26], was used as a cutoff to evaluate associations between characteristics and adherence. The same approach was used regardless of dose escalation.

Statistical Analyses

Data analyses were conducted in SAS v9.4 (Cary, NC, USA). Demographic and clinical characteristics, treatments, dose escalation, healthcare costs, and adherence are reported descriptively. Frequencies and percentages are reported for categorical variables, while means and standard deviations are reported for continuous variables. Where statistical testing across groups was applicable, p values were generated from χ^2 tests for the rates of the categorical variables, or F -tests for the means of continuous variables.

Treatment cohorts were compared with respect to adherence (defined dichotomously by a PDC ≥ 80 vs. a PDC < 80) using multivariable (generalized linear) models controlling for demographic and clinical characteristic differences, and specifying a binomial distribution and logit link function. Interactions between concomitant immunosuppressants and index therapies were also analyzed using these models, to predict dose escalation and adherence.

Variables thought to influence the dependent variables were compiled as a single set of confounding variables applied in all the subsequent multivariable models. All models controlled for age, sex, region, insurance type (Medicare vs. commercial insurance), health plan (health plan vs. employer), Quan-Charlson Comorbidity Index score, extent of disease based on ICD-9/ICD-10 codes, years to UC diagnosis during baseline, number of pre-index gastroenterology visits, number of pre-index UC hospitalizations, total pre-index UC-related healthcare costs, concomitant immunosuppressant (defined as azathioprine or 6-mercaptopurine) use, and index therapy. Adalimumab was selected as the reference cohort for the index therapy variable. Regression parameters, 95% confidence intervals, χ^2 values, p values, and adjusted probabilities (by index therapy only) are reported from these multivariable models.

Results

Demographic and Clinical Characteristics

A total of 2,331 patients were included in the study (Fig. 1), with most patients treated with adalimumab ($N = 1,291$, 55.4%), followed by infliximab ($N = 810$, 34.7%), golimumab ($N = 127$, 5.4%), and vedolizumab ($N = 103$, 4.4%). Treatment cohort demographics were largely similar, although patients initiating vedolizumab were more likely to be male (58.3%) compared with those initiating other treatments (50.4–51.5%; Table 1).

The most common medications in the 12-month pre-index period (prior to initiation of biologic therapy) are

Fig. 1. Attrition during the determination of the study sample. *N*, number of patients. UC, ulcerative colitis. ^aPatient data were drawn from a broader analysis of advanced therapies in UC, including biologic and immunosuppressant therapy. Patients initiating immunosuppressants only at index were excluded from this study.

summarized in Table 2. Treatment with 5-ASA, prednisone, and/or other steroids and immunosuppressants occurred frequently (Table 2).

During the 12-month post-index period (following initiation of biologic therapy), combination therapy was common, with 27.9% of adalimumab-treated patients, 29.6% of infliximab-treated patients, 26.0% of golimumab-treated patients, and 21.4% of vedolizumab-treated patients also using an immunosuppressant.

Dose Escalation

Dose escalation was examined among patients with at least 1 administration of their index therapy during maintenance (since dose escalation was only examined in maintenance). Of these patients ($N=1,831$), 1,335 (72.9%) were classified as not having a dose escalation and 496 (27.1%) were classified as having a dose escalation. Dose escalation was highest in patients initiating infliximab or vedolizumab (Fig. 2).

Table 1. Demographic and clinical characteristics at index, by treatment cohort

	Total (N = 2,331)	Adalimumab (N = 1,291)	Infliximab (N = 810)	Golimumab (N = 127)	Vedolizumab (N = 103)	<i>p</i> value
Male, <i>n</i> (%)	1,200 (51.5)	659 (51.0)	417 (51.5)	64 (50.4)	60 (58.3)	0.560
Age, mean (SD), years	44.5 (15.0)	44.8 (14.4)	43.8 (15.8)	45.3 (15.2)	44.4 (15.7)	0.455
Region, <i>n</i> (%)						
Northeast	407 (17.5)	229 (17.7)	132 (16.3)	30 (23.6)	16 (15.5)	0.138
Midwest	560 (24.0)	278 (21.5)	240 (29.6)	20 (15.7)	22 (21.4)	
South	969 (41.6)	555 (43.0)	312 (38.5)	58 (45.7)	44 (42.7)	
West	377 (16.2)	218 (16.9)	120 (14.8)	18 (14.2)	21 (20.4)	
Unknown	18 (0.8)	11 (0.9)	6 (0.7)	1 (0.8)	0 (0.0)	
Quan-Charlson Comorbidity Index score, mean (SD)	0.6 (1.0)	0.6 (1.1)	0.6 (1.1)	0.6 (1.3)	0.4 (0.9)	0.172

N, number of patients; *n*, number of patients within the given category; SD, standard deviation. *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 the 4 biologic therapies.

Table 2. The most common UC-related medications during the 12-month pre-index period, by treatment cohort

	Total (N = 2,331)	Adalimumab (N = 1,291)	Infliximab (N = 810)	Golimumab (N = 127)	Vedolizumab (N = 103)	<i>p</i> value
5-ASA, <i>n</i> (%)						
Mesalamine	1,728 (74.1)	983 (76.1)	578 (71.4)	95 (74.8)	72 (69.9)	0.073
Steroids, <i>n</i> (%)						
Budesonide	665 (28.5)	372 (28.8)	216 (26.7)	45 (35.4)	32 (31.1)	0.193
Hydrocortisone	538 (23.1)	291 (22.5)	188 (23.2)	43 (33.9)	16 (15.5)	0.008
Methylprednisolone	430 (18.4)	259 (20.1)	133 (16.4)	24 (18.9)	14 (13.6)	0.107
Prednisone	1,647 (70.7)	929 (72.0)	584 (72.1)	83 (65.4)	51 (49.5)	<0.001
Immunosuppressants, <i>n</i> (%)						
Azathioprine/6-mercaptopurine	655 (28.1)	360 (27.9)	240 (29.6)	33 (26.0)	22 (21.4)	0.312

5-ASA, 5-aminosalicylates; *N*, number of patients; *n*, number of patients within the given category. The 25 most common concomitant medications were obtained; only 5-ASAs, steroids, and immunosuppressants are shown. *p* values were determined using χ^2 tests to compare rates among the 4 treatment cohorts. *N*, number of patients; *n*, number of patients within the given category.

Total all-cause and UC-related costs were significantly higher overall (USD 19,662 and USD 20,106 higher, respectively) in patients who had a dose escalation in the 12-month post-index period compared with those who did not (Table 3). Total all-cause costs were higher in patients who had a dose escalation on adalimumab, infliximab, or vedolizumab than in those who did not. Patients who had a dose escalation on adalimumab, infliximab, or vedolizumab had total UC-related costs that were USD 22,247, USD 16,287, and USD 47,734 higher, respectively, than those for patients who did not have a dose escalation on these treatments (all *p* < 0.05). Dose escalation in patients using golimumab was uncommon (Fig. 2), and the total all-cause and UC-related costs in the 12-month post-index period among patients using golimumab were

USD 9,922 and USD 7,758 less, respectively, for patients who had a dose escalation (*N* = 10) compared with those who did not (*N* = 91).

UC-related inpatient and outpatient costs were not significantly different (*p* = 0.98 and *p* = 0.20, respectively) between patients who did or did not have a dose escalation (Table 3). UC-related prescription and drug administration costs were higher among those who had a dose escalation than those who did not (both *p* < 0.05). Large differences were also seen between UC-related prescription and drug administration costs. For adalimumab and golimumab, prescription costs were much higher than drug administration costs, and for infliximab and vedolizumab, drug administration costs were much higher than prescription costs.

Fig. 2. Percentage of patients who had a dose escalation (i.e., received an average daily dose >20% higher than specified in the label) during the maintenance phase of the 12-month post-index period, by treatment cohort.

The effect of concomitant immunosuppressants on the proportion of patients with dose escalation was also assessed (Fig. 3). Across index therapies, the proportion of patients with dose escalation was largely similar among those receiving and not receiving concomitant immunosuppressants. In all treatment groups, except for golimumab, the proportion of patients with dose escalation appeared numerically higher among patients who received concomitant immunosuppressants than among those who did not. However, a multivariable model assessing the interaction between immunosuppressants and index therapy to predict dose escalation did not reveal any significant interactions (data not shown). The data from this model suggest that using concomitant immunosuppressants did not affect dose escalation.

Adherence

Adherence, measured by PDC, was as follows: overall, 0.71; adalimumab, 0.68; infliximab, 0.76; golimumab, 0.67; and vedolizumab, 0.77. Overall, the proportion of adherent patients (those achieving a PDC ≥ 0.80) was 56.2%. A PDC ≥ 0.80 was achieved by 51.9% of patients treated with adalimumab and 55.1% of patients treated with golimumab, both of which were administered subcutaneously [27, 28]. By comparison, a PDC ≥ 0.80 was achieved by 62.5% and 63.1% of patients treated with the intravenous infusion therapies [29, 30] infliximab and vedolizumab, respectively.

A similar pattern was observed after adjusting for patient characteristic variables (age, sex, region, insurance type, health plan, Quan-Charlson Comorbidity Index score, extent of disease, years to UC diagnosis during

baseline, number of pre-index gastroenterology visits, number of pre-index UC hospitalizations, total pre-index UC-related healthcare costs, concomitant immunosuppressant use, and index therapy). The adjusted PDC was 0.63 for patients treated with golimumab and 0.65 for patients treated with adalimumab. Compared with the adalimumab cohort, PDC for the infliximab and vedolizumab cohorts was significantly higher at 0.73 and 0.71, respectively (both $p < 0.05$). Analysis of predictors of adherence defined as a PDC ≥ 0.80 is shown in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000521299). Being from the Midwest region (vs. the Northeast region; odds ratio = 1.33), having longer disease duration (odds ratio = 1.18), and having more gastroenterology visits during the pre-index period (odds ratio = 1.04) were other factors associated with greater adherence (all $p < 0.05$). Having a higher number of pre-index UC-related hospitalizations (odds ratio = 0.83; $p < 0.05$) was associated with lower adherence. A multivariable model assessing the interaction between immunosuppressants and index therapy to predict adherence did not reveal any significant interactions, suggesting that the use of concomitant immunosuppressants did not affect the likelihood of patients being adherent to their index therapy.

Discussion

This study explored dose escalation and treatment adherence over a 12-month period in patients with UC initiating biologic therapies in the USA. In this study, dose

Table 3. All-cause and UC-related costs by dose escalation

	All-cause costs							
	no dose escalation			dose escalation			difference between dose escalation and no dose escalation	p value
	N	mean	SD	N	mean	SD		
Total costs								
Adalimumab	815	USD 63,983	USD 34,194	252	USD 85,944	USD 39,410	USD 21,961	<0.05
Infliximab	384	USD 63,966	USD 41,985	205	USD 79,544	USD 49,141	USD 15,578	
Golimumab	91	USD 73,523	USD 44,847	10	USD 63,601	USD 23,880	USD −9,922	
Vedolizumab	45	USD 50,616	USD 12,899	29	USD 102,892	USD 48,744	USD 52,276	
Total	1,335	USD 64,177	USD 37,053	496	USD 83,839	USD 44,351	USD 19,662	
Inpatient visit costs								
Adalimumab	815	USD 5,336	USD 20,568	252	USD 6,398	USD 22,133	USD 1,062	0.89
Infliximab	384	USD 5,686	USD 21,827	205	USD 9,404	USD 30,068	USD 3,718	
Golimumab	91	USD 6,730	USD 33,120	10	USD 0	USD 0	USD −6,730	
Vedolizumab	45	USD 770	USD 3,629	29	USD 1,346	USD 5,192	USD 576	
Total	1,335	USD 5,378	USD 21,685	496	USD 7,216	USD 25,058	USD 1,838	
Outpatient visit costs								
Adalimumab	815	USD 11,301	USD 20,323	252	USD 15,812	USD 21,668	USD 4,511	<0.05
Infliximab	384	USD 48,610	USD 34,829	205	USD 60,672	USD 37,183	USD 12,062	
Golimumab	91	USD 11,135	USD 19,106	10	USD 4,103	USD 3,434	USD −7,032	
Vedolizumab	45	USD 39,129	USD 14,651	29	USD 82,431	USD 59,281	USD 43,302	
Total	1,335	USD 22,959	USD 30,378	496	USD 38,012	USD 40,115	USD 15,053	
Prescription costs								
Adalimumab	815	USD 47,346	USD 18,553	252	USD 63,734	USD 27,281	USD 16,388	<0.05
Infliximab	384	USD 9,669	USD 15,308	205	USD 9,469	USD 12,616	USD −200	
Golimumab	91	USD 55,657	USD 17,180	10	USD 59,498	USD 22,691	USD 3,841	
Vedolizumab	45	USD 10,717	USD 13,188	29	USD 19,115	USD 22,037	USD 8,398	
Total	1,335	USD 35,840	USD 25,081	496	USD 38,612	USD 34,409	USD 2,772	
	UC-related costs							
	no dose escalation			dose escalation			difference between dose escalation and no dose escalation	p value
	N	mean	SD	N	mean	SD		
Total costs								
Adalimumab	815	USD 54,598	USD 25,704	252	USD 76,845	USD 32,908	USD 22,247	<0.05
Infliximab	384	USD 56,258	USD 36,627	205	USD 72,545	USD 45,163	USD 16,287	
Golimumab	91	USD 66,003	USD 41,867	10	USD 58,245	USD 23,461	USD −7,758	
Vedolizumab	45	USD 45,551	USD 10,291	29	USD 93,285	USD 45,549	USD 47,734	
Total	1,335	USD 55,548	USD 30,358	496	USD 75,654	USD 39,321	USD 20,106	
Inpatient visit costs								
Adalimumab	815	USD 4,398	USD 18,346	252	USD 5,472	USD 18,520	USD 1,074	0.98
Infliximab	384	USD 4,549	USD 16,629	205	USD 8,611	USD 26,713	USD 4,062	
Golimumab	91	USD 6,259	USD 32,483	10	USD 0	USD 0	USD −6,259	
Vedolizumab	45	USD 423	USD 2,837	29	USD 1,346	USD 5,192	USD 923	
Total	1,335	USD 4,434	USD 18,894	496	USD 6,418	USD 21,779	USD 1,984	
Outpatient visit costs								
Adalimumab	815	USD 3,391	USD 8,776	252	USD 5,110	USD 11,577	USD 1,719	0.20
Infliximab	384	USD 6,514	USD 8,714	205	USD 7,950	USD 8,132	USD 1,436	
Golimumab	91	USD 3,783	USD 10,035	10	USD 1,295	USD 1,796	USD −2,488	
Vedolizumab	45	USD 3,385	USD 3,076	29	USD 7,620	USD 6,733	USD 4,235	
Total	1,335	USD 4,316	USD 8,824	496	USD 6,354	USD 10,014	USD 2,038	
Prescription costs								
Adalimumab	815	USD 44,361	USD 16,168	252	USD 60,985	USD 26,709	USD 16,624	<0.05
Infliximab	384	USD 7,846	USD 14,638	205	USD 7,448	USD 11,093	USD −398	
Golimumab	91	USD 53,220	USD 17,999	10	USD 56,946	USD 22,690	USD 3,726	
Vedolizumab	45	USD 8,785	USD 12,149	29	USD 16,426	USD 20,331	USD 7,641	
Total	1,335	USD 33,262	USD 23,587	496	USD 36,171	USD 33,644	USD 2,909	
Drug administration costs								
Adalimumab	815	USD 2,449	USD 10,670	252	USD 5,278	USD 14,331	USD 2,829	<0.05
Infliximab	384	USD 37,349	USD 31,983	205	USD 48,536	USD 35,371	USD 11,187	
Golimumab	91	USD 2,740	USD 10,461	10	USD 5	USD 15	USD −2,735	
Vedolizumab	45	USD 32,959	USD 14,478	29	USD 67,893	USD 56,271	USD 34,934	
Total	1,335	USD 13,536	USD 25,229	496	USD 26,711	USD 36,657	USD 13,175	

N, number of patients; SD, standard deviation; UC, ulcerative colitis. *p* values represent the statistical testing of the main effect of dose escalation on each cost variable; costs are broken out by index therapy only for descriptive purposes.

Fig. 3. The proportion of patients who had a dose escalation 12 months post-index, by concomitant immunosuppressants and index treatment. *N*, total number of patients in which dose escalation was examined; *n*, number of patients in each group (patients with dose escalation; patients receiving concomitant immunosuppressants; or not receiving concomitant immunosuppressants). The 25 most common concomitant medications were obtained.

escalation was observed in up to 39.2% of patients in the first year after initiating biologic therapies, and incurred USD 20,106 more in total UC-related annual costs than in patients who did not have a dose escalation. Overall, the proportion of adherent patients was 56.2%. The proportion of adherent patients was around 10% higher in patients initiating intravenous biologic therapies than in those initiating subcutaneous biologic therapies. Concomitant immunosuppressants were used in 29.1% of the 1,831 patients who were examined for dose escalation. In all treatment groups, except for golimumab, the proportion of patients with dose escalation was numerically higher in patients who received concomitant immunosuppressants than in those who did not. This is an interesting finding because treatment with biologics in combination with immunosuppressants, particularly infliximab and thiopurines, has been observed as superior to biologic monotherapy in patients with moderately to se-

verely active UC [31]. However, multivariable modeling assessing the interaction between immunosuppressants and index therapy to predict dose escalation did not reveal any significant interactions. However, this result should be interpreted with caution because patients being treated with concomitant immunosuppressants may be more likely to have a dose escalation in some cases, e.g., in patients with low serum drug trough concentration and borderline antidrug antibody formation to biologics [32]. It is also possible that this group of patients had more severe disease at baseline, thus requiring a concomitant immunosuppressant alongside their biologic therapy.

The rates of dose escalation observed in this study may reflect the challenges in achieving remission in many patients initiating biologic therapies, indicating that currently approved doses may be insufficient to control UC in some patients. Interestingly, recent randomized con-

trolled trial data have demonstrated that dose intensification of adalimumab was not associated with improved endoscopic or clinical outcomes after induction [33]. There are also economic considerations to dose escalation. Patients who had a dose escalation incurred higher total annual costs, based on increased pharmacy and administration costs, although this varied by therapy. This cost increase for patients who had a dose escalation suggests that total all-cause and UC-related costs are proportional to the dose or dose frequency used. Prescription costs were much higher than drug administration costs for adalimumab and golimumab, whereas drug administration costs were much higher than prescription costs for infliximab and vedolizumab. This is likely due to the fact that adalimumab and golimumab are self-administered, so costs would be recorded under prescription claims, whereas infliximab and vedolizumab are physician-administered, so costs would be recorded under medical claims.

The study demonstrated that adherence, measured by PDC, was higher for intravenous infusion therapies (infliximab and vedolizumab) than for subcutaneous therapies (adalimumab and golimumab), suggesting that adherence is better in patients who attend scheduled appointments to receive physician-administered intravenous therapy, compared with those who self-administer subcutaneous treatment. However, overall, 36.9–48.1% of patients were nonadherent (with adherence defined as a PDC ≥ 0.80). These real-world data reinforce the pervasive problem of nonadherence, which is often underestimated by clinicians in inflammatory bowel disease treatment [34]. Multivariable analysis demonstrated that patients with longer disease duration and more regular contact with their gastroenterologists were less at risk of being nonadherent. Longer times between gastroenterologist visits (at least 3 months) have previously been associated with nonadherence [35]. It is possible that patients with more severe disease have more contact with their gastroenterologist and, as such, may be more adherent than patients with less severe disease who have less frequent contact with their gastroenterologist. Multivariable analysis also identified an association between UC hospitalizations and lower rates of adherence, suggesting that patients with a history of UC hospitalizations could also be more at risk of being nonadherent. However, the increase in hospitalizations could be a result of nonadherence due to poorer disease control. It is difficult to speculate on these results because hospitalizations may have interrupted patients' treatment schedules. Hospitalizations may also have confounded adherence results be-

cause they are associated with a more aggressive disease course and increased risk of colectomy [36]. Other etiologies for nonadherence, such as concurrent infection where physicians recommend holding therapy, which leads to a delayed treatment schedule, can be difficult to determine from administrative claims data. An alternate indication for discontinuation of therapy is colectomy; in this study, however, nonadherence was defined by the patients' prescription record only. More research is necessary to clarify the factors that impact adherence.

This study was subject to several additional limitations due to the nature of the analyses. Outpatient administrations of biologic therapy were included in these analyses; however, IBM[®] MarketScan[®] Commercial and Medicare Supplemental Databases did not contain data on inpatient medication administration; therefore, administration of biologic therapy during an inpatient stay could not be determined. Real-world dosing and administration is complex, and a set of simplifying assumptions therefore had to be imposed for research purposes. A different set of assumptions (e.g., for dose escalation) may yield different results. Multivariable modeling controlled for observed differences in demographic and clinical characteristics, but some issues may be associated with this. For example, extent of disease was included as a covariate in the models, based on ICD-9/10 codes that have been associated with a large degree of variability. Despite this variability, the inclusion of extent of disease would not have influenced the models. Another potential limitation with multivariable modeling is that there may be other variables, not included in the data, which may explain some of the variation among treatment cohorts. For example, replacement shipments and refrigeration issues were not taken into account when performing average dose escalation calculations. Additionally, patients treated with infliximab might have experienced weight gain, leading to an increase in dose (as dosing is weight-based) that could have resulted in an overrepresentation of the frequency of dose escalation in these patients. Weight was not available in the claims data, so this could not be verified. Furthermore, patients who were initiated on doses of infliximab $>20\%$ higher than the product label and maintained on these doses would not be considered in this study to have dose escalated; however, such patients may be expected to generate higher costs from higher doses.

Another limitation of this study is that the duration of evaluation was limited to 12 months following initiation, and these findings cannot be extrapolated to later years where dose escalation may be higher. Patients were only excluded if they had received a biologic therapy up to 12

months before the index period; therefore, they may have received a biologic therapy prior to the pre-index period and hence would not be considered truly biologic-naïve. Moreover, the sample used for this study comprised patients with UC, newly treated with a biologic therapy, who were continuously enrolled in a commercial health insurance plan. Therefore, the findings reported here may not be generalizable to other populations, such as uninsured patients.

Patient numbers were not evenly weighted across treatment cohorts. Adalimumab was the most common index therapy, with 1,291/2,331 (55.4%) patients in this treatment cohort. Switching to a treatment with a different mechanism of action following secondary loss of response only became an option when vedolizumab was approved in the USA in 2014 [30]. Since this study included data from 2012 to 2017, there could be an overrepresentation of the number of patients that had a dose escalation compared with current clinical practice.

Additionally, patients were assumed to have moderately to severely active UC based on the fact that their physician prescribed a biologic therapy. However, the study may have excluded patients who had UC alongside another inflammatory disease and were treated primarily for the other condition, and it may have included patients with UC who had a concomitant diagnosis of another inflammatory condition, such as rheumatoid arthritis, ankylosing spondylitis, psoriasis, or psoriatic arthritis, whose prescriptions for the biologic therapy were intended to treat these other comorbidities.

Patients who underwent colectomy prior to index therapy were not excluded from this study; therefore, it is possible that the analysis population included some patients who were receiving therapy for post-colectomy pouchitis. However, it is expected that this would represent only a very small proportion of the overall patient population in this study.

Finally, patients who filled their prescription but did not take their biologic therapy could not be accounted for when measuring adherence and patients who were considered to have discontinued their biologic therapy may actually have bridged the gap between biologics with steroids, leading to possible misrepresentation of adherence. Measurement of adherence could also have been affected by the administration method of the biologic therapy, because only medication possession could be recorded in patients prescribed self-administered injectables (adalimumab and golimumab), whereas patients prescribed physician-administered intravenous biologic therapies (infliximab and vedolizumab) were known to have received the drug.

Conclusions

In this study of patients initiating biologic therapies for the treatment of moderately to severely active UC, who were followed for 12 months, up to 39.2% of patients had a dose escalation within the first year, resulting in up to USD 47,734 higher UC-related costs compared with patients who did not have a dose escalation. Furthermore, suboptimal adherence was observed in the 12-month post-index period. The treatment patterns observed in this study suggest that new treatment options offering additional mechanisms of action, dosing regimens, and/or other characteristics should be pursued in patients with moderately to severely active UC.

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Statement of Ethics

In compliance with the Health Insurance Portability and Accountability Act, patient data included in the study were de-identified. As a retrospective analysis of de-identified data, Institutional Review Board review was not required or sought for this study and written informed consent from participants was not required in accordance with local/national guidelines.

Conflict of Interest Statement

M.D.L. has received consultancy fees from AbbVie, Janssen, Pfizer Inc., Takeda, Target PharmaSolutions, and Theravance, and has received grant support from Pfizer Inc and Takeda. R.D.C. has received speaker fees from AbbVie and Takeda and has received consultancy fees from AbbVie, Celgene, Janssen, Pfizer Inc., and Takeda. T.W.S. and D.B. were employees of Pfizer Inc. at the time this research was conducted. M.D.B., D.G., L.S., and D.Q. are employees and stockholders of Pfizer Inc.

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Author Contributions

M.D.L., R.D.C., T.W.S., M.D.B., D.G., D.B., L.S., and D.Q. contributed to the manuscript's conception and design and critically reviewed it. All authors read and approved the final manuscript.

Data Availability Statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

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