Living with Ulcerative Colitis in Japan: Biologic Persistence and Health-Care Resource Use

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Keywords

Adherence · Tumor necrosis factor inhibitor · Health-care resource utilization · Persistence · Ulcerative colitis

Abstract

Objective: The aim of the study was to improve understanding of adherence and persistence to biologics, and their association with health-care resource utilization (HCRU), in Japanese patients with moderate to severe ulcerative colitis (UC). **Methods:** Data were from Medical Data Vision, a secondary care administrative database. A retrospective, longitudinal cohort analysis was conducted of data from UC patients initiating biologic therapy between August 2013 and July 2016. Data collected for 2 years prior (baseline) and 2 years after (follow-up) the index date were evaluated. Patients completing biologic induction were identified, and adherence/persistence to biologic therapy calculated. HCRU, steroid, and immunosuppressant use during baseline and follow-up were assessed. Biologic switching during the follow-up was evaluated. Descriptive statistics (e.g., means and proportions) were obtained and inferential analyses (from Student's *t* tests, Fisher's exact tests, χ^2 tests, the Cox

proportional hazard model, and negative binomial regression) were performed. **Results:** The analysis included 649 patients (adalimumab: 265; infliximab: 384). Biologic induction was completed by 80% of patients. Adherence to adalimumab was higher than that to infliximab ($p < 0.001$). Persistence at 6, 12, 18, and 24 months was higher with infliximab than with adalimumab ($p < 0.05$). Overall, gastroenterology outpatient visits increased, and hospitalization frequency and duration decreased, from baseline to follow-up. UC-related hospitalizations were fewer and shorter, and endoscopies fewer, in persistent than in nonpersistent patients, although persistent patients made more outpatient visits than nonpersistent patients. Hospitalization duration was lower in persistent than nonpersistent patients. Approximately 50% of patients received an immunosuppressant during biologic therapy; 5% received a concomitant steroid during biologic therapy. Overall, 17% and 3% of patients, respectively, received 2nd line and 3rd line biologics. **Conclusions:** Poor biologic persistence was associated with increased non-medication-associated HCRU. Effective treatments with high persistence levels and limited associated HCRU are needed in UC.

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease, in which there is inflammation of a continuous section of the colonic mucosa from the rectum extending proximally for variable distances [1–3]. UC is characterized by periods of remission and relapse, with patients who initially present with UC affecting a limited section of the colon often progressing to more extensive disease [4]. The most common presenting symptoms are bloody diarrhea, abdominal pain, urgency, and tenesmus [1, 5].

The prevalence of UC ranges from 2.4 to 505 cases per 100,000 people across different regions of the world [6]. The prevalence in Japan has been reported to be 18.1/100,000 in 1991 [7], 63.6/100,000 in 2005 [8], and 172.9/100,000 in 2014 [9], in line with a reported increase in the incidence of UC [6, 10].

Pharmacological interventions available for UC include aminosalicylates (5-ASA), corticosteroids, immunosuppressants (IMs), and biologics. Surgery is an option for nonresponsive patients with severe disease [11, 12]. Japanese, European, and US guidelines for the management of UC recommend that disease extent, severity, and current activity are taken into account when selecting treatment, although Japanese guidelines do not specify a treatment target [13–16]. For the induction of remission in moderate-to-severe UC, systemic steroids are the most common first-line treatment; biologics are an option for second-line therapy; intravenous steroids are usual given in acute severe UC; intravenous IM therapy or the biologic infliximab may be used as rescue therapy if there is insufficient response to first-line treatment. For patients in remission, maintenance treatment options include oral 5-ASA, oral IMs, or biologics if these have been used in inducing remission. Biologics approved for treatment of UC in Japan include infliximab, adalimumab, golimumab, and vedolizumab [17, 18], although golimumab was only approved in March 2017 and vedolizumab in July 2018 [19, 20].

Although biologics are effective in a high proportion of patients with UC, a substantial proportion of patients fail to reach treatment targets [18, 21], with ~50% of patients achieving clinical response, and fewer than 25% achieving remission [17]. Furthermore, the development of anti-drug antibodies can lead to a secondary loss of response; a systematic review of international studies reported anti-drug antibodies in up to 41% of patients with UC receiving biologics [22].

A study of Japanese claims data reported that 55% of patients with UC persisted to biologic medication

Fig. 1. Study design.

throughout the maintenance period, with persistence to infliximab slightly better than adalimumab [23]. There is also little known about the impact of suboptimal adherence and persistence to biologics, which are known to be associated with suboptimal outcomes for 5-ASA [24, 25].

The aim of this study was to describe adherence and persistence to infliximab and adalimumab in Japanese patients with moderate-to-severe UC, as these are indicators of treatment response to biologics. A better understanding of these variables may inform management of patients with UC. This study also assessed the association of adherence and persistence to these biologics; the use of steroids and IMs in combination with biologic therapy; the extent to which patients had changes in the biologic agent received; and potential predictors of biologic therapy persistence and UC-related hospitalizations.

Materials and Methods

Study Design

Data were obtained from Medical Data Vision (MDV), a secondary care administrative database in Japan [26, 27]. MDV holds data from 22% of all acute care hospitals in Japan. It should be noted that although “acute care” is specified, data are available on all types of care provided by these institutions. Information on >25 million individuals (outpatient and inpatient) is held. MDV includes data from 2008 onward.

A retrospective, longitudinal cohort analysis was conducted using data from patients with UC initiating biologic therapy between August 1, 2013 and July 31, 2016 – the index date (Fig. 1). As only infliximab and adalimumab were approved for use in UC in Japan during this period, the analysis included these 2 biologics. Data collected during the 2 years prior to the index date (baseline period) and the 2 years after the index date (follow-up period) were evaluated. This study is one of two studies conducted to describe real-world outcomes in patients with UC, and the other to describe health-care resource utilization (HCRU) and treatment patterns among patients with UC in Germany [28] (shown in Fig. 1).

Patients

Eligible patients were 18 years or older on the index date, had one confirmed diagnosis code for UC (International Classification of Diseases, 10th Revision [ICD-10] code K51.X) in the 2 years prior to or including the index date, had an outpatient prescription or inpatient administration of either adalimumab or infliximab between August 2013 and July 2016, and had data available in MDV throughout the baseline and follow-up periods. Patients were excluded from the analysis if they had a prescription or administration of ≥ 2 of either specified biologic therapy on the index date, one or more prescription(s) or administration(s) of one of the specified biologic therapies in the baseline period, or one or more confirmed ICD-10 diagnosis code for Crohn's disease (K50.X) in the baseline or follow-up period.

Outcomes

Patient demographics and clinical characteristics (including extent of disease and Charlson Comorbidity Index (CCI) at end of baseline) were reported [29]. Patients completing biologic induction were identified using standard induction periods: adalimumab: a prescription after 21 days; infliximab: a prescription after 56 days. When the induction period for adalimumab was defined as 35 days, an equal number of patients were shown to reach maintenance therapy.

Adherence to the indexed biologic therapy during the maintenance period was measured as the proportion of days covered (PDC: the number of days in period covered by prescription/the number of days in period) [30]. The number of days' supply of adalimumab was estimated using the amount prescribed and a defined daily dose (DDD) of 2.86 mg (40 mg every other week), as defined by the World Health Organization ATC/DDD index. For infliximab, a dosage of 6.25 mg/kg was used to better reflect clinical practice (5 mg/kg every 8 weeks for a 70-kg patient corresponds to 6.25 mg/kg daily). PDC was calculated until discontinuation or end of the follow-up, with discontinuation defined as a gap of ≥ 60 days between fills/infusions. Patients were categorized as adherent (PDC $\geq 80\%$) or nonadherent (PDC $< 80\%$).

Persistence to the indexed biologic therapy was defined as the time from the index date to discontinuation, with discontinuation defined as a gap of ≥ 60 days between fills/infusions, and the number of days' supply of biologic medication estimated using the amount prescribed and recommended doses, as described before. The proportions of patients persisting at 6, 12, 18, and 24 months were calculated. Sensitivity analyses were performed to explore persistence rates with discontinuation defined as a gap of ≥ 30 days and ≥ 90 days between fills/infusions.

HCRU was assessed in the baseline and follow-up periods. Resources considered were therapy for UC (biologics, 5-ASA, steroids and IMs), outpatient appointments, hospital stays, visits to the emergency room, and any UC-related procedures or surgeries. Resource uses with an associated diagnosis code for UC were considered "UC-related." These were reported, and HCRU was compared between persistent and nonpersistent patients at 6, 12, and 18 months.

Assessment of the use of steroids and IMs in the baseline and follow-up periods included consideration of combination treatment strategies (biologic + steroid, biologic + IM, biologic + steroid + IM). To account for steroid tapering, patients were required to have received a steroid prescription 14 weeks or more after initiation of biologic therapy to be considered to have received biologic + steroid therapy.

Any overlap in biologic and IM prescriptions was considered to indicate biologic + IM therapy. Biologic + IM use was further split into those who initiated IM within 3 months of initiating biologic therapy and those who initiated IM > 3 months after initiating biologic therapy. The proportions of patients switching to a different tumor necrosis factor inhibitor (TNFi) during the follow-up period for treatment beyond first-line (referred to as cycling) were calculated. In addition to infliximab and adalimumab, golimumab was included as second- or third-line biologic therapy.

Analysis

All outcomes were analyzed descriptively and reported using frequencies and percentages for categorical variables, and counts, means, medians, standard deviations, and interquartile ranges (IQR) for continuous variables. For unpaired statistical comparisons between the 2 independent groups (adalimumab vs. infliximab), we have applied the following tests: Student's *t* test for difference in outcome means, Fisher's exact test (for 2×2 cross-classification tables when an expected cell count was < 5), and χ^2 test (for cross-classification tables when each expected cell count is 5 or greater) for binary or multinomial outcomes [31, 32].

Predictors for patients persisting with their indexed therapy in the 2-year follow-up period were examined using a Cox proportional hazards model [32], with potential predictors including indexed biologic, steroid and IM use, sex, baseline CCI, and years since diagnosed with UC (≤ 1 year/ > 1 year). Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported for each predictor/covariate, with the predictor/covariate considered statistically significant if the 95% CIs did not overlap the null effect of 1.

The same set of potential predictors use were included as in the analysis of predictors of UC-related hospitalizations, and incidence rate ratios and 95% CIs reported for each predictor, with statistical significance again indicated by 95% CIs not overlapping 1. Such predictors for patients experiencing a UC-related hospitalization within the 2-year follow-up period were examined using a negative binomial regression model for nonnegative count estimates [33]. All analyses were performed using Stata, version 15.1 or later [34].

Results

Eligible Patients

A total of 649 patients were included in the analysis, of whom 265 (41%) received adalimumab and 384 (59%) received infliximab as the indexed biologic (shown in Fig. 2).

Demographics and Clinical Characteristics

Patient demographics and general health based on the CCI were broadly similar between those receiving adalimumab and those receiving infliximab as the indexed biologic (Table 1). Compared with patients receiving infliximab, patients receiving adalimumab had been diagnosed with UC for longer (3.3 and 4.5 years, respectively; $p < 0.01$) (shown in Table 1).

Fig. 2. Consort flow diagram. CD, Crohn's disease; UC, ulcerative colitis.

Primary Objectives

Adherence and Persistence to Biologic Therapy

Overall, 80% of patients completed the induction period with the indexed biologic. The proportion of patients completing induction was similar in those receiving adalimumab (82%) and infliximab (78%). Adherence to the indexed biologic during the maintenance period was high with both indexed biologics, but patients receiving adalimumab were slightly more adherent than those receiving infliximab, based on PDC (0.95 vs. 0.90); $p <$

0.001) (Fig. 3a). The percentage of patients classified as adherent (PDC $\geq 80\%$) was similar for those receiving adalimumab and infliximab (93.6% vs. 91.0%, respectively, $p = 0.33$) (shown in Fig. 3).

Based on discontinuation defined as a gap of at least 60 days between refill/infusions, a higher proportion of patients prescribed infliximab on the index date persisted on therapy at 6, 12, 18, and 24 months than those prescribed adalimumab (all $p < 0.05$) (Fig. 3b). Sensitivity analyses using a gap of ≥ 30 days and ≥ 90 days between

Table 1. Patient demographics and clinical characteristics

	Total (<i>n</i> = 649)	ADA (<i>n</i> = 265)	INF (<i>n</i> = 384)	<i>p</i> value ^a
Age at index date, years ^b				
Mean (SD)	43.6 (16.1)	44.1 (16.2)	43.3 (16.0)	0.542 ^c
Min, max	18.0, 90.0	18.0, 90.0	18.0, 87.0	
Median	42	42	43	
IQR	30.0, 56.0	30.0, 56.0	29.0, 55.0	
Sex, <i>n</i> (%)				0.1966 ^d
Female	274 (42)	120 (45)	154 (40)	
Male	375 (58)	145 (55)	230 (60)	
Time since diagnosis, years				
Mean (SD)	3.8 (4.6)	4.5 (4.9)	3.3 (4.3)	0.0019 ^c
Min, max	0.0, 26.7	0.0, 26.7	0.0, 22.9	
Median	1.9	2.5	1.4	
IQR	0.4, 5.9	0.6, 7.0	0.4, 4.7	
Categorized, <i>n</i> (%)				0.007 ^d
≤1 year	247 (38)	84 (32)	163 (42)	
>1 year	402 (62)	181 (68)	221 (58)	
Baseline CCI				
Mean (SD)	0.7 (1.3)	0.8 (1.4)	0.7 (1.3)	0.473 ^c
Min, max	0, 10	0, 8	0, 10	
Median	0	0	0	
IQR	0, 1	0, 1	0, 1	
Categorized, <i>n</i> (%)				0.9155 ^f
0	427 (66)	173 (65)	254 (66)	
1–2	168 (26)	68 (26)	100 (26)	
3–4	42 (7)	18 (7)	24 (6)	
5+	12 (2)	6 (2)	6 (2)	
Known baseline extent of disease, <i>n</i> (%) ^e				
<i>N</i>	340	114	226	0.27 ^f
Pancolitis	248 (73)	78 (68)	170 (75)	
Left-side	64 (19)	28 (25)	36 (16)	
Proctosigmoiditis	16 (5)	4 (4)	12 (5)	
Proctitis	12 (4)	4 (4)	8 (4)	

ADA, adalimumab; CCI, Charlson Comorbidity Index; IFX, infliximab; IQR, interquartile range; SD, standard deviation. ^a Difference adalimumab versus infliximab. ^b Maximum age in MDV is 90 years; patients >90 years were included as 90 years of age. ^c Student's *t* test. ^d Chi-square test. ^e Percentages calculated based on patients with disease extent reported. ^f Fisher's exact test; test excludes unknown category (total: 309, ADA: 151, INF: 158).

fills/infusions to define discontinuation confirmed these findings.

Health-Care Resource Utilization

The proportion of patients attending outpatient gastroenterology visits and the mean number of visits per patient were numerically higher in the follow-up than the baseline period (Table 2). By contrast, the mean number of UC-related hospitalizations in the follow-up period was numerically lower than that in the baseline period, and lengths of stay were numerically shorter (Table 2). Low numbers of endoscopies and no colectomies

were reported during the baseline period and very low numbers of both procedures during the follow-up period, with the reduction in endoscopies presumably reflecting improvements in disease control due to biologic initiation (Table 2). A higher proportion of persistent than nonpersistent patients attended outpatient gastroenterology visits ($p < 0.001$, $p < 0.01$, $p < 0.05$ when persistence was assessed at 6, 12, and 18 months, respectively) and the mean number of visits made was higher ($p < 0.001$, $p < 0.001$, $p < 0.01$ when persistence was assessed at 6, 12, and 18 months, respectively) for persistent than non-persistent patients (Table 2). However, these visits

Fig. 3. a Adherence to biologic therapy during the maintenance period. **b** Persistence to biologic therapy. p values show adalimumab versus infliximab. For **a** (adherence), Student's t test was used. For **b** (persistence), the χ^2 test was used (Fisher's exact test used if cell count <5). ADA, adalimumab; IFX, infliximab; PDC, proportion of days covered; SD, standard deviation.

Fig. 4. Biologic use across 1st, 2nd, and 3rd line. ADA, adalimumab; IFX, infliximab.

include visits for patients to receive infliximab infusions, which resulted in increased visits in persistent versus nonpersistent patients. The mean numbers of UC-related hospitalizations and endoscopies were lower, and hospital stays were of shorter duration, in persistent versus nonpersistent patients, regardless of the time at which persistence was assessed (Table 2). HCRU was not compared between adherent and nonadherent patients because of the very low numbers of nonadherent patients (shown in Table 2).

Secondary Objectives

Biologic Cycling

Of the total study population, 17.4% ($n = 113$) received at least a second-line of biologic therapy (Fig. 4); as only infliximab, adalimumab, and golimumab were considered in this analysis, this indicates 17.4% of patients switching from one TNFi to another. Of these, 47%, 44%, and 9% received infliximab, adalimumab, and golimumab, respectively, as second-line therapy. Overall, 2.6% ($n = 17$) of patients received third-line biologic therapy, with infliximab, adalimumab, and golimumab prescribed for 12%, 47%, and 41% of these patients, respectively.

Table 2. UC-related HCRU in baseline versus follow-up and in persistent versus nonpersistent patients

	Baseline (<i>n</i> = 649)	Follow-up						
		total (<i>n</i> = 649)	6 months		12 months		18 months	
			nonpersistent (<i>n</i> = 215)	persistent (<i>n</i> = 434)	nonpersistent (<i>n</i> = 272)	persistent (<i>n</i> = 377)	nonpersistent (<i>n</i> = 313)	persistent (<i>n</i> = 336)
Patients with outpatient								
gastroenterology visit(s), <i>n</i> (%)	363 (56)	397 (61)	107 (50)	290 (67)***	148 (54)	249 (66)**	177 (57)	220 (66)*
Outpatient gastroenterology visits, <i>n</i>								
Mean (SD)	9.1 (11.7)	12.6 (14.0)	9.3 (14.7)	14.2 (13.4)***	10.3 (14.9)	14.2 (13.2)***	10.9 (14.6)	14.1 (13.3)**
Min, max	0, 59	0, 77	0, 77	0, 68	0, 77	0, 68	0, 77	0, 68
Median	2	11	0	15	2	15	2	15
IQR	0, 17	0, 20	0, 16	0, 21	0, 17	0, 21	0, 19	0, 20.5
UC-related hospitalizations, <i>n</i>								
Mean (SD)	0.8 (0.9)	0.5 (0.9)	0.8 (1.2)	0.3 (0.7)***	0.8 (1.1)	0.2 (0.6)***	0.7 (1.1)	0.2 (0.6)***
Min, max	0, 6	0, 7	0, 7	0, 4	0, 7	0, 4	0, 7	0, 4
Median	1	0	0	0	0	0	0	0
IQR	0, 1	0, 1	0, 1	0, 0	0, 1	0, 0	0, 1	0, 0
Length of UC-related hospitalizations, days								
Mean (SD)	23.8 (35.0)	10.8 (26.7)	19.8 (36.6)	6.4 (18.7)***	19.6 (35.6)	4.5 (14.8)***	18.5 (34.9)	3.6 (11.9)***
Min, max	0, 301	0, 232	0, 232	0, 149	0, 232	0, 149	0, 232	0, 106
Median	10	0	0	0	0	0	0	0
IQR	0, 36	0, 6	0, 26	0, 0	0, 25	0, 0	0, 23	0, 0
Endoscopies, <i>n</i>								
Mean (SD)	0.8 (1.4)	0.4 (1.0)	0.5 (0.9)	0.4 (1.0)*	0.6 (1.0)	0.3 (0.9)**	0.6 (1.2)	0.3 (0.7)***
Min, max	0, 13	0, 10	0, 4	0, 10	0, 7	0, 10	0, 10	0, 4
Median	0	0	0	0	0	0	0	0
IQR	0, 1	0, 1	0, 1	0, 0	0, 1	0, 0	0, 1	0, 0
Colectomies, <i>n</i>								
Mean (SD)	0.0 (0.0)	0.0 (0.2)	0.0 (0.2)	0.0 (0.1)	0.0 (0.2)	0.0 (0.1)*	0.0 (0.2)	0.0 (0.1)
Min, max	0, 0	0, 1	0, 1	0, 1	0, 1	0, 1	0, 1	0, 1
Median	0	0	0	0	0	0	0	0
IQR	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0	0, 0

IQR, interquartile range; SD, standard deviation; HCRU, health-care resource utilization; UC, ulcerative colitis. *** $p < 0.001$. ** $p < 0.01$. * $p < 0.05$ for persistent versus nonpersistent. Student's t test was used for numeric variables. Fisher's exact test was used for patients with/without an outpatient gastroenterology visit.

Fig. 5. a Use of biologics, steroids, and IMs across lines of biologic therapy. **b** Use of steroids across biologic therapy lines and persistence groups. **c** Use of IMs across biologic therapy lines and persistence groups. For **a**, the χ^2 test was used. For **b** and **c** Fisher's exact test was used.

(For figure see next page.)

Fig. 6. Predictors of indexed biologic nonpersistence^a. ^aCox proportional hazards model of persistence to biologic therapy. * Indexed therapy. ADA, adalimumab; Bio, biologic; CCI, Charlson Comorbidity Index; IM, immunosuppressant.

Use of Steroids and IMs

Approximately half of all patients received a biologic in combination with an IM at first, second, and third line (Fig. 5a), the majority of whom received an IM prescription within 3 months of initiating that line of biologic therapy. Less than 5% of patients received a steroid prescription during a line of biologic therapy (when discounting steroid tapering). There were no significant differences in patterns of concomitant use of steroids and use of IMs between patients receiving adalimumab and those receiving infliximab at any line of therapy (Fig. 5a).

Among patients who persisted with indexed biologic therapy, the use of steroids during biologic therapy in the 6 months prior to assessment of persistence decreased over time (Fig. 5b). Among those persistent at 12 and 18 months, steroid use was significantly lower among those indexed on adalimumab than among those indexed on infliximab. IM use in the 6 months prior to assessment of biologic persistence remained at ~50% in patients who persisted with indexed biologic therapy at 6, 12, 18, and 24 months (shown in Fig. 5c).

Predictors of Nonpersistence with Biologic Therapy

Age, sex, and baseline CCI had no observable effect on the likelihood of patients persisting with biologic therapy (Fig. 6). Patients prescribed infliximab as their indexed therapy were statistically ($p < 0.05$) more likely to remain persistent than those initiated on adalimumab (Fig. 6).

Patients taking biologic therapy in combination with steroids (with or without IMs) were more likely to persist with biologic therapy. Among those receiving prescription for IM >3 months after initiating their indexed biologics, the statistically significant ($p < 0.05$) HR of nonpersistence was 0.44; among those who received an IM prescription within 3 months of initiating biologic therapy, the HR of nonpersistence was 0.89, which was not statistically significant. There was no evidence of a difference in persistence between patients diagnosed ≤ 1 year/>1 year prior to index, or between patients with or without pancolitis (shown in Fig. 6).

Factors Associated with UC-Related Hospitalizations

The hospitalization rate was significantly higher among female patients than male patients but did not differ significantly between the indexed biologics (Fig. 7). Patients were more likely to experience hospitalizations when prescribed an IM within 3 months of initiating biologic therapy than when taking biologics as monotherapy (shown in Fig. 7).

Discussion/Conclusion

In this real-world study in Japanese patients with moderate-to-severe UC, completion of the biologic treatment induction period and adherence to the indexed biologic

Fig. 7. Predictors of UC-related hospitalizations^a. ^aNegative binomial regression model of hospitalizations. *Indexed therapy. ADA, adalimumab; Bio, biologic; CCI, Charlson Comorbidity Index; FU, follow-up period; IM, immunosuppressant; UC, ulcerative colitis.

during the maintenance period were high, but only just over half of patients persisted with the indexed biologic at 18 months, reducing to 40% at 24 months. Although several studies have reported adherence to biologics to be a problem in patients with inflammatory bowel disease [35–37], in this study, a high level of adherence was observed with both infliximab and adalimumab, and similar to self-reported adherence levels from a survey linked to a US claims database [38], and to levels observed in studies included in a systematic review [37]. High medication adherence levels have been reported in Japan compared with other countries in dialysis patients, possibly as a result of the Japanese health-care system reducing the incidence of cost-related nonadherence [39].

Adherence to adalimumab in the maintenance period was observed to be 0.95 among those indexed on adalimumab and 0.90 among those indexed on infliximab. Higher adherence to infliximab than adalimumab in Crohn's disease but higher adherence to adalimumab than infliximab in RA were reported in a systematic literature review [40].

Patients indexed on an infliximab prescription had been diagnosed with UC for less time than those indexed on adalimumab. This reflects expected care in Japan where infliximab is more frequently used for acute severe UC, which will likely occur earlier in the disease course.

Persistence in our analysis was 67%, 58%, 52%, and 40% at 6, 12, 18, and 24 months, respectively. This is broadly consistent with the findings from other studies. A claims-based study of patients with UC in South Korea reported 12-month persistence to infliximab and adalimumab of 66.1% and 62.4% [41]. A chart review study in South Korea showed that 34.4% of patients with UC had shown suboptimal response to biologic therapy by 12 months [42]. In the USA, a retrospective claims database cohort study reported 1-year persistence to adalimumab and infliximab of 48% and 55% [43], while a retrospective chart review in 14 US community gastroenterology clinics reported 61% persistence to infliximab at 12 months in biologic-naïve patients with UC [44].

Analysis of Japanese claims data reported much higher persistence to biologics in patients with rheumatoid arthritis (RA) who were previously biologic-naïve: 99%, 96%, and 95% at 6, 12, and 18 months, respectively [45]. Persistence beyond 6 months was high between both indexed TNFi medications; 75% of patients persistent to adalimumab 6 months after index remained persistent at 18 months and 79% of patients persistent to infliximab 6 months after index remained persistent after 18 months.

In our study, the number of gastroenterology outpatient visits increased from the baseline to the follow-up period, while the number and length of UC-related hospitalizations decreased. These findings suggest that pa-

tients require closer clinical monitoring but have a reduced need for inpatient care, following initiation of a biologic.

Both the number and length of hospital stays were lower in persistent than nonpersistent patients; if hospitalizations are taken as a proxy for treatment effectiveness, these findings indicate that biologic persistence improves effectiveness and presumably patient outcomes. A similar finding was reported in a US claims analysis, with significantly fewer hospitalizations observed in patients with UC with good adherence to infliximab maintenance therapy than those with poor adherence [46].

In our analysis, 17% of patients switched to another TNFi as second-line treatment, with 9% of patients who initiated treatment with infliximab switching to adalimumab, in contrast to a US retrospective claims database cohort study of patients with UC in which 31% of patients who initiated treatment with infliximab switched to adalimumab [43]. Two studies in patients with RA have reported that patients switching from a TNFi to an agent with an alternative mode of action had significantly higher treatment persistence than those who cycled between TNFi agents [47, 48].

Approximately half of patients used an IM with a TNFi in follow-up, slightly higher than the 41% of patients who used an IM with biologic therapy in an equivalent study of German patients [28]. Steroid use with a TNFi was substantially lower (<5%) than was observed among German patients when accounting for steroid tapering (25%) [28].

Our study found patients were more likely to persist with biologic therapy if they received infliximab, rather than adalimumab, if they were prescribed a steroid at the same time a TNFi (with or without concomitant IM), and if they received IM therapy >3 months after initiating biologic therapy. Higher persistence among those who received concomitant steroid prescriptions may in part result from a group of steroid-dependent patients who initiate biologic therapy as part of a steroid withdrawal strategy and continue therapy with TNFi as a long-term alternative to steroid therapy. In another study of TNFi persistence among Japanese patients with UC, persistence was higher when an IM was taken with infliximab than when on monotherapy; the same trend was not observed among patients who received adalimumab [23]. Concomitant use of 5-ASA was associated with higher persistence of first-line TNFi treatment in patients with UC in a retrospective cohort analysis of a single European center [49].

Patients who started IM >3 months after biologic initiation, likely due to poor response to treatment, were ob-

served to be more persistent than those who started IM within 3 months of their biologics. It is expected that patients who started biologics as monotherapy are likely to have less severe UC than those who started biologics alongside an IM. Furthermore, patients who initiated IM >3 months after biologic may have overcome the secondary loss of response by the addition of IM, resulting in greater persistence to biologics.

This study has several limitations. The identification of patients with UC via the use of ICD-10 diagnosis codes, with potential for miscoding, might have led to inappropriate inclusion or exclusion of patients from the analysis, and as patients were identified as having moderate-to-severe UC only by initiation of biologic therapy, patients with less severe disease may have been included, although the cost of biologics ensures a very low level of inappropriate prescribing. Although patients using biologics in the 2-year baseline period prior to initiation of a biologic were excluded from this analysis, patients may have received biologic therapy >2 years prior to index. It would be unusual however for a biologic to be prescribed after a break of >2 years.

While the MDV database is large and is considered largely generalizable to the wider Japan population, the sample only includes patients treated at acute care hospitals. It should be noted however that secondary care takes a highly prominent role in Japanese health care and that there is no system of general practitioners. It is also possible that patients were discharged back to their local units for management after initiating a biologic and might be designated as nonpersistent with decreased outpatient appointments when they were persistent to therapy and attending regular outpatient clinics in a local unit, rather than an acute care hospital. MDV have published results to show that the proportion of patients by age category and major disease category is largely similar between MDV and Ministry of Health, Labour and Welfare of Japan data [50]. It is therefore expected that the UC patient population in MDV will be sufficiently representative of the wider Japanese UC patient population.

Calculation of adherence used the amount of biologic prescribed and recommended dose to estimate the days' medication supply. This approach could lead to an overestimate of adalimumab adherence as prescribed drugs might not necessarily have been taken; a cross-sectional survey of Japanese prescription data suggested that universal public health insurance and relatively low co-payments in Japan result in patients with chronic diseases consulting their physician regularly, and having drugs prescribed depending on the consultation schedule, with

potential storage of unused drugs [51]. To derive days' supply/coverage, the ATC/DDD system was used for adalimumab, and the recommended dose for a 70-kg patient was used for infliximab; estimated doses may differ from the actual dose and/or duration prescribed to, and taken by, the patient, particularly where individual characteristics are used to determine individual therapeutic doses. Because of a lack of data on dosages prescribed, we were also not able to observe whether a patient had experienced a dosage escalation.

Our analysis did not include any controls for proxies of disease severity as standard proxies are not recorded in the data. Due to the delayed launch of various biologics in Japan, only adalimumab and infliximab could be observed.

It may be concluded that persistence to biologics in Japanese patients with moderate-to-severe UC was poor, and poor persistence was associated with increased non-medication-associated HCRU, reflecting suboptimal patient outcomes, and resulting in increased burden on the Japanese health-care system. Further research is needed to identify novel treatments for UC that are efficacious, are not associated with substantial HCRU, and that will have high levels of persistence.

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Statement of Ethics

For this study, we used de-identified data provided by a commercial database provider: Medical Data Vision, Co., Ltd. No personal information was provided or could be revealed from the de-

identified data. For this reason, no ethical restrictions are imposed on data access by researchers, and ethical approval was not required in accordance with local/national guidelines.

Conflict of Interest Statement

Joseph C. Cappelleri, Irene Modesto, Marco DiBonaventura, Timothy W. Smith, Sean Gardiner, and Irene Modesto are stockholders and employees of Pfizer Inc (who funded this study). At the time of conducting the study, Danielle Bargo and Takanori Tsuchiya were employees of Pfizer Inc. Theo Tritton and Tim Holbrook are employed by Adelphi Real World, which received funding from Pfizer in connection with the development of this manuscript. At the time of conducting the study, Daniel Bluff was an employee of Adelphi Real World.

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Author Contributions

All authors contributed to conception and design, have been involved in drafting the manuscript and revising it for critically important intellectual content, have given final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Data Availability Statement

The authors had access to the data for the purposes of this work. Data were accessed through an existing Pfizer license to address the prespecified research questions only. Due to data licensing agreements, the data are not available to include in the submission. The dataset may be obtained on application to MDV: <https://en.mdv.co.jp/application/contactus/form.php>.

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