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CITATION:

Masui, Sho ...[et al]. Infliximab Treatment Persistence among Japanese Patients with Chronic Inflammatory Diseases: A Retrospective Japanese Claims Data Study. Biological and Pharmaceutical Bulletin 2022, 45(3): 323-332

ISSUE DATE:

2022-03

URL:

http://hdl.handle.net/2433/268973

Regular Article

Infliximab Treatment Persistence among Japanese Patients with Chronic Inflammatory Diseases: A Retrospective Japanese Claims Data Study

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Received October 21, 2021; accepted December 20, 2021

Infliximab (IFX) has contributed to the treatment of several chronic inflammatory diseases, including Crohn's disease (CD), ulcerative colitis (UC), psoriasis (Pso), and rheumatoid arthritis (RA). However, the loss of response in some patients with long-term IFX therapy has been a major problem. Randomized controlled trials (RCTs) are limited in their short duration and lack of generalizability to the real-world population. We aimed to describe the persistence rates of IFX therapy to estimate its long-term effectiveness in clinical practice. Claims data from the Japan Medical Data Center database from January 2005 to June 2017 were used. The study population was identified based on the International Classification of Diseases, 10th Revision and the Anatomical Therapeutic Chemical Classification System. The 5-year persistence rates of IFX therapy were estimated using the Kaplan–Meier method. Overall, 281, 235, 41, and 222 patients with CD, UC, Pso, and RA, respectively, were selected. The 5-year persistence rates for IFX claims were 62.9, 38.9, 22.1, and 28.1% in patients with CD, UC, Pso, and RA, respectively. Patients with CD and UC administered IFX beyond the median dose had higher persistence rates. In patients with RA, female sex and no prior use of other biologics were associated with longer persistence. In conclusion, IFX persistence rates differed across chronic inflammatory diseases, which did not correspond to the results of the major RCTs. Factors associated with longer IFX persistence were identified in each disease group. Our findings may provide useful information to facilitate the proper use of IFX.

Key words chronic inflammatory disease; Infliximab; real-world database; therapeutic persistence; treatment pattern

INTRODUCTION

Infliximab (IFX) is the first chimeric monoclonal antibody against tumor necrosis factor (TNF). It received initial marketing approval from the Japanese Ministry of Health, Labour and Welfare for the treatment of Crohn's disease (CD) in January 2002, followed by additional approval for other indications, including ulcerative colitis (UC), psoriasis (Pso), and rheumatoid arthritis (RA). The introduction of IFX has improved the QOL of several patients who were refractory to previously available therapies[1]; however, loss of response with long-term IFX therapy in some patients has been a major problem.[2–4] Several factors can potentially affect inter-individual variability in pharmacokinetics and response to therapeutic monoclonal antibodies.[5] For example, immunogenicity, higher disease activity, longer disease duration, higher body mass index, and higher previous use of biologics have been linked to earlier loss of response.[6–10] Understanding the predictors of therapeutic response can be helpful for clinicians to individualize IFX therapy and improve outcomes.

Randomized controlled trials (RCTs) are the gold standard for assessing the efficacy and safety of therapeutic interventions[11,12]; however, efficacy may not translate to usefulness in clinical settings.[13] Additionally, RCTs may not always mimic real-world treatment situations due to study design limitations.[14] Study participants are screened based on patient characteristics such as age, disease stage, concomitant treatments, and laboratory test results. The short duration of RCTs may hinder the detection of late-onset events. Previous studies on patients with RA[15] and CD[16] treated with biologics demonstrated improved responses in patients who were eligible for the RCTs than in those who were not. Considering safety, an increased risk of serious adverse events was detected in trial-ineligible patients with Pso.[17,18] These reports emphasize the need for observational studies which can provide valuable evidence from real-life routine clinical care and identify previously unrecognized aspects related to treatment characteristics.[19] Non-interventional and longitudinal observational studies are essential to assess the treatment patterns and to estimate the effectiveness of IFX in real-world situations.

The purpose of this study was to describe the long-term treatment pattern of IFX in clinical practice. Treatment persistence is a well-reported and important measure of the effectiveness of a therapy in observational settings. The duration of therapy can account for a sustained positive therapeutic effect, as well as a negative therapeutic effect, which would represent inefficacy, loss of efficacy, and adverse events.[13] In the present study, the 5-year persistence rates of IFX therapy in patients with CD, UC, Pso, and RA were described based on data from a large-scale, real-world claims database in Japan. Furthermore, we investigated patient factors related to higher IFX persistence rates in each disease group.

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MATERIALS AND METHODS

Study Design and Data Source A retrospective observational cohort study was conducted in patients with CD, UC, Pso, and RA selected from a large claims database constructed by the Japan Medical Data Center Co., Ltd. (JMDC; Tokyo, Japan).[20] The JMDC database consists of information about the subscribers and their dependents from multiple society-managed, employment-based health insurances since 2015. Our study included enrollee data between January 2005 and June 2017. This database has no enrollees aged ≥75 years, while enrollees aged ≥65 years only account for a minor fraction because the subscribers are working-age employees. The JMDC database is based on monthly medical claims submitted to health insurance societies from hospitals and community pharmacies in Japan, which contains patient demographic information (sex, age, and insurance type), inpatient and outpatient medical and pharmacy claims data, and clinical diagnoses.

Ethical Considerations The protocol was approved by the Ethics Committee of Kyoto University Graduate School, and the Faculty of Medicine, and Kyoto University Hospital (Approval No. R2517). All data have unique identification numbers created for each insured person, and no personally identifiable data were used in the study. As patient data were anonymized by the database provider, no informed consent was obtained. None of the authors had access to the original data containing personal information.

Study Population The study population was identified based on the International Classification of Diseases, 10th Revision (ICD-10) and the Anatomical Therapeutic Chemical (ATC) Classification System. Patients who had both IFX claims (ATC: L04AB02, does not distinguish between biosimilars and originators) and diagnoses of CD, UC, Pso, or RA at least once during the study period were selected for analysis. We defined CD as ICD-10: K50, UC as ICD-10: K51, Pso as ICD-10: L40, and RA as ICD-10: M058, M059, M060, M068, and M069.[21–24] Patients were classified into one of four diagnostic categories. Some patients had several diagnostic codes for analysis (*e.g.*, K50 and K51) as differential diagnoses that could not be ruled out. In such cases, the principal diagnosis was defined as the one most frequently registered during the IFX treatment period. When different diagnoses for analysis were registered the same number of times during the IFX treatment period, the one most frequently registered during the study period was selected. Patients who still had more than one diagnosis were excluded.

Patients with continuous enrollment in the JMDC database for at least 4 months prior to and 12 months after the IFX initiation date were included in the analysis of persistence rates. The index date was the first prescription date for IFX during the study period. To include only new users of IFX, similar to RCTs, patients were required to have their first IFX claim verified by a period of at least 4 months without a previous claim for IFX. Patients initiating IFX before approval from the Japanese Ministry of Health, Labour and Welfare for maintenance therapy were further excluded. In Japan, IFX was approved for maintenance therapy for RA in July 2003, CD in November 2007, Pso in January 2010, and UC in June 2010. Additionally, patients with at least a 6-month follow-up period after IFX discontinuation were further identified for sub-analysis of treatment patterns after IFX discontinuation.

Definition of Variables and Outcomes The primary outcome of this study was the 5-year persistence rate of IFX claims. The persistence of IFX therapy was defined as the time from the index date until discontinuation or the end of each observation (insurance) period. Discontinuation of IFX was defined as the absence of an IFX claim for at least 4 months. Continuous variables included observational period, age at IFX initiation, and average dose of IFX. Categorical variables were sex, use of other biologics within a maximum of 12 months prior to IFX initiation, and use of concomitant drugs within 3 months before and after IFX initiation. Prior biologics used included the following: abatacept (ABT, ATC: L04AA24), etanercept (ETN, ATC: L04AB01), adalimumab (ADL, ATC: L04AB04), certolizumab pegol (CTZp, ATC: L04AB05), golimumab (GLM, ATC: L04AB06), tocilizumab (TCZ, ATC: L04AC07), ustekinumab (UST, ATC: L04AC05), secukinumab (SEC, ATC: L04AC10), brodalumab (BRO, ATC: L04AC12), and ixekizumab (IXE, ATC: L04AC13); these were approved for the treatment of CD, UC, Pso, or RA until June 2017 in Japan. Concomitant medications included azathioprine (AZA, ATC: L04AX01), methotrexate (MTX, ATC: L04AX03), and prednisolone (PSL, ATC: H02AB06).

Additionally, treatment patterns within 3 and 12 months of IFX discontinuation were analyzed. Patients who discontinued IFX treatment during the study period and had at least a 6-month follow-up period after IFX discontinuation were further included in the analysis. The events were defined as the need for a new prescription of other biologics described above or calcineurin inhibitors, including tacrolimus (ATC: L04AD02) and cyclosporine (ATC: S01XA18), with the exception of topical agents.

Statistical Analysis Kaplan–Meier curves were plotted to show the persistence rates of IFX. Log-rank tests were used to assess differences in the persistence rates. The significance of the effect of each variable on IFX persistence rates in each disease group in the Cox model was verified by the Wald test. Patients were divided into two groups based on the extracted significant variables, and IFX persistence rates were compared between the two groups. When significant differences were observed by crude survival time analysis, one-to-one propensity score (PS) matching was used to adjust for differences in patient characteristics between the two groups and adjusted p-values were calculated. To estimate the PS, we fitted a logistic regression model, and the c-index was calculated to evaluate the accuracy of the fit. Using a nearest-neighbor matching method, each patient in one group was matched with one patient in another group without replacement, with the closest estimated propensity within a caliper (0.2 standard deviations). All variables listed in Table 1 were included in the PS model, except for those focused on for each group comparison. Statistical significance was set at $p < 0.05$. The analysis was performed using JMP® Pro 15 (SAS Institute Inc., Cary, NC, U.S.A.).

RESULTS

Study Population A flow diagram of the patient selection process is shown in Fig. 1. From the JMDC database, we obtained data pertaining to the 1933 people who were prescribed IFX at least once during the observational period. Of these,

Table 1. Demographics of Patients for the Analysis of Infliximab Persistence

	CD ($n=281$)	UC ($n=234$)	Pso ($n=41$)	RA ($n=222$)
Observation (insurance) period, mean months (S.D.)				
	86.0 (39.0)	82.4 (36.4)	91.4 (38.2)	87.5 (37.6)
Sex, *n* (%)				
Male	233 (82.9)	152 (65.0)	34 (82.9)	68 (30.6)
Female	48 (17.1)	82 (35.0)	7 (17.1)	154 (69.4)
Age at IFX initiation, mean years (S.D.)				
	32.8 (11.6)	37.0 (13.0)	47.7 (9.1)	48.1 (11.7)
Dose of IFX (mg)				
Mean (S.D.)	379.2 (108.2)	325.9 (70.4)	399.3 (82.9)	276.0
Median	356.7	300.0	400.0	256.3
Pre-IFX biologics within 12 months before IFX initiation, *n* (%)				
None	243 (86.5)	217 (92.7)	38 (92.7)	203 (91.4)
Abatacept	NA	NA	NA	3 (1.4)
Adalimumab	38 (13.5)	17 (7.3)	2 (4.9)	3 (1.4)
Etanercept	NA	NA	NA	7 (3.2)
Tocilizumab	NA	NA	NA	6 (2.7)
Ustekinumab	0 (0.0)	NA	1 (2.4)	NA
Drug use within 3 months before IFX initiation, *n* (%)				
Azathioprine (ATC index: L04AX01)				
No	233 (82.9)	168 (71.8)	41 (100.0)	220 (99.1)
Yes	48 (17.1)	66 (28.2)	0 (0.0)	2 (0.9)
Methotrexate (ATC index: L04AX03)				
No	281 (100.0)	229 (97.9)	36 (87.8)	31 (14.0)
Yes	0 (0.0)	5 (2.1)	5 (12.2)	191 (86.0)
Prednisolone (ATC index: H02AB06)				
No	223 (82.9)	101 (43.2)	36 (87.8)	110 (49.6)
Yes	48 (17.1)	133 (56.8)	5 (12.2)	112 (50.5)
Drug use within 3 months of IFX initiation, *n* (%)				
Azathioprine (ATC index: L04AX01)				
No	228 (81.1)	161	41 (100.0)	220 (99.1)
Yes	53 (18.9)	73 (31.2)	0 (0.0)	2 (0.9)
Methotrexate (ATC index: L04AX03)				
No	279 (99.3)	230 (98.3)	37 (90.2)	20 (9.0)
Yes	2 (0.7)	4 (1.7)	4 (9.8)	202 (91.0)
Prednisolone (ATC index: H02AB06)				
No	237 (84.3)	114 (48.7)	34 (82.9)	99 (44.6)
Yes	44 (15.7)	120 (51.3)	7 (17.1)	123 (55.4)

ATC, Anatomical Therapeutic Chemical; *CD*, Crohn's disease; *IFX*, infliximab; *NA*, not applicable; *Pso*, psoriasis; *RA*, rheumatoid arthritis; *S.D.*, standard deviation.

1155 patients were extracted by applying the exclusion criteria, and there were 778 subjects in total (CD, $n=281$; UC, $n=234$; Pso, $n=41$; RA, $n=222$).

IFX Persistence Rates The characteristics of the selected patients are shown in Table 1. Except for patients with RA, more than half of the patients were male (CD, 82.9%; UC, 65.0%; Pso, 82.9%; RA, 30.6%). Biologic use was not observed within 12 months before IFX initiation in almost 90% of the patients (CD, 86.5%; UC, 92.7%; Pso, 92.7%; RA, 91.4%). AZA was used in 17.1% of patients with CD and 28.2% of patients with UC before IFX initiation. After IFX initiation, 18.9% of patients with CD and 31.2% of patients with UC received AZA as a concomitant medication. For RA therapy, 86.0 and 91.0% of patients received MTX before and after IFX initiation, respectively.

Figure 2 presents the Kaplan–Meier curves for IFX persistence in each disease group (log-rank $p<0.001$). The 5-year persistence rates (95% confidence interval) for IFX claims were 62.9% (55.8–69.4%) for CD, 38.7% (31.4–46.5%) for UC, 22.1% (11.1–39.2%) for Pso, and 28.1% (21.2–36.2%) for RA. The median persistent time of IFX treatment for the UC, Pso, and RA groups were 24, 12, and 27 months, respectively. In the CD group, the median persistent time was not estimated because more than 50% of the patients were still receiving IFX treatment.

Factors Associated with Persistence Rates The Wald test was performed to assess the significance of the variables (Table 2). The following parameter estimates were significant independent covariates for each model: individual average dose of IFX in CD, UC, and RA groups; sex in the RA group; prior exposure to biologics in the RA group; and MTX use within 3 months of IFX initiation in the Pso group. Due to the small sample size of patients with Pso who used MTX as a concomitant medication, we focused on IFX dosage, sex, and prior biologics use in further analysis.

As shown in Fig. 3, patients with CD and UC who had taken high-dose (*i.e.*, over the median dose) IFX therapy had significantly higher persistence rates (log-rank $p=0.007$ and $p<0.001$ for patients with CD and UC, respectively). The demographics of patients with CD and UC in the two groups are

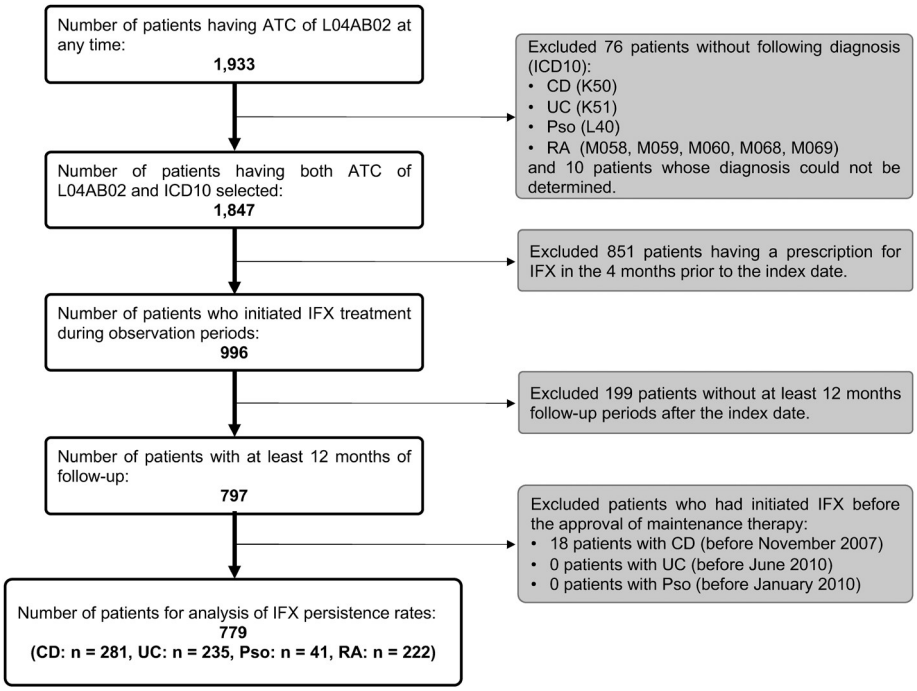

Fig. 1. Flow Chart of the Study Selection

Patients with CD, UC, Pso, and RA who had IFX records were selected based on the ICD-10 and ATC indices. For the persistence rate analysis, patients who had IFX records within 4 months prior to the index date and follow-up periods of less than 12 months after the index date were excluded. *ATC*: Anatomical Therapeutic Chemical, *CD*: Crohn's disease, *ICD-10*: International Classification of Diseases 10th Revision, *IFX*: infliximab, *Pso*: psoriasis, *RA*: rheumatoid arthritis, *UC*: ulcerative colitis.

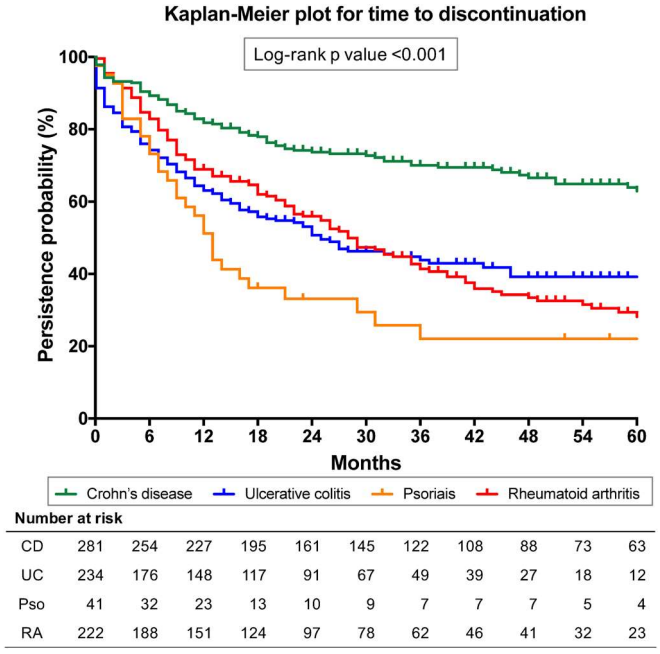

Fig. 2. Kaplan–Meier Curve for IFX Persistence among Patients with CD, UC, Pso, and RA

The x-axis represents months after IFX initiation. The y-axis represents the rate of IFX persistence. Patients having over 5-year IFX persistence or less than 5-year observation without discontinuation were censored. *CD*: Crohn's disease, *IFX*: infliximab, *Pso*: psoriasis, *RA*: rheumatoid arthritis, *UC*: ulcerative colitis.

summarized in Supplementary Table 1. The distributions of variables in the PS-matched groups were well balanced. After matching, a similar pattern was observed for CD (log-rank $p = 0.082$, $n = 108$ in each group, c-index = 0.660) and UC (log-rank $p = 0.026$, $n = 82$ in each group, c-index = 0.745).

In the RA group, female patients had higher IFX persistence than male patients (log-rank $p = 0.016$, Fig. 4). The differences in demographics between male and female patients with RA are summarized in Supplementary Table 2. The distributions of variables in the PS-matched groups were well balanced. After PS matching, a similar pattern was described (log-rank $p = 0.011$, $n = 59$ in each group, c-index = 0.737). As shown in Fig. 5, patients with RA who did not have prior exposure to biologic agents tended to continue IFX therapy (log-rank $p = 0.052$).

Treatment Patterns after Discontinuation of IFX Of the 778 patients enrolled in the persistence analysis, 415 patients who did not complete the 6-month follow-up period after IFX discontinuation were excluded from treatment pattern analysis, including retreatment with IFX. In total, there were 363 patients who discontinued IFX therapy during the study period (CD, $n = 85$; UC, $n = 120$; Pso, $n = 30$; RA, $n = 128$). The number and proportion of events within 3 or 12 months of IFX discontinuation are shown in Table 3. More than half of the patients with Pso and RA initiated other biologics or calcineurin inhibitors within 3 months of discontinuation. Patients with Pso demonstrated the highest frequency of new treatment initiation and most frequent retreatment with ADL next to UST (36.7 and 30.0%, respectively, in 12 months). Initiation of ETN, GLM, or TCZ was observed in more than 10% of patients with RA (12.5, 10.9, and 17.2% in 12 months, respectively). ADL retreatment was most frequently observed in patients with CD (42.4% in 12 months). In UC, 63.3 and 53.3% of patients had no events within 3 and 12 months, respectively. Retreatment with ADL was most frequently observed in patients with UC within both 3 and 12 months (22.5 and 25.0%, respectively). Restarting of IFX therapy was frequently observed in patients with CD and RA (21/24 and 12/16, respectively).

Table 2. Wald Test for the Significance of Variables on the Persistence of Infliximab Therapy

	CD			UC			Pso			RA		
	df	Chi-square	*p*-Value*	df	Chi-square	*p*-Value*	df	Chi-square	*p*-Value*	df	Chi-square	*p*-Value*
Continuous variables												
Observation (insurance) period	1	1.598	0.206	1	2.362	0.124	1	1.975	0.160	1	0.000	0.998
Age at IFX initiation	1	2.258	0.133	1	1.436	0.231	1	3.525	0.060	1	0.320	0.572
Average dose of IFX (mg)	1	4.773	*0.029*	1	8.689	*0.003*	1	2.482	0.115	1	8.708	*0.003*
Categorical variables												
Sex	1	0.420	0.517	1	0.075	0.785	1	0.592	0.442	1	11.743	*<0.001*
Pre-IFX biologics within 12 months before IFX initiation	1	0.443	0.506	1	0.319	0.572	1	1.425	0.233	1	6.917	*0.009*
AZA use within 3 months before IFX initiation	1	0.010	0.921	1	0.266	0.606	0	0.000	—	1	1.008	0.315
MTX use within 3 months before IFX initiation	0	0.000	—	1	0.053	0.819	1	0.475	0.491	1	1.091	0.296
PSL use within 3 months before IFX initiation	1	1.207	0.272	1	0.012	0.913	1	0.620	0.431	1	0.002	0.968
AZA use within 3 months of IFX initiation	1	2.591	0.108	1	2.812	0.094	0	0.000	—	1	0.513	0.474
MTX use within 3 months of IFX initiation	1	0.156	0.693	1	0.228	0.633	1	7.351	*0.007*	1	0.545	0.461
PSL use within 3 months of IFX initiation	1	0.000	0.996	1	0.067	0.796	1	2.125	0.145	1	0.634	0.426

AZA, azathioprine; *CD*, Crohn's disease; *df*, degree of freedom; *IFX*, infliximab; *MTX*, methotrexate; *PSL*, prednisolone; *Pso*, psoriasis; *RA*, rheumatoid arthritis; *UC*, ulcerative colitis. **Italics* were statistically significant.

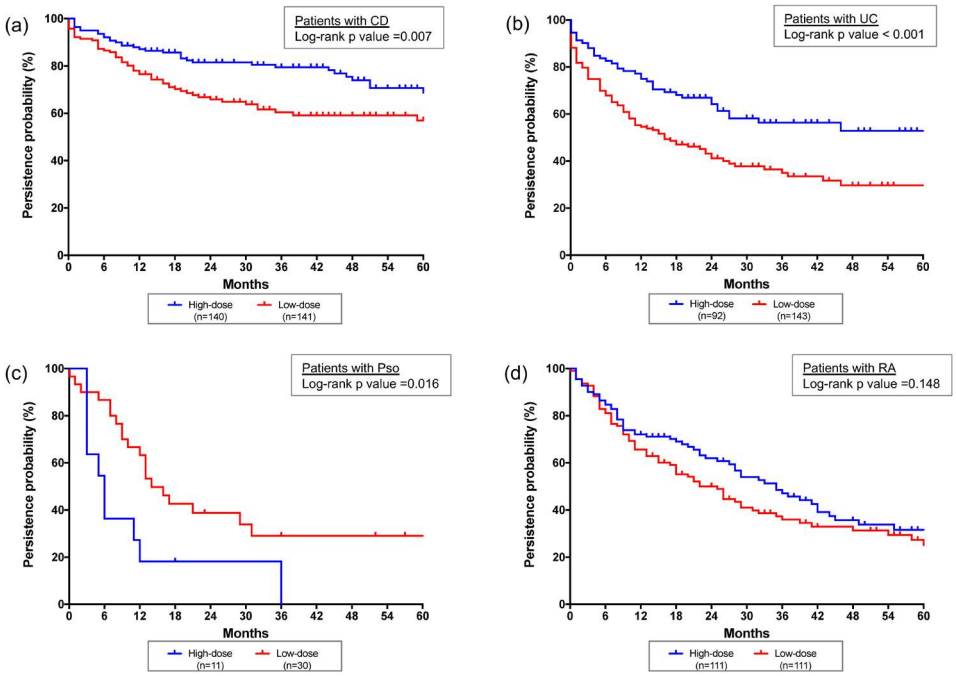

Fig. 3. Kaplan–Meier Curve for IFX Persistence in Patients with (a) CD, (b) UC, (c) Pso, and (d) RA Comparing High-Dose and Low-Dose IFX

The patients were divided by each median IFX dosage (CD; 356.7 mg, UC; 300.0 mg, Pso; 400.0 mg, RA; 256.3 mg). Patients who were administered IFX beyond the median dose were categorized into the "High-dose" group, while the rest were categorized into the "Low-dose" group. *CD*: Crohn's disease, *IFX*: infliximab, *Pso*: psoriasis, *RA*: rheumatoid arthritis, *UC*: ulcerative colitis.

DISCUSSION

The introduction of IFX has improved the QOL of many patients who were refractory to previously available therapies. In previous reports of RCTs, the response rates of IFX in 1 year were 40% for CD, 45% for UC, 60% for Pso, and 52% for RA.[25–28] Notably, the 5-year persistence rate in the CD group was the highest in our study, despite the lower clinical response rates in the RCT.[25] Additionally, 1-year persistence rates in patients with Pso (52%) or RA (69%) were lower compared to the results of the RCTs (80% at week 78 in the Pso study, and 79% at week 54 in the RA study),[27,28] whereas the short-term persistence rate in the CD group was similar to that in the RCT (78 and 79% at year 1, respectively).[25] Taken together, these results suggest that the clinical responses reported from RCTs did not always reflect the persistence rates in routine clinical settings.

How long the patients remain on the therapy is an important measure of effectiveness.[13] The present study showed that the persistence rates of IFX treatment varied by disease. Although the study design, including the study duration, patient selection, and definition of discontinuation, were different among the studies, previous long-term observational studies in patients with CD,[21,29,30] UC,[22,31] Pso,[23,32] and RA[24,33–35]

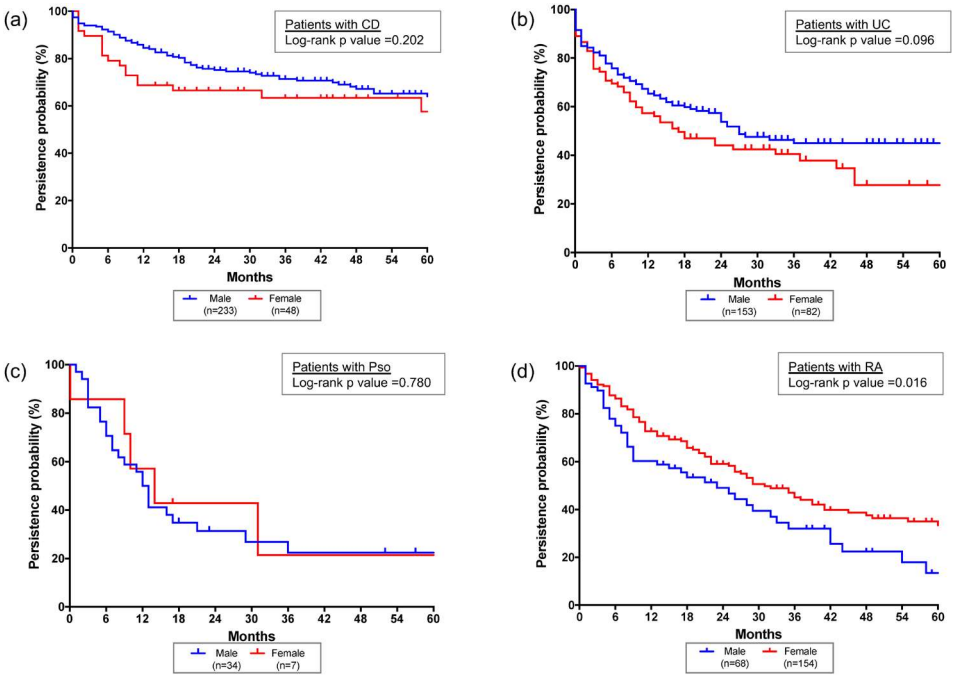

Fig. 4. Kaplan–Meier Curve for IFX Persistence Comparing Sex in Patients with (a) CD, (b) UC, (c) Pso, and (d) RA

CD: Crohn's disease, *IFX*: infliximab, *Pso*: psoriasis, *RA*: rheumatoid arthritis, *UC*: ulcerative colitis.

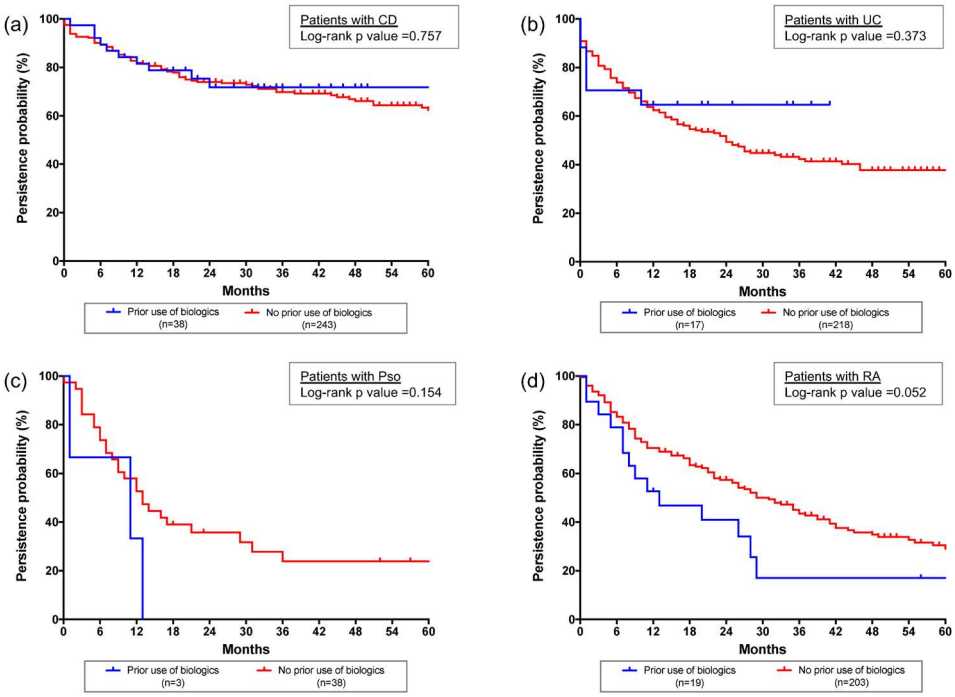

Fig. 5. Kaplan–Meier Curve for IFX Persistence in Patients with (a) CD, (b) UC, (c) Pso, and (d) RA, Comparing the Presence or Absence of Prior Exposure to Other Biologic Agents within 12 Months before IFX Initiation

Patients who were exposed to at least one biologic approved for the treatment of CD, UC, Pso, or RA in Japan during the study period were categorized into the "Prior use of biologics" group. *CD*: Crohn's disease, *IFX*: infliximab, *Pso*: psoriasis, *RA*: rheumatoid arthritis, *UC*: ulcerative colitis.

reported similar results to those of the present study. One of the causes of secondary non-response is anti-drug antibody formation, but the proportions of patients who developed anti-drug antibody against IFX in each disease[7] did not show a relationship with the IFX persistence rates in our study. Although a possible factor could be the sensitivity to IFX, the characteristics of adverse events or the number of alternative treatment options, the underlying mechanism of the difference in the persistence rates across diseases is unclear. In the following sections, we discussed the factors of IFX persistence according to each disease.

We assessed the possible factors associated with the persistence of IFX. Our results indicated that the high-dose IFX treatment group, divided by the median dose, resulted in lon-

Table 3. Number (Proportions) of Patients Who Started Biologics or Immunosuppressants within 3 and 12 Months of Discontinuation of Infliximab

	CD ($n=85$)			UC ($n=120$)			Pso ($n=30$)			RA ($n=128$)		
	3 M	12 M	Δ*	3 M	12 M	Δ*	3 M	12 M	Δ*	3 M	12 M	Δ*
None	52 (61.2)	28 (32.9)	−24	76 (63.3)	64 (53.3)	−12	10 (33.3)	4 (13.3)	−6	63 (49.2)	47 (36.7)	−16
Biologics												
Abatacept	NA		—	NA		—	NA		—	4 (3.1)	4 (3.1)	±0
Adalimumab	33 (38.8)	36 (42.4)	+3	27 (22.5)	30 (25.0)	+3	9 (30.0)	11 (36.7)	+2	8 (6.3)	9 (7.0)	+1
Etanercept	NA		—	NA		—	NA		—	15 (11.7)	16 (12.5)	+1
Golimumab	NA		—	0 (0.0)	0 (0.0)	±0	NA		—	13 (10.2)	14 (10.9)	+1
Infliximab	—	21 (24.7)	+21	—	8 (6.7)	+8	—	1 (3.3)	+1	—	12 (9.4)	+12
Secukinumab	NA		—	NA		—	3 (10.0)	3 (10.0)	±0	NA		—
Tocilizumab	NA		—	NA		—	NA		—	21 (16.4)	22 (17.2)	+1
Ustekinumab	0 (0.0)	0 (0.0)	±0	NA		—	7 (23.3)	9 (30.0)	+2	NA		—
Immunosuppressant (Calcineurin inhibitor)												
Tacrolimus	0 (0.0)	0 (0.0)	±0	16 (13.3)	17 (14.2)	+1	0 (0.0)	1 (3.3)	+1	4 (3.1)	4 (3.1)	±0
Cyclosporine	NA		—	1 (0.8)	1 (0.8)	±0	1 (3.3)	1 (3.3)	±0	NA		—

Analysis was conducted for patients who discontinued IFX during the study period and had at least a 6-month follow-up period. *CD*, Crohn's disease; *M*, month; *NA*, not applicable; *Pso*, psoriasis; *RA*, rheumatoid arthritis; *UC*, ulcerative colitis. *Δ was defined as the difference in the number of patients from 3-month to 12-month.

ger persistence in patients with CD and UC. In an RCT, higher clinical response rates were observed in patients with CD in the 10 mg/kg maintenance dose group than in the 5 mg/kg group.[25] In an RCT for patients with UC, no significant differences in clinical response were observed between the 5 and 10 mg/kg groups.[26] Corresponding with RCT data, dose escalations of IFX up to 10 mg/kg have been approved in Japan for the treatment of CD since 2011, but not for UC (maximum dose, 5 mg/kg). Although the data on body weight were unavailable in the present study, the median single dosages in CD (356.7 mg) were higher than those in UC (300.0 mg), corresponding to the approved dosage for each disease. It was suggested that high-dose IFX treatment within the approved doses could avert the loss of response in patients with CD and UC.

In this study, sex differences were also found in several inflammatory diseases. Current data showed that female patients with CD and UC tended to discontinue IFX therapy earlier. Conversely, female patients with RA continued IFX treatment significantly longer than men, despite adjustment for various confounders including age, dosage, prior exposure to biologics, and use of concomitant medication. In previous reports, female sex was reported as a poor prognostic factor for the persistence of anti-TNF therapy.[8,10,36] Female patients with Pso were slightly less satisfied with treatment regarding side-effects.[36] In patients with early-onset RA, female sex tended to be associated with low serum IFX levels and anti-drug antibody positivity.[37] Sex differences in the percentage of body fat and fat distribution were also discussed as the underlying mechanisms.[38] Although some studies indicated no influence of sex on IFX persistence,[39–41] the impact of sex differences is still an important study subject. Notable heterogeneity in the methods used to measure treatment persistence has been reported.[42] Our current analyses, being conducted under the same methodology with a Japanese claims database, indicated a different influence of sex on IFX persistence rates between patients with inflammatory bowel disease (CD and UC) and patients with RA in Japan. Female patients with RA may benefit more from IFX treatment than male patients with RA. The difference in the influence of sex on the persistence rate between patients with CD/UC and RA in the present study remains unclear; however, it may be attributed to unbalanced, hidden factors, such as smoking status.[43] Thus, further studies are required to determine the influence of sex on the persistence of IFX.

We compared the persistence of IFX as a first- and second-line treatment. In the present study, patients with RA who received previous biologic treatment showed shorter IFX persistence, whereas such differences were not observed in patients with CD or UC. Gil-Candel *et al.* reported similar survival curves with respect to first- and second-line IFX treatment for inflammatory bowel disease,[44] which is consistent with our results. Some studies on patients with RA also reported that switching to IFX was effective for those who were refractory to previous biologics[45–47]; however, the relatively small sample size and short duration were noted as limitations. Additionally, other studies reported that prior biologic treatment was significantly associated with a reduced likelihood of achieving a therapeutic response or remission.[48,49] Our results suggest that the long-term effectiveness of second-line IFX treatment could be lower than that of first-line IFX in patients with RA. Careful monitoring would be required in patients with RA undergoing second-line IFX therapy.

This study has some limitations. First, our data were generated from the JMDC database which contains claims data of employees and their family members from the employees' insurance program in Japan. There was bias towards the younger population, and the results cannot be representative of all patients, especially elderly patients. Second, we could not distinguish discontinuation due to adverse events or remission. Some clinical data, including disease activities, laboratory data, and reasons for IFX discontinuation, were unavailable in this database. Although adverse events have been reported as a common reason for discontinuation, clinical remission is not the main reason for discontinuation.[50,51] In the present study, alternative treatments were required in approximately 40–70% of patients within 3 months of IFX discontinuation. The withdrawal of biologics after remission has been attempted in several clinical trials, but not in clinical practice.[52–55] Third, the sample size of the Pso group was very small. Future studies with larger sample sizes are needed to test the determinants of IFX continuation in Pso therapy. Finally, as with all claims

analyses, there is a potential for improper coding. In the present study, patients were classified according to the CD, UC, Pso, or RA diagnostic codes, which were most often recorded in their treatment or observation periods.

In conclusion, the persistence rates of IFX treatment differed across chronic inflammatory diseases, suggesting the potential differences in response to IFX therapy among the diseases. Our real-world data analysis indicated that the clinical responses reported from RCTs did not always reflect the persistence rates in routine clinical settings. Additionally, patient characteristics, such as sex and prior exposure to biologic agents, could potentially impact IFX persistence in RA therapy. Dose escalation could have contributed to the longer duration of successful IFX treatment in patients with CD and UC. These findings could facilitate the proper use of IFX for persistent successful treatment.

Acknowledgments This study was supported in part by a Grant-in-Aid for Scientific Research (KAKENHI) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grants-in-Aid for Scientific Research (B 19H03389), by the Japan Agency for Medical Research and Development (AMED) under Grant Number 20mk0101152h0502, and by the Nakatomi Foundation to AY.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials This article contains supplementary materials.

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