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Impact of immunomodulator use on treatment persistence in patients with ulcerative colitis: A claims database analysis

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Key words
colitis, ulcerative, medication adherence, outcome assessment (health care), retrospective studies.

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Abstract

Background and Aim: It is unclear how adding an anti-tumor necrosis factor alpha agent to immunomodulator (IM) treatment, as a step-up strategy, affects long-term outcomes in ulcerative colitis. This retrospective study investigated persistence associated with biologic anti-tumor necrosis factor alpha agents combined with IMs *versus* biologic monotherapy in patients with ulcerative colitis.

Methods: This was a longitudinal cohort study of patients in the Japan Medical Data Center claims database who had been newly prescribed infliximab or adalimumab as induction (completed) and maintenance (2010–2016). Biologic persistence (i.e. no switch/discontinuation during maintenance) was compared among patients prescribed biologic monotherapy (Bio) and those prescribed a biologic combined with an IM, as step-up (Bio + prior IM) or simultaneously (Bio + IM).

Results: Three hundred and sixty-nine eligible patients were analyzed (233, 78, and 58 in the Bio, Bio + prior IM, and Bio + IM subgroups, respectively). Multivariate analysis showed a lower probability of nonpersistence during maintenance for infliximab-treated patients in the Bio + prior IM *versus* Bio subgroup (hazard ratio: 0.53; 95% confidence interval: 0.29–0.99; $P = 0.045$). No such effect was seen in adalimumab-treated patients ($P = 0.222$) or in the overall population ($P = 0.398$). The probability of nonpersistence during maintenance in the Bio + IM subgroup was not significantly different from that in the Bio subgroup in either the biologic subpopulation or in the overall population.

Conclusions: Adding infliximab to an existing IM results in a lower probability of nonpersistence compared with infliximab monotherapy in ulcerative colitis patients. This effect is not seen in adalimumab-treated patients.

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Introduction

Ulcerative colitis (UC) is a chronic, relapsing/remitting, and sometimes progressive inflammatory bowel disease (IBD).[1–3] Incidence has been increasing over recent years except in Europe and North America, where the number of new cases appears to have stabilized.[4–7] As UC remains incurable, the main goals of treatment are to achieve and maintain long-term clinical remission, obtain mucosal healing, and improve patient quality of life.[1–3] Drugs approved in Japan for treating UC include 5-aminosalicylates; immunomodulators (IMs; azathioprine); calcineurin inhibitors (tacrolimus); corticosteroids; the Janus kinase inhibitor, tofacitinib; and biologic therapies, such as anti-tumor necrosis factor alpha (anti-TNFα) therapies (adalimumab, infliximab, and golimumab) and the $\alpha_4\beta_7$-specific integrin antagonist, vedolizumab.[6,8–10]

Biologic anti-TNFα therapies are recommended to treat moderate-to-severe UC that is nonresponsive to conventional treatment with steroids and/or IMs.[6] As such, in daily practice, anti-TNFα therapies are often prescribed to patients already on an IM, as part of a "step-up" treatment approach. Several studies have evaluated the effectiveness of combining an anti-TNFα agent, adalimumab or infliximab, with an IM in patients with moderate-to-severe UC.[11–15] Data collected so far have been contradictory; some studies have reported a benefit in terms of UC remission for combination treatment using anti-TNFα agents with IMs, while others have reported no effect compared with monotherapy.[11–15] Importantly, none of these studies investigated the clinical outcomes according to the timing of dosing (i.e. step-up addition of an anti-TNFα agent to existing IM treatment *vs* starting both treatments at the same time). In fact, the absence of benefit from a concomitant IM in a step-up approach for Crohn's disease (CD) has been shown previously.[16,17] Furthermore, previous combination studies, such as SUCCESS (in UC patients) and SONIC and DIAMOND (both in CD patients), only investigated the efficacy of anti-TNFα agents during the induction phase of treatment, where treatment duration range was 16–30 weeks;[13,18–22] consequently, long-term outcomes data for these agents, when used as both induction and maintenance treatment, are not available.

Patients who respond to induction treatment with anti-TNFα agents typically continue maintenance treatment with the same agent; therefore, drug persistence is one of the most important measures of long-term success of treatment. Studies in UC comparing persistence rates between combination treatments with anti-TNFα agents and IMs, and single-agent anti-TNFα drugs, are currently lacking, although clinical trials using traditional efficacy and safety endpoints are available. Our retrospective, claims-based study aimed to evaluate long-term persistence associated with anti-TNFα biologic agents (adalimumab and infliximab) combined with an IM (given as step-up treatment or simultaneously) compared with anti-TNFα monotherapy during the maintenance phase of treatment in patients with UC.

Methods

Study design. This was a retrospective, longitudinal cohort study of new users of anti-TNFα therapy (adalimumab or infliximab) among UC patients included in the Japan Medical Data Center (JMDC) claims database (Supporting Information). Medical and pharmacy claims data were analyzed for the index period, January 1, 2010 (around the time when adalimumab was launched in Japan), through to July 31, 2016.

Although this study involves human patients, it was conducted as a retrospective database analysis using only anonymized data. As such, formal consent from patients was impossible to obtain and thus was not required.

Study population. Patients were included in this analysis if they had evidence of at least one prescription for adalimumab or infliximab between January 1, 2010, and July 31, 2016; had at least one confirmed diagnosis code for UC (International Classification of Diseases 10th revision code, K51, and standard disease nomenclature) prior to starting anti-TNFα therapy; and were aged ≥ 18 years at the index date. Only patients without a prior claim (initiated or ongoing) for any anti-TNFα agent in the 6 months before the index date (defined as the date of first prescription of adalimumab or infliximab) were included in order to only include patients who were likely to be responsive to biologic therapy. Patients were also required to have completed the induction phase of biologic therapy without switching or discontinuing treatment and entered the maintenance phase of treatment with the same drug, with a minimum of 12 months' valid insurance status after initiation of maintenance therapy.

Exposure definition. For the purposes of the analyses, and in accordance with a similar study in CD,[17] anti-TNFα monotherapy and combination therapy were defined as follows: (i) monotherapy without prior IMs (defined as no use of IMs in the 90 days before or 90 days after initiating anti-TNFα therapy; Bio subgroup); (ii) step-up combination therapy with prior IMs (defined as continuous use of IMs for > 90 days before and 90 days after initiating anti-TNFα therapy; Bio + prior IM subgroup); and (iii) simultaneous combination therapy where treatment with IMs was started at the same time (defined as use of IMs initiated or reinitiated within ±90 days of starting anti-TNFα therapy; Bio + IM subgroup). Continuous IM use was defined as no gap > 120 days between two consecutive prescriptions. Reinitiation was defined as IM treatment initiated > 90 days before the index date but then discontinued with a gap > 120 days between the previous and the next prescription (i.e. reinitiation date).

Outcomes. The primary outcome measure was biologic persistence during the maintenance phase, assessed from the date of first maintenance prescription. Persistence was defined as the absence of a switch or discontinuation of adalimumab or infliximab (Supporting Information).[23] The secondary outcome measure was hospitalizations (where hospitalizations were defined as any inpatient procedure with a code of "hospitalization" or "other hospitalization") during the maintenance phase.

Covariates. Covariates were chosen based on their potential for confounding the results and availability of data in the JMDC database. The covariates that were included in these analyses were age (18–39 *vs* ≥ 40 years at the index date), sex (male *vs* female), steroid use (any of prednisone, prednisolone, methylprednisolone, budesonide, or betamethasone) within 90 days prior to the index

date (none *vs* 29–90 days' *vs* < 29 days' use prior to the index date), cumulative dose of steroids within 90 days prior to the index date, and time from first confirmed UC diagnosis to the index date.

Statistical analysis. The analyses were run in the overall population, and according to which biologic (adalimumab or infliximab) patients had been prescribed (Supporting Information). Time to switch or discontinuation of anti-TNFα treatment (persistence) and time to hospitalization were estimated for the three patient subgroups using Kaplan–Meier methods. Time to the first occurrence of each of these events was analyzed. Observations were censored at the end of follow-up for persistence and time of first event, treatment switch or discontinuation, or end of available data (whichever was earliest) for hospitalizations. A log-rank test was used to compare Kaplan–Meier estimates among the three treatment subgroups.

Multivariate Cox regression models were used to evaluate the probability of a switch or discontinuation of adalimumab or infliximab (nonpersistence) and hospitalization, according to treatment subgroup and covariates. Data are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs).

All statistical analyses were performed using SAS version 9.3. The data extraction and analyses were undertaken by CreativCeutical K.K. (Tokyo, Japan), under the direction of the authors.

Results

Patient selection. Over the study period (January 1, 2010, to July 31, 2016), 876 patients with UC in the JMDC database claimed at least one prescription for adalimumab or infliximab. Of these patients, 369 met all inclusion criteria (Fig. 1). A total of 233 patients were prescribed biologic (anti-TNFα) monotherapy (Bio subgroup), 78 were prescribed combination therapy with prior IMs (Bio + prior IM subgroup), and 58 were prescribed combination therapy without prior IMs (Bio + IM subgroup). Of the 369 patients, 165 were prescribed adalimumab (Bio, n = 106; Bio + prior IM, n = 34; Bio + IM, n = 25) and 204 were prescribed infliximab (Bio, n = 127; Bio + prior IM, n = 44; Bio + IM, n = 33) at the index date.

Baseline characteristics at the index date are shown in Table 1. There was a higher proportion of men in the Bio + prior IM subgroup compared with the other two subgroups (P = 0.044). There were also imbalances among subgroups in the time from first confirmed UC diagnosis to the index date. Median time from first diagnosis to the index date was 25.1, 5.1, and 12.4 months in the Bio + prior IM, Bio + IM, and Bio subgroups, respectively (P = 0.002).

Persistence. Biologic persistence rates during maintenance were not significantly different among the three patient subgroups, either in the total population (P = 0.803) or in patients who were prescribed adalimumab (P = 0.388) or infliximab (P = 0.189) (Table 2). Numerically, the highest rates of persistence during maintenance in infliximab-prescribed patients were seen in the Bio + prior IM subgroup (68.2% *vs* 63.6% in the Bio + IM subgroup and 53.5% in the Bio subgroup). Time to discontinuation or switch of biologic (anti-TNFα) therapy (persistence) from the date of first maintenance prescription is shown for all patients and by prescribed biologic (adalimumab and infliximab) in Figure 2.

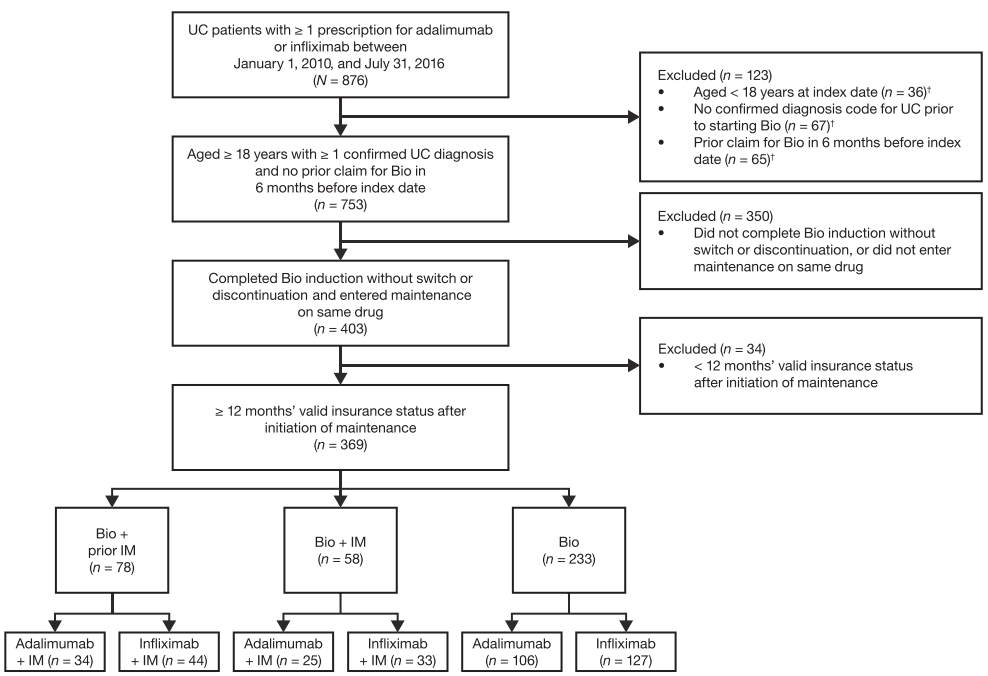

Figure 1 Patient selection (N = 369). The index date was defined as the date of first prescription of adalimumab or infliximab. †The numbers indicate patients excluded due to one specified reason only. As patients can be excluded for multiple reasons, the sum of excluded patients by reason exceeds the total number excluded. Bio, biologic (anti-tumor necrosis factor alpha) therapy; IM, immunomodulator; UC, ulcerative colitis.

Table 1 Patient characteristics at the date of first prescription (index date) of a new biologic agent (adalimumab or infliximab) by patient subgroup

Variable	All patients (N = 369)	Comparator subgroups			
		Bio + prior IM (n = 78)	Bio + IM (n = 58)	Bio (n = 233)	P value[†]
Biologic, n (%)					
Adalimumab	165 (44.7)	34 (43.6)	25 (43.1)	106 (45.5)	0.924
Infliximab	204 (55.3)	44 (56.4)	33 (56.9)	127 (54.5)	
Sex, n (%)					
Female	129 (35.0)	18 (23.1)	21 (36.2)	90 (38.6)	0.044
Male	240 (65.0)	60 (76.9)	37 (63.8)	143 (61.4)	
Age, years					
Mean (SD)	38.9 (12.1)	39.1 (11.6)	37.2 (12.4)	39.2 (12.3)	0.535
Median (IQR)	38.0 (29.0–48.0)	38.0 (31.0 47.0)	35.5 (26.0–47.0)	39.0 (29.0–49.0)	
Age category, n (%)					
18–39 years	195 (52.9)	43 (55.1)	34 (58.6)	118 (50.6)	0.498
≥ 40 years	174 (47.2)	35 (44.9)	24 (41.4)	115 (49.4)	
Steroid use within 90 days prior to index date, n (%)					
None	130 (35.2)	25 (32.1)	21 (36.2)	84 (36.1)	0.600
29–90 days of use	27 (7.3)	9 (11.5)	4 (6.9)	14 (6.0)	
< 29 days of use	212 (57.5)	44 (56.4)	33 (56.9)	135 (57.9)	
Cumulative steroid dose within 90 days prior to index date, g					
Mean (SD)	1.00 (0.84)	0.91 (0.74)	1.11 (1.00)	1.01 (0.83)	0.537
Median (IQR)	0.78 (0.42–1.37)	0.75 (0.32–1.35)	0.89 (0.41–1.40)	0.78 (0.48–1.33)	
Time from first confirmed UC diagnosis name to index date, months					
Mean (SD)	21.7 (24.2)	27.1 (20.5)	12.6 (16.6)	22.1 (26.3)	0.002
Median (IQR)	13.9 (4.0–31.9)	25.1 (11.2–35.6)	5.1 (0.9–19.8)	12.4 (3.7–32.0)	

Bio, biologic (anti-tumor necrosis factor alpha) therapy; IM, immunomodulator; IQR, interquartile range; SD, standard deviation; UC, ulcerative colitis. [†]Categorical variables were compared among the three patient subgroups (Bio, Bio + IM, and Bio + prior IM) using a two-sided χ^2 test (if ≤ 20% of cells had a frequency of < 5) or Fisher's exact test (if > 20% of cells had a frequency of < 5). A Student's t-test (if the data were normally distributed with homogeneous variance) or Wilcoxon signed-rank test (if the data were not normally distributed) was used to compare continuous variables among the subgroups.

Multivariate Cox regression analysis revealed a significantly lower probability of biologic nonpersistence during maintenance in the Bio + prior IM subgroup compared with the Bio subgroup in patients who were prescribed infliximab (HR: 0.53; 95% CI: 0.29–0.99; P = 0.045; Table 3). This effect was not seen in Bio + prior IM subgroup in patients who were prescribed adalimumab or in the overall population. The probability of nonpersistence during maintenance was also not significantly different for the comparisons of the Bio + IM subgroup with the Bio subgroup, in all patients and in those who were prescribed adalimumab or infliximab (Table 3). No other tested covariates significantly affected the likelihood of nonpersistence during maintenance, either in the total population or in patients who were prescribed adalimumab or infliximab ($P > 0.05$ for all comparisons; data not shown).

In an exploratory analysis, the probability of nonpersistence during maintenance was significantly lower in patients who received any combination therapy (Bio + prior IM/Bio + IM) compared with those who received monotherapy (Bio) in infliximab-treated patients (HR: 0.55; 95% CI: 0.34–0.91; P = 0.018) but not in adalimumab-treated patients (HR: 1.29; 95% CI: 0.82–2.04; P = 0.272).

Survival analysis revealed a statistically significant difference between adalimumab and infliximab in the time to treatment switch or discontinuation (persistence) during induction and maintenance in the 78 patients in the Bio + prior IM subgroup (P = 0.0033; Fig. S1a). A trend to higher persistence with infliximab compared with adalimumab was observed in the 58 patients in the Bio + IM subgroup, although the difference between the two biologics was not statistically significant (P = 0.1613; Fig. S1b). No significant differences were observed between adalimumab and infliximab in the Bio subgroup (P = 0.6218; Fig. S1c).

Hospitalizations. There were no significant differences in hospitalizations (Table S1 and Fig. S2) among the three patient subgroups during the maintenance phase of the study (total population; $P > 0.05$ for all comparisons). Multivariate Cox regression analysis confirmed the lack of effect of patient subgroup on the probability of hospitalization during maintenance (Table S2; $P > 0.05$ for all comparisons). No other covariates impacted the probability of hospitalization during maintenance (Table S2). Neither patient subgroup nor any other covariate affected the likelihood of hospitalization during maintenance in patients who were prescribed adalimumab or infliximab ($P > 0.05$ for all comparisons; data not shown).

Discussion

This retrospective analysis of 369 patients with UC who were prescribed biologic therapy (adalimumab or infliximab) as induction and maintenance between 2010 and 2016 was conducted to explore whether persistence and another associated treatment

Table 2 Persistence during the maintenance phase of treatment with a newly prescribed biologic agent (adalimumab or infliximab) by patient subgroup

Variable	All patients	Comparator subgroups			
		Bio + prior IM	Bio + IM	Bio	*P* value[†]
All patients (*N* = 369)					
Persistence, *n* (%)					
No	165 (44.7)	34 (43.6)	24 (41.4)	107 (45.9)	0.803
Yes	204 (55.3)	44 (56.4)	34 (58.6)	126 (54.1)	
Discontinuation, *n* (%)					
No	241 (65.3)	51 (65.4)	38 (65.5)	152 (65.2)	> 0.999
Yes	128 (34.7)	27 (34.6)	20 (34.5)	81 (34.8)	
Switch, *n* (%)					
No	332 (90.0)	71 (91.0)	54 (93.1)	207 (88.8)	0.590
Yes	37 (10.0)	7 (9.0)	4 (6.9)	26 (11.2)	
Patients who were prescribed adalimumab (*n* = 165)					
Persistence, *n* (%)					
No	80 (48.5)	20 (58.8)	12 (48.0)	48 (45.3)	0.388
Yes	85 (51.5)	14 (41.2)	13 (52.0)	58 (54.7)	
Discontinuation, *n* (%)					
No	102 (61.8)	16 (47.1)	16 (64.0)	70 (66.0)	0.136
Yes	63 (38.2)	18 (52.9)	9 (36.0)	36 (34.0)	
Switch, *n* (%)					
No	148 (89.7)	32 (94.1)	22 (88.0)	94 (88.7)	0.748
Yes	17 (10.3)	2 (5.9)	3 (12.0)	12 (11.3)	
Patients who were prescribed infliximab (*n* = 204)					
Persistence, *n* (%)					
No	85 (41.7)	14 (31.8)	12 (36.4)	59 (46.5)	0.189
Yes	119 (58.3)	30 (68.2)	21 (63.6)	68 (53.5)	
Discontinuation, *n* (%)					
No	139 (68.1)	35 (79.6)	22 (66.7)	82 (64.6)	0.181
Yes	65 (31.9)	9 (20.5)	11 (33.3)	45 (35.4)	
Switch, *n* (%)					
No	184 (90.2)	39 (88.6)	32 (97.0)	113 (89.0)	0.391
Yes	20 (9.8)	5 (11.4)	1 (3.0)	14 (11.0)	

Bio, biologic (anti-tumor necrosis factor alpha) therapy; IM, immunomodulator.

[†]Categorical variables were compared among the three patient subgroups (Bio, Bio + IM, and Bio + prior IM) using a two-sided χ^2 test (if ≤ 20% of cells had a frequency of < 5) or Fisher's exact test (if > 20% of cells had a frequency of < 5).

outcome (hospitalizations) were impacted when patients were co-prescribed an IM in combination therapy (either as a new combination [simultaneous prescribing: Bio + IM] or through the addition of a biologic to prior IM [Bio + prior IM] therapy [step-up approach]). To our knowledge, this is the first long-term study to report treatment persistence associated with anti-TNFα biologic agents, alone or combined with IMs, in UC patients using Japanese claims data. Studies such as this provide valuable information on real-world prescribing outcomes and on persistence to biologic therapies, which is recognized as an important concern in clinical practice. Results of our study are not equivalent to those reported in clinical trials, as patients receiving IM are typically excluded from clinical trials, which traditionally focuses on efficacy and safety of the test drug.

Several trials have compared biologic monotherapy with combination therapy (biologic agents plus IMs) in patients with UC or CD. In addition to SUCCESS in UC,[13] the SONIC and DIAMOND studies investigated infliximab and adalimumab treatment, respectively, in patients with CD.[18–22] Combination treatment with a biologic and an IM was started simultaneously in all three studies,[13,18–22] whereas in the real-world setting, many UC patients may receive an IM prior to starting biologic therapy and may already be failing to respond to treatment.[6,24] In such cases, physicians may not have adequate information on previous treatments to make an informed decision as to which biologic to prescribe (infliximab or adalimumab) or whether to continue long-term (potentially failing) IM treatment when initiating anti-TNFα therapy; these decisions must therefore be made on a case-by-case basis. Furthermore, compared with the SUCCESS, SONIC, and DIAMOND studies, where treatment lasted for 16–30 weeks,[13,18,20] our study focused on patients who had successfully completed induction treatment (i.e. patients whose symptoms had stabilized) and entered the maintenance phase of treatment. The results from our study will hopefully provide physicians with additional insight to guide their daily practice on their choice of anti-TNFα agents to use in patients requiring long-term therapy.

Multivariate analysis according to the type of prescribed biologic showed a significantly lower likelihood of nonpersistence (a surrogate endpoint of efficacy and tolerability) during maintenance in the Bio + prior IM subgroup compared with the Bio

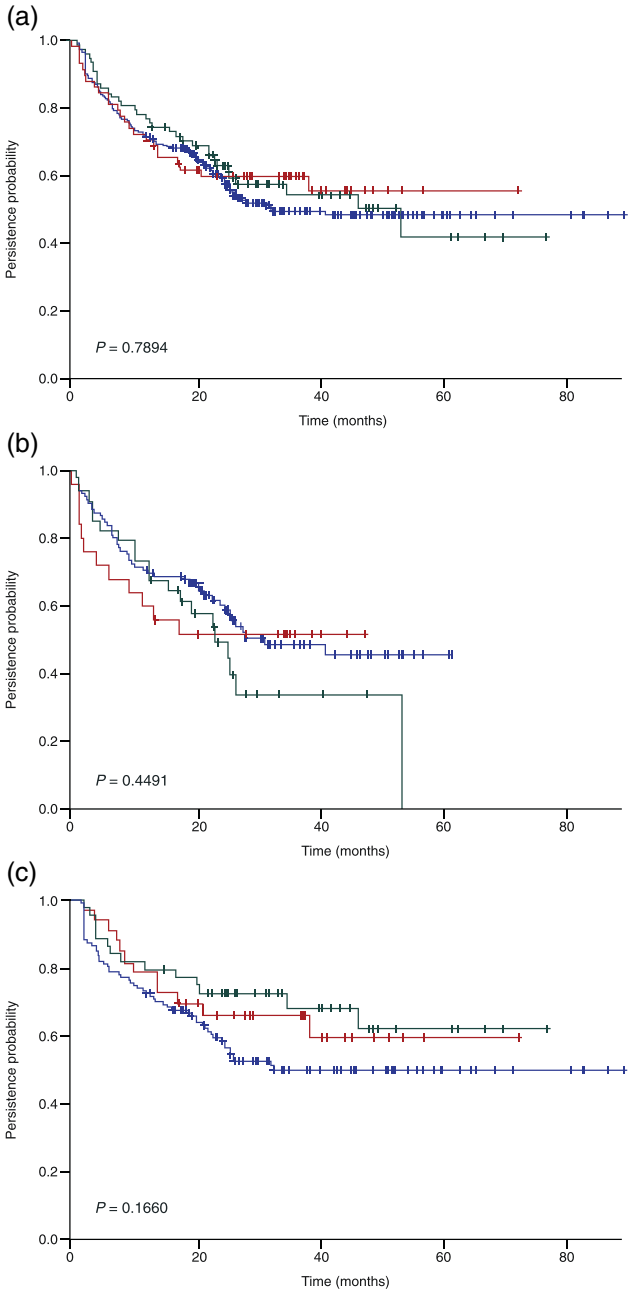

Figure 2 Kaplan–Meier survival curves for time to switch or discontinuation of biologic therapy (adalimumab or infliximab) from the start of maintenance treatment, by patient subgroup: (a) all patients (N = 369); (b) patients who were prescribed adalimumab (n = 165); and (c) patients who were prescribed infliximab (n = 204). ——, Bio; ——, Bio + IM; ——, Bio + prior IM. Bio, biologic (anti-tumor necrosis factor alpha) therapy; IM, immunomodulator. [Color figure can be viewed at wileyonlinelibrary.com]

Table 3 Multivariate Cox regression analysis of biologic persistence in patient subgroups, overall and according to which biologic agent (adalimumab or infliximab) was prescribed

	Nonpersistence[†]	
	HR (95% CI)	*P* value
All patients (N = 369)		
Patient subgroup		
Bio (ref.)		
Bio + prior IM	0.84 (0.57–1.25)	0.398
Bio + IM	0.84 (0.54–1.33)	0.460
Patients who were prescribed adalimumab (n = 165)		
Patient subgroup		
Bio (ref.)		
Bio + prior IM	1.40 (0.82–2.40)	0.222
Bio + IM	1.15 (0.60–2.20)	0.670
Patients who were prescribed infliximab (n = 204)		
Patient subgroup		
Bio (ref.)		
Bio + prior IM	0.53 (0.29–0.99)	0.045
Bio + IM	0.58 (0.30–1.11)	0.100

An HR of < 1 indicates a lower probability of nonpersistence (defined as a switch or discontinuation of adalimumab or infliximab) compared with the reference, while an HR of > 1 indicates a higher probability of nonpersistence. Bio, biologic (anti-tumor necrosis factor alpha) therapy; CI, confidence interval; HR, hazard ratio; IM, immunomodulator; ref., reference; UC, ulcerative colitis.

[†]For all three analyses, no significant differences were observed for any other covariate (chosen based on their potential for confounding the results and availability of data in the database): age (18–39 *vs* ≥ 40 years at the index date); sex (male *vs* female); steroid use (any of prednisone, prednisolone, methylprednisolone, budesonide, or betamethasone) within 90 days prior to the index date (none *vs* 29–90 days' *vs* < 29 days' use prior to the index date); cumulative dose of steroids within 90 days prior to the index date; and time from first confirmed UC diagnosis name to the index date.

subgroup, in patients who were prescribed infliximab. Persistence rates were also numerically higher in the Bio + IM subgroup than in the Bio subgroup in patients who were prescribed infliximab. Conversely, no such effect was seen in Bio + prior IM patients who were prescribed adalimumab. Our study therefore demonstrates the superiority of "step-up" infliximab over "step-up" adalimumab in terms of persistence for patients who were already prescribed an IM. In contrast, drug persistence was comparable between infliximab and adalimumab when treatment with anti-TNFα agents was started alone, without IMs. As the analysis focused on persistence during maintenance in patients who had completed the induction phase of biologic therapy without switching or discontinuing treatment, differences in the duration of induction between the two biologics were not considered to be relevant.

Numerous discussions exist on the relative merits of "step-up" *versus* monotherapy treatment strategies in IBD, especially for patients with CD.[25,26] Our results indicate that in UC, step-up from a single-agent IM to biologic/IM combination treatment (in the Bio + prior IM subgroup) may be better maintained over the long term than biologic monotherapy if infliximab is chosen. Higher persistence with combination therapy in infliximab-prescribed patients supports the clinical findings from the SUCCESS study, which demonstrated superior short-term efficacy (corticosteroid-free remission) for an infliximab/azathioprine combination over

either monotherapy, when given as induction therapy to patients with moderate-to-severe UC.[11,13,14] Furthermore, the lack of impact of combination therapy on persistence in adalimumab-prescribed patients is consistent with clinical data in IBD patients showing no clear efficacy advantages for adalimumab/IM combinations over monotherapy.[12,14,19–22]

There was no significant impact of combination treatment on persistence in the Bio + IM subgroup in either the infliximab or the adalimumab analysis; the lack of effect on persistence in infliximab-prescribed patients in the Bio + IM subgroup implies that persistence is likely to be high when infliximab is added to an existing IM. However, the lack of impact of combination treatment on persistence in the Bio + IM subgroup could be related to the small sample size of the subgroup. For reference, a previous population-based study has shown that IM use at the time of anti-TNFα dispensation is associated with a significantly decreased likelihood of anti-TNFα discontinuation in patients with UC.[27]

In the multivariate analysis of the total study population, there were no differences among the monotherapy and combination subgroups with respect to hospitalizations during maintenance. These findings are consistent with previous data.[27–33] The risk of hospitalization would not be expected to increase in the combination subgroups given that there were no significant differences in treatment persistence among the three subgroups. A previous US claims analysis has shown an increase in hospitalizations for UC patients without therapeutic persistence to infliximab.[28]

This study was subject to limitations. As this was not a randomized prospective study, the data will inevitably be impacted by measurement bias (selection bias and measurement error). Potentially confounding factors were adjusted for in the multivariate models; however, it was not possible to control for all possible variables. Because the data were extracted retrospectively from a claims database, no information was available on disease severity (although it is not unreasonable to assume that disease was at least somewhat under control, and not in flare, at the start of maintenance treatment in this maintenance population); reasons for stopping or switching treatment; whether drugs were taken as prescribed at the right time of day; if extra doses were taken to compensate for any forgotten doses; whether there were any instances of pill dumping or stockpiling; or how efficacious treatment had been against the signs and symptoms of UC. For this study, it was assumed that patients who were issued with a prescription would fill their prescription and be fully compliant with their medication. The study also did not calculate sample size a priori, and the number of patients in some subgroups was small; as such, any conclusions made can only be tentative. The similar rate of steroid use in the 90 days prior to the index date suggests little difference in UC disease activity among the three patient subgroups at the start of induction therapy.

In conclusion, the clinical benefit of existing concomitant IM therapy as part of a step-up treatment strategy has been suggested in this study of real-world patients who were newly prescribed infliximab, compared with those who were prescribed infliximab alone. This effect was not seen in patients who were prescribed adalimumab as step-up therapy. In addition, infliximab was superior to adalimumab when the anti-TNFα agent was added to an existing IM as part of a step-up therapy, while the persistence of both anti-TNFα agents was similar when prescribed without IM (a "biologic monotherapy first" approach). These results imply that when adding a biologic to existing IMs as a step-up therapy, long-term persistence is better when infliximab is used. If confirmed in prospective studies, these findings may result in changes to the way we use these medicines in clinical practice.

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References

1 Blonski W, Buchner AM, Lichtenstein GR. Treatment of ulcerative colitis. *Curr. Opin. Gastroenterol.* 2014; **30**: 84–96.
2 National Institute of Diabetes and Digestive and Kidney Diseases Health Information Center. Ulcerative colitis. 2014. Cited 24 March 2019. Available from URL: https://www.niddk.nih.gov/health-information/digestive-diseases/ulcerative-colitis.
3 Ordas I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet* 2012; **380**: 1606–19.
4 Asakura K, Nishiwaki Y, Inoue N, Hibi T, Watanabe M, Takebayashi T. Prevalence of ulcerative colitis and Crohn's disease in Japan. *J. Gastroenterol.* 2009; **44**: 659–65.
5 Japanese Ministry of Health Labor and Welfare. Heisei 26 nenndo eisei-gyousei-houkokurei no gaikyou (2014 Report on Public Health Administration and Services) [in Japanese]. 2014. Cited 28 March 2019. Available from URL: http://www.mhlw.go.jp/toukei/saikin/hw/eisei_houkoku/14/dl/kekka7.pdf.
6 Matsuoka K, Kobayashi T, Ueno F *et al*. Evidence-based clinical practice guidelines for inflammatory bowel disease. *J. Gastroenterol.* 2018; **53**: 305–53.
7 Ng SC, Shi HY, Hamidi N *et al*. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018; **390**: 2769–78.
8 Janssen Pharma. Simponi® (golimumab) product insert [in Japanese]. April 2018. Cited 13 February 2019.
9 Pfizer Inc. Xeljanz® (tofacitinib) product insert [in Japanese]. October 2018. Cited 13 February 2019.
10 Takeda Pharmaceuticals Company Limited. Entyvio® (vedolizumab) product insert [in Japanese]. November 2018. Cited 13 February 2019.
11 Bots S, Gecse K, Barclay M, D'Haens G. Combination immunosuppression in IBD. *Inflamm. Bowel Dis.* 2018; **24**: 539–45.
12 Colombel JF, Jharap B, Sandborn WJ *et al*. Effects of concomitant immunomodulators on the pharmacokinetics, efficacy and safety of adalimumab in patients with Crohn's disease or ulcerative colitis who had failed conventional therapy. *Aliment. Pharmacol. Ther.* 2017; **45**: 50–62.
13 Panaccione R, Ghosh S, Middleton S *et al*. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology* 2014; **146**: 392–400.
14 Sultan KS, Berkowitz JC, Khan S. Combination therapy for inflammatory bowel disease. *World J. Gastrointest. Pharmacol. Ther.* 2017; **8**: 103–13.

15 Targownik LE, Benchimol EI, Bernstein CN *et al*. Upfront combination therapy, compared with monotherapy, for patients not previously treated with a biologic agent associates with reduced risk of inflammatory bowel disease-related complications in a population-based cohort study. *Clin. Gastroenterol. Hepatol.* 2018; **17**: 1788–98. https://doi.org/10.1016/j.cgh.2018.11.003.
16 Jones JL, Kaplan GG, Peyrin-Biroulet L *et al*. Effects of concomitant immunomodulator therapy on efficacy and safety of anti-tumor necrosis factor therapy for Crohn's disease: a meta-analysis of placebo-controlled trials. *Clin. Gastroenterol. Hepatol.* 2015; **13**: 2233–40 e1–2 quiz e177–8.
17 Osterman MT, Haynes K, Delzell E *et al*. Effectiveness and safety of immunomodulators with anti-tumor necrosis factor therapy in Crohn's disease. *Clin. Gastroenterol. Hepatol.* 2015; **13**: 1293–301 quiz e70–2.
18 Colombel JF, Sandborn WJ, Reinisch W *et al*. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N. Engl. J. Med.* 2010; **362**: 1383–95.
19 Hisamatsu T, Matsumoto T, Watanabe K *et al*. Concerns and side effects of azathioprine during adalimumab induction and maintenance therapy for Japanese patients with Crohn's disease: a sub-analysis of a prospective randomized clinical trial (DIAMOND study). *J. Crohns Colitis* 2019 (in press). https://doi.org/10.1093/ecco-jcc/jjz030.
20 Matsumoto T, Motoya S, Watanabe K *et al*. Adalimumab monotherapy and a combination with azathioprine for Crohn's disease: a prospective, randomized trial. *J. Crohns Colitis* 2016; **10**: 1259–66.
21 Nakase H, Motoya S, Matsumoto T *et al*. Significance of measurement of serum trough level and anti-drug antibody of adalimumab as personalised pharmacokinetics in patients with Crohn's disease: a subanalysis of the DIAMOND trial. *Aliment. Pharmacol. Ther.* 2017; **46**: 873–82.
22 Watanabe K, Matsumoto T, Hisamatsu T *et al*. Clinical and pharmacokinetic factors associated with adalimumab-induced mucosal healing in patients with Crohn's disease. *Clin. Gastroenterol. Hepatol.* 2018; **16**: 542–9 e1.
23 Yokoyama K, Yamazaki K, Katafuchi M, Ferchichi S. A retrospective claims database study on drug utilization in Japanese patients with Crohn's disease treated with adalimumab or infliximab. *Adv. Ther.* 2016; **33**: 1947–63.
24 Harbord M, Eliakim R, Bettenworth D *et al*. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J. Crohns Colitis* 2017; **11**: 769–84.
25 Chen QQ, Yan L, Wan J. Select a suitable treatment strategy for Crohn's disease: step-up or top-down. *EXCLI J.* 2014; **13**: 111–22.
26 Tsui JJ, Huynh HQ. Is top-down therapy a more effective alternative to conventional step-up therapy for Crohn's disease? *Ann. Gastroenterol.* 2018; **31**: 413–24.
27 Targownik LE, Tennakoon A, Leung S *et al*. Factors associated with discontinuation of anti-TNF inhibitors among persons with IBD: a population-based analysis. *Inflamm. Bowel Dis.* 2017; **23**: 409–20.
28 Carter CT, Leher H, Smith P, Smith DB, Waters HC. Impact of persistence with infliximab on hospitalizations in ulcerative colitis. *Am. J. Manag. Care* 2011; **17**: 385–92.
29 Chen C, Hartzema AG, Xiao H *et al*. Real-world pattern of biologic use in patients with inflammatory bowel disease: treatment persistence, switching, and importance of concurrent immunosuppressive therapy. *Inflamm. Bowel Dis.* 2019. https://doi.org/10.1093/ibd/izz001.
30 Govani SM, Lipson R, Noureldin M *et al*. Adalimumab persistence for inflammatory bowel disease in veteran and insured cohorts. *Am. J. Manag. Care* 2018; **24**: e374–9.
31 Pouillon L, Baumann C, Rousseau H *et al*. Treatment persistence of infliximab versus adalimumab in ulcerative colitis: a 16-year single-center experience. *Inflamm. Bowel Dis.* 2018; **25**: 945–54. https://doi.org/10.1093/ibd/izy322.
32 Khan S, Rupniewska E, Neighbors M, Singer D, Chiarappa J, Obando C. Real-world evidence on adherence, persistence, switching and dose escalation with biologics in adult inflammatory bowel disease in the United States: a systematic review. *J. Clin. Pharm. Ther.* 2019. https://doi.org/10.1111/jcpt.12830.
33 Sartini A, Scaioli E, Liverani E *et al*. Retention rate, persistence and safety of adalimumab in inflammatory bowel disease: a real-life, 9-year, single-center experience in Italy. *Dig. Dis. Sci.* 2019; **64**: 863–74.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Kaplan–Meier survival curves for time to switch or discontinuation of biologic therapy (adalimumab or infliximab) from the date of first prescription (index date), by biologic therapy received for patients in the: (a) Bio + prior IM subgroup (n = 78); (b) Bio + IM subgroup (n = 58); and (c) Bio subgroup (n = 233). ADA, adalimumab; Bio, biologic (anti-tumor necrosis factor alpha) therapy; IFX, infliximab; IM, immunomodulator.
Figure S2. Kaplan–Meier survival curves from the date of first maintenance prescription for time to first hospitalization, by patient subgroup. Bio, biologic (anti-tumor necrosis factor alpha) therapy; IM, immunomodulator.
Table S1. Hospitalizations during the maintenance phase of treatment with a newly prescribed biologic agent (adalimumab or infliximab) by patient subgroup.
Table S2. Multivariate Cox regression analysis of hospitalizations in the total population.