Treatment Patterns, Direct Cost of Biologics, and Direct Medical Costs for Rheumatoid Arthritis Patients: A Real-world Analysis of Nationwide Japanese Claims Data

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ABSTRACT

Purpose: The aims of this article were to characterize the patterns of treating rheumatoid arthritis with biologics and to evaluate costs using claims data from the Japan Medical Data Center Co, Ltd.

Methods: Patients aged 16 to <75 years who were diagnosed with rheumatoid arthritis and prescribed adalimumab (ADA), etanercept (ETN), infliximab (IFX), tocilizumab (TCZ), abatacept, certolizumab, or golimumab between January 2005 and August 2014 were included. For the cross-sectional analysis, the annual costs of ETN, IFX, ADA, and TCZ from 2009 to 2013 were assessed. For the longitudinal analysis, patients prescribed these biologics as the first line of biologics, from January 2005 to August 2014, were included. The cost of biologic treatment over 1, 2, and 3 years (including prescription of subsequent biologics) and direct medical costs (including treatment of comorbidities) were compared between groups. Discontinuation and switching rates in each group were estimated, and multivariate analyses were conducted to estimate an adjusted hazard ratio of discontinuation and switching rates among each group. The dose of each first-line biologic treatment until discontinuation was analyzed to calculate relative dose intensity.

Findings: The cross-sectional annual biologic costs of ETN, IFX, ADA, and TCZ were ~$8000 (2009 and 2013), $13,000 (2009) and $15,000 (2013), $10,000 (2009) and $11,000 (2013), and $9000 (2009) and $8000 (2013), respectively. In longitudinal analyses (n = 764), 276 (36%) initiated ETN; 242 (32%), IFX; 147 (19%), ADA; and 99 (13%), TCZ. The 1-year cumulative annual biologic costs per patient from the initial prescription of ETN, IFX, ADA, and TCZ as the first-line biologic treatment were ~$11,000, $19,000, $16,000, and $12,000. The corresponding direct medical costs over 1 year from the initial prescription were ~$17,000, $26,000, $22,000, and $22,000. Costs remained greatest in the IFX-initiation group at year 3. The discontinuation rates at 36 months with ETN, IFX, ADA, and TCZ were 37.7%, 52.3%, 55.8%, and 39.5%; the switching rates were 12.5%, 27.1%, 31.0%, and 16.7%. The mean (95% CI) relative dose intensities until discontinuation of ETN 25 mg, ETN 50 mg, IFX, ADA, and TCZ were 1.02 (0.95–1.10), 0.82

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(0.79–0.85), 1.16 (1.12–1.20), 0.95 (0.90–0.99), and 0.96 (0.93–1.00).

Implications: Considered costs and discontinuation and switching event rates were lowest with ETN versus IFX, ADA, or TCZ used as the first-line biologic. Despite limitations, these findings imply clinical cost-reductive benefits of ETN as the first-line biologic treatment option for rheumatoid arthritis in Japan. (*Clin Ther*. 2016;38:1359–1375)

Key words: biologics, claims data, cost, Japan, rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by joint pain and stiffness, followed by progressive joint destruction and disability. In addition to physical impairment and a shortened life expectancy, RA can result in substantial socioeconomic costs.[1,2] The prevalence of RA in Japan is estimated to be between 0.6% and 1.0%,[3] which is comparable to that in other parts of the world.[4] Thus, the socioeconomic impact of RA cannot be overlooked.

Despite the debilitating nature of RA, several biologic immunotherapies have been approved for inhibiting the progression of structural damage and for improving physical function in patients with moderate to severe disease.[5] For over a decade, biologics—including the tumor necrosis factor (TNF)-α inhibitors etanercept (ETN; approved by the Pharmaceuticals and Medical Devices Agency [PMDA] in Japan in 2005 and by the US Food and Drug Administration [FDA] in 1998), infliximab (IFX; PMDA, 2003; FDA, 1999), and adalimumab (ADA; PMDA, 2008; FDA, 2002)—have been used for treating RA in global markets including Japan. The interleukin-6 inhibitor tocilizumab (TCZ) was first approved by the PMDA in 2008, followed by the FDA in 2010. The cluster of differentiation 80/86 inhibitor abatacept was approved by the PMDA in 2010 and by the FDA in 2005. The TNF inhibitors certolizumab pegol and golimumab were approved by the PMDA in 2012 and 2011, respectively, and by the FDA in 2009. To date, few head-to-head randomized clinical trials have assessed the comparative effectiveness of these biologics in the treatment of RA, but those few have generally demonstrated comparable efficacy.[6–12]

The treatment of RA is required long term, which creates a significant clinical and economic burden for patients and payers. The cost of RA varies widely between countries,[13] partly because of the varying use of biologic treatments, which are substantially more costly than are conventional synthetic disease-modifying antirheumatic drugs.[14–16] The market for developing original biologics for the treatment of RA is saturated, and cost considerations by rheumatologists are becoming more important, especially as biosimilar biologics become more available.[17] The impact of drug costs on direct medical expenditures is also a cause for concern owing to the widespread use of biologics for the treatment of RA. However, a recent study from Germany showed that improvements in functional status and reductions in health care resource utilization as a result of biologic use have largely offset the increased drug costs.[18]

Accumulating data from global registries[19–21] and from Japanese cohorts[22] suggest that continuance rates differ among biologic treatments for RA, even between members of the same drug class. The main reasons for discontinuations are lack of efficacy and adverse events (AEs). Poor adherence to medications can reduce effectiveness and increase the utilization of health care services, thereby increasing overall costs.[23,24]

Current RA treatment practices in Japan are poorly documented,[3] and the impact of biologic use on costs is unknown. The aim of this study was therefore to characterize the patterns of treating RA with biologics and to evaluate the direct costs of biologics and medical costs using claims data from Japan.

MATERIALS AND METHODS

Data Source

This retrospective analysis utilized reimbursement data from the Japan Medical Data Center Co, Ltd (JMDC). Data were received from the JMDC on February 4, 2015. The JMDC, in collaboration with multiple health insurance societies, has accumulated inpatient, outpatient, and pharmacy claims data from approximately 2.8 million insured members cumulatively from 2005 to 2014. Claims data contained within this database are nationwide and are

representative of RA-related prescriptions from rheumatologists and general practitioners.

Patient Population

Two types of analyses were conducted in this study; cross sectional and longitudinal. The study design is depicted in Figure 1. In the cross-sectional analysis, patients diagnosed with RA by a code from the *International Classification of Diseases, Tenth Revision* (M058, M059, M060, M068, or M069) and who were prescribed ETN, IFX, ADA, TCZ, abatacept, certolizumab, or golimumab between January 2005 and August 2014 were included in this study. For cross-sectional annual cost analysis, 2014 data were excluded because there were <12 months in the 2014 study period. In longitudinal analysis, only patients who had been prescribed ETN, IFX, ADA, or TCZ as the first-line biologic (defined as the first prescription of a biologic in the JMDC database between April 2005 and August 2014 after a 3-month period during which no biologic prescriptions were made) and who were aged 16 to <75 years at the first prescription of a biologic were included. Due to the small numbers of patients receiving ETN 10 mg (<17.5 mg/wk) or abatacept, certolizumab, or golimumab (<50 patients per drug), data from these patients were not included in the analysis.

Codes from the *International Classification of Diseases, Tenth Revision* and Anatomical Therapeutic Chemical were used for identifying patients' concurrent medications and comorbidities. The analysis included data from only deidentified patients, and as such, institutional review board approval and patient consent were not required.

Statistical Analysis

Descriptive statistics (mean [SD]) were used for summarizing patients' demographic and disease

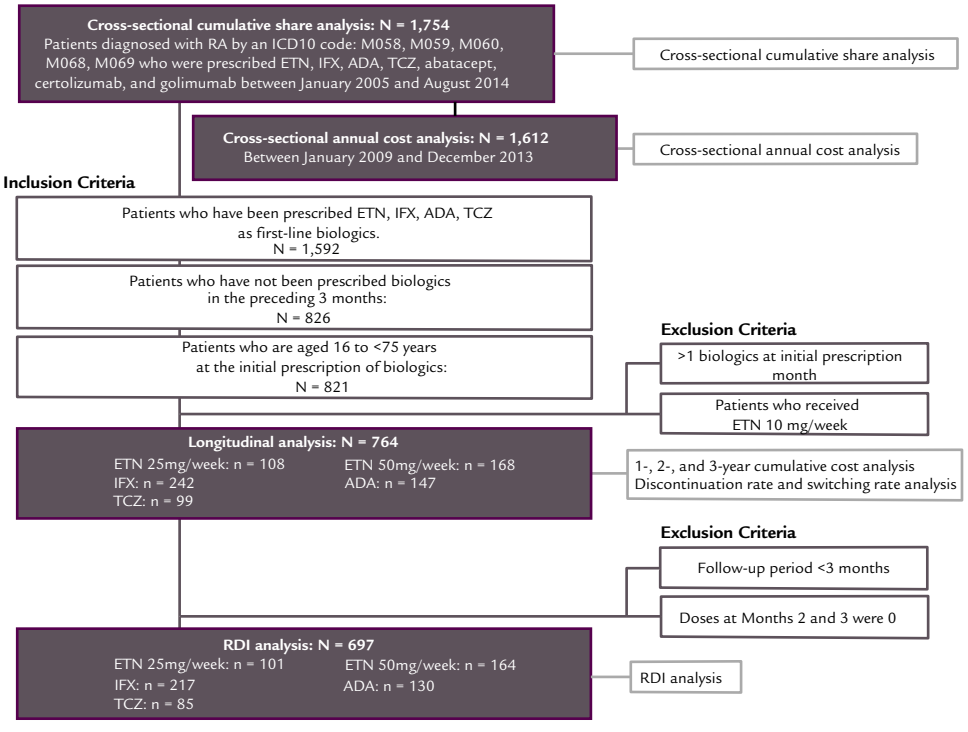

Figure 1. Study design. Patients diagnosed with rheumatoid arthritis (RA) were included in a cross-sectional cumulative share analysis, a cross-sectional annual cost analysis, longitudinal analysis, and relative dose intensity (RDI) analysis, according to the inclusion and exclusion criteria shown. ADA = adalimumab; ETN = etanercept; ICD-10 = *International Classification of Diseases, Tenth Revision*; IFX = infliximab; RDI = relative dose intensity; TCZ = tocilizumab.

characteristics in the month of biologic initiation; continuous parameters were analyzed with 1-way ANOVA; categorical parameters, by χ^2 tests. If a statistically significant difference was found, a multiple comparison test was conducted using a Tukey test for continuous parameters and adjusted χ^2 test by the Bonferroni method for categorical parameters. SPSS version 18 (SPSS Inc, Chicago, Illinois, USA) was used for all analyses.

The cross-sectional cumulative share of each biologic (ETN, IFX, ADA, TCZ, abatacept, certolizumab, and golimumab) prescribed from 2005 to 2014 was calculated. The cross-sectional annual cost of ETN, IFX, ADA, TCZ, and a mean of all biologics (including abatacept, certolizumab, and golimumab) per patient, were also assessed from 2009 to 2013 based on actual prescribing and corresponding US National Institutes of Health drug price. If biologic use spanned several years, costs were calculated from the initial claim month from the JMDC database to December of that year, then yearly (from January) thereafter. Annual data on the costs of ADA and TCZ were not available or were very limited between 2005 and 2008; this time period was therefore excluded from the cross-sectional cost analysis.

The 1-, 2-, and 3-year cumulative biologic-related and direct medical costs in patients with a >1-, >2-, or >3-year follow-up period, respectively, were compared between each treatment group after the initial prescription of biologics to biologic-naive patients (see **Supplemental Figure** in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.03.022). Biologic-related costs included prescribing of ≥ 2 biologics after a switch, and direct medical costs included the costs of treating comorbidities. Costs (including patients' copayments) in Japanese yen were converted to US dollars (1¥ = \$0.01). The differences in direct medical costs between treatment groups over 3 years were analyzed by Steel-Dwass tests (conducted using the statistical software package R version 2.15.0, R Foundation for Statistical Computing, Vienna, Austria).

Month-36 rates of discontinuing and switching to other biologics (after the initial prescribing of biologics to biologic-naive patients) were estimated using Kaplan-Meier survival analysis. An event was considered a *discontinuation* if the drug was prescribed for an administration interval not longer than can be explained by the dosing schedule for each biologic (ETN, 4 months; IFX, 5 months; ADA, 4 months; and TCZ, 4 months) or when one biologic was switched to another. Data were censored if a patient was withdrawn from the JMDC or was coming to the end of the observation period. Exploratory analysis of pairwise comparisons of discontinuation rates between treatment groups were by log-rank (Mantel-Cox) tests. If there were significant differences in baseline demographic and disease characteristics between treatment groups, multivariate analyses with these baseline variables using a Cox proportional hazards model were conducted to estimate adjusted hazard ratios (HRs) of discontinuation and switching rates among each group.

The dose of each biologic after initial prescribing to biologic-naive patients until discontinuation or switching to another biologic was analyzed to calculate *relative dose intensity* (RDI), calculated as (Actual cumulative dose)/(Initial dose · Period until discontinuation). The initial dose was estimated from the dose information from months 1, 2, and 3. ETN is prescribed weekly, whereas ADA is prescribed biweekly; therefore, the dose at month 1 was excluded (to avoid underestimation of dose in the case of a patient initiating the treatment from the end of the month), and the mean doses of ETN and ADA at months 2 and 3 were used for calculating the initial dose per month. If the doses at months 2 and 3 were zero, then the data from those patients were excluded from the analysis owing to difficulties in estimating the initial dose accurately. Because TCZ is prescribed monthly, the median doses of TCZ at months 1, 2, and 3 were used for calculating the initial dose per month. IFX has a 1- to 2-month titration phase and a maintenance phase at month ≥ 3; therefore, the actual dose at month 1 to 2 and the estimated maintenance dose for month ≥ 3 were separately calculated and added to the denominator. The dose at month 3 (or the first month thereafter when the dose was not zero) was used as the initial dose of the maintenance phase. The data from patients with a follow-up of <3 months were excluded from the analysis, so population sizes in the RDI analysis may be smaller than the overall population size. In the RDI analysis, patients receiving a mean dose of ETN of 17.5 to 37.5 mg/wk or >37.5 mg/wk between months 2 and 3 were assigned to the ETN 25 or 50 mg dose group, respectively. If a patient was identified as a censored case when he/she withdrew from the JMDC or was coming to the end of the observation period before biologic discontinuation or switching, the period until

discontinuation in the denominator of the RDI equation was defined to be continued until the censored month.

In Japan, the approved dose of ETN is 10 to 25 mg twice per week, or 25 to 50 mg once per week; for IFX, the initial dose is 3 mg/kg at 0, 2, and 6 weeks, and 3 to 10 mg/kg every 8 weeks or ≤6 mg/kg every 4 to 8 weeks; for ADA, the dose is 40 to 80 mg every 2 weeks; and for TCZ, the dose is 8 mg/kg every 4 weeks.

In the analyses of cumulative costs, discontinuation rate, switching rate, and RDI, the initial prescribing of a biologic to a biologic-naive patient aged 16 to <75 years was defined as the first prescribing of a biologic after a 3-month period during which no biologic prescriptions were made.

RESULTS

A total of 1754 patients were identified for the cross-sectional analysis of cumulative share of biologics between January 2005 and August 2014 (Figure 1). Of these patients, data from 1612 were included in the annual cost analysis, conducted between January 2009 and December 2013. A total of 764 patients were identified for the longitudinal analysis of 1-, 2-, and 3-year cumulative costs and an analysis of discontinuation and switching rates. Data from a subset of these patients (n = 697) were also included in the RDI analysis.

Cross-Sectional Cumulative Share and Cost Analysis

The proportion of patients receiving each biologic varied from 2005 to 2014 (Figure 2). In 2013, 37% of patients were receiving ETN; 20%, IFX; 13%, ADA; and 16%, TCZ. The proportion of patients receiving abatacept was 6%; certolizumab, 1%; and golimumab, 6%. Data from 2014 represent the first half of the year only.

The cross-sectional cost of ETN per patient per year was ~$8000 from 2009 to 2013 (Figure 3). The mean cost of IFX increased over the observation period, from ~$13,000 in 2009 to $15,000 in 2013. The approved maximum dose of IFX changed in 2009 (from 3 mg/kg every 8 weeks to 10 mg/kg every 8 weeks or ≤6 mg/kg every 4–8 weeks), accounting for some of this increase. The cost of ADA per patient per year was ~$10,000 to $11,000 from 2009 to 2013. The cost of TCZ increased from ~$9000 in 2009 to $11,000 in 2011 and then decreased to ~$8000 in 2012 and 2013, owing to a 25% reduction in price in 2012, per the National Institutes of Health.

Longitudinal Analysis

Patients' Demographic and Characteristics

Of the 764 patients included in the longitudinal analysis, 36% (n = 276) initiated ETN; 32% (n = 242), IFX; 19% (n = 147), ADA; and 13% (n = 99), TCZ (Figure 1). Age distribution and the

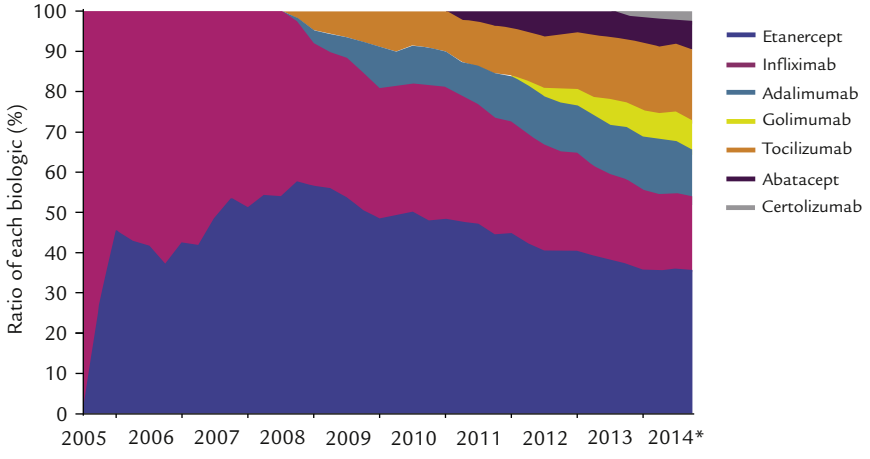

Figure 2. Share of biologics prescribed per year. Data represent the cumulative proportion of biologics prescribed between 2005 and 2014. *Data from 2014 represent quarters 1 and 2.

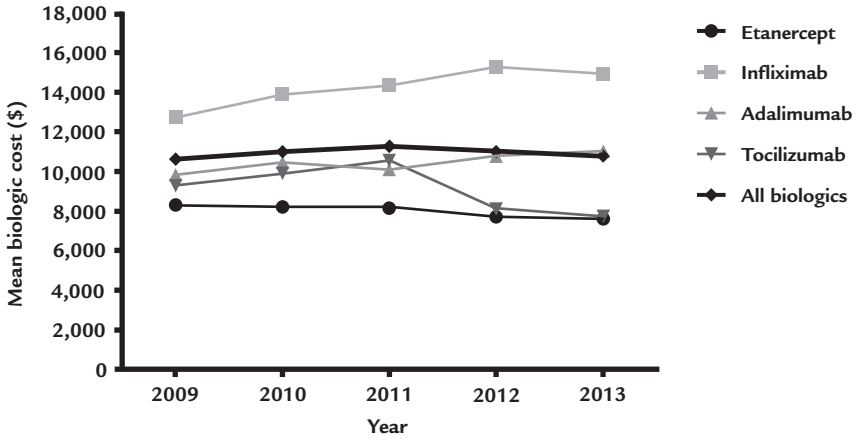

Figure 3. Annual cost of biologics per patient. Data are given as mean US $ (1 yen = $0.01).

prevalence of comorbidities were generally similar across treatment groups (Table I). There were more males in the IFX and ADA groups than in the ETN and TCZ groups ($P = 0.014$), and the methotrexate dose, in milligrams per week per person, at biologic initiation was greater in those receiving ADA than in the other treatment groups ($P = 0.039$).

Longitudinal 1-, 2-, and 3-Year Cumulative Cost Analysis

The 1-year cumulative first-line biologic costs per patient per year from the initial prescription of ETN, IFX, ADA, and TCZ were ~$11,000, $19,000, $16,000, and $12,000, respectively (Figure 4**A**). After 1, 2, and 3 years, the cost of the biologic was significantly less when ETN was prescribed as the first-line biologic treatment versus when ADA or IFX was prescribed (both, $P < 0.01$). The cost of the biologic was also significantly greater when IFX or ADA was prescribed first versus TCZ after 1 and 2 years (all, $P < 0.001$). After 3 years, IFX remained significantly more costly than TCZ if prescribed first ($P < 0.05$), but the cost of ADA as the first-line biologic treatment was no longer significantly greater than that of TCZ. Across all 3 years, the costs of the biologics in those initially prescribed ETN were comparable to that in those initially prescribed TCZ.

The cumulative direct medical costs of the initial prescribing of ETN, IFX, ADA, and TCZ were ~$17,000, $26,000, $22,000, and $22,000, respectively, in 1 year and $46,000, $65,000, $60,000, and $49,000 in 3 years (Figure 4**B**). These costs represent not only RA-related costs but also the total costs accepted by the health insurance societies. Some common comorbidities and their contributions to these costs are shown in Table II. Over all 3 years, direct medical costs were significantly less when ETN was prescribed as the first-line biologic compared with IFX (all years, $P = 0.001$) and ADA (all years, $P < 0.05$). The direct medical costs in year 1 were also less in those prescribed ETN versus TCZ ($P = 0.008$) and ADA versus IFX ($P < 0.05$) as the first-line biologic treatment. Direct medical costs were less over 1 and 2 years in patients prescribed TCZ first versus IFX first ($P \leq 0.001$). TCZ was associated with significantly lesser total costs than was ADA after 2 years only ($P < 0.05$).

Overall, the costs of concurrent medications increased from 1 year to 3 years in all of the groups. but there were no significant differences between groups (Table II). Self-injection and outpatient chemotherapy management fees were greatest in the ETN group in 1 year versus IFX and ADA (both, $P < 0.01$), 2 years versus ADA ($P < 0.05$), and 3 years versus ADA and IFX (both, $P < 0.05$). In 1 year, medical practice costs were greatest with TCZ versus ETN and IFX (both, $P < 0.001$) and with ADA versus ETN and IFX (both, $P < 0.05$). Significant differences in medical practice costs were not seen at 2 and 3 years.

Discontinuation and Switching Rate Analysis

The discontinuation rates (95% CI) at 36 months for the TNF inhibitors ETN, IFX, ADA, and TCZ as

Table I. Baseline demographic and clinical characteristics of the patients at treatment initiation.

Characteristic	ETN (n = 276)	IFX (n = 242)	ADA (n =147)	TCZ (n = 99)	P*
Age					
Group, no. (%)					
≥16–<30 y	14 (5.1)	21 (8.7)	14 (9.5)	7 (7.1)	1.000
30–<40 y	64 (23.2)	38 (15.7)	31 (21.1)	13 (13.1)	0.236
40–<50 y	75 (27.2)	77 (31.8)	39 (26.5)	24 (24.2)	1.000
50–<60 y	74 (26.8)	72 (29.8)	37 (25.2)	27 (27.3)	1.000
60–<75 y	49 (17.8)	34 (14.0)	26 (17.7)	28 (28.3)	0.085
Mean (SD), y	47.5 (11.9)	46.9 (11.5)	46.9 (12.4)	50.9 (13.0)	0.036[a]
Male, no. (%)	54 (19.6)	72 (29.8)	35 (23.8)	13 (13.1)	0.014[b]
Oral corticosteroid dose,† mean (SD), mg/d	6.0 (4.6)	5.8 (4.4)	5.5 (3.6)	7.7 (8.6)	0.427
Methotrexate dose,‡ mean (SD), mg/wk	8.1 (2.8)	8.4 (3.1)	9.3 (3.5)	8.4 (3.2)	0.039[c]
Comorbidity§, no. (%)					
Renal failure	5 (1.8)	7 (2.9)	2 (1.4)	3 (3.0)	1.000
Interstitial pneumonia	8 (2.9)	12 (5.0)	7 (4.8)	8 (8.1)	1.000
COPD	2 (0.7)	1 (0.4)	1 (0.7)	2 (2.0)	0.138
Peptic ulcer	43 (15.6)	38 (15.7)	31 (21.1)	19 (19.2)	1.000
Chronic liver disease	10 (3.6)	6 (2.5)	9 (6.1)	9 (9.1)	1.000
Depression	83 (30.1)	67 (27.7)	46 (31.3)	39 (39.4)	1.000
Osteoporosis	7 (2.5)	5 (2.1)	5 (3.4)	5 (5.1)	0.807
Diabetes	72 (26.1)	61 (25.2)	38 (25.9)	26 (26.3)	0.797
None	128 (46.4)	107 (44.2)	64 (43.5)	37 (37.4)	1.000

ADA = adalimumab; COPD = chronic obstructive pulmonary disease; ETN = etanercept; IFX = infliximab; TCZ = tocilizumab.

In multiple comparison tests:

[a]$P = 0.030$ for IFX vs TCZ.

[b]$P = 0.029$ for ETN vs IFX and $P = 0.005$ for IFX versus TCZ.

[c]$P = 0.022$ ETN vs ADA.

*ANOVA was used for continuous variables; χ^2 was used for categorical variables.

†Converted to prednisolone dose. Patients who were prescribed oral corticosteroid without sufficient information for prednisolone conversion were excluded from the calculation of oral corticosteroid dose. Patients included: ETN, n = 129; IFX, n = 86; ADA, n = 59; TCZ, n = 47.

‡Weekly methotrexate dose at the same month as biologic initiation was calculated using only dispensing claims due to missing prescription date information from inpatient/outpatient claims.

§Comorbidities at biologic initiation were identified by *International Classification of Diseases, Tenth Revision* (ICD-10) codes and/or by drug prescriptions (Anatomic Therapeutic Chemical [ATC] codes), or extracted using standard Japanese disease terms: renal failure, ICD-10 N18 or N19; interstitial pneumonia, standard disease term in Japan (間質性肺炎); COPD, ICD-10 J42, J43, J44; peptic ulcer, ICD-10 K25, K26, K27; chronic liver disease; ICD-10 K74, K73; depression, ICD-10 F32; osteoporosis, ICD-10 M80, M81, M82; diabetes, E10, E11, E13, E14 with ATC code A10.

the first-line biologic treatments were 37.7% (30.5–44.9), 52.3% (44.7–59.9), 55.8% (43.0–68.6), and 39.5% (25.3–53.6), respectively (Figure 5A). From the long-rank test, the unadjusted discontinuation rate was less with ETN as the first-line biologic compared with ADA and IFX ($P = 0.014$ and $P = 0.004$,

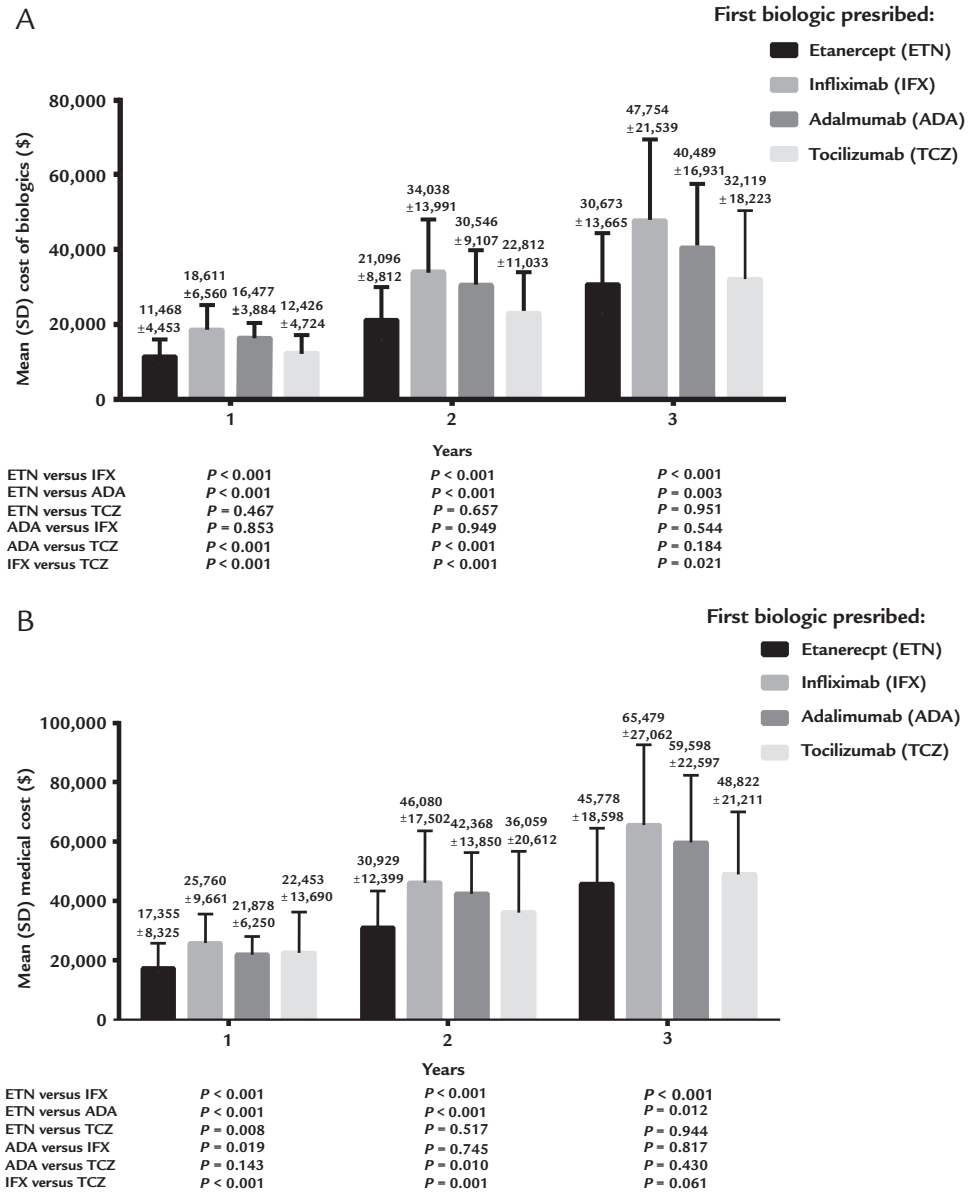

Figure 4. Cumulative biologic costs (A) and direct medical costs (B) incurred over 3 years after the initial prescription. Direct medical costs include cost of treatments for comorbidities. Data are given as mean (SD) US $ (1 yen = $0.01). *P* values obtained by Steel-Dwass test.

respectively) but did not largely differ between ADA, IFX, and TCZ (Figure 5A). Mean (95% CI) survival times (in months) with ETN, IFX, ADA, and TCZ were 28.1 (26.5–29.6), 24.5 (22.7–26.3), 24.4 (21.9–26.8), and 26.9 (24.0–29.9) (Figure 5A). Survival time was significantly longer with ETN versus ADA and IFX (both, $P < 0.05$). Because the distribution of age, sex, and methotrexate dose significantly differed between treatment groups, multivariate analyses with these baseline variables using a Cox proportional hazards model was conducted to estimate an adjusted HR of the discontinuation rate in each group. The adjusted HRs (95% CI) versus ETN (reference) were significantly greater for ADA and IFX (1.618 [1.132–2.313] and 1.534 [1.138–2.068]) (Table III).

Table II. Cost of concurrent medications and rheumatoid arthritis treatment-related costs. Data are given as mean (SD) US $ (1¥ = $0.01).

Item	ETN (n = 276)	IFX (n = 242)	ADA (n = 147)	TCZ (n = 99)
csDMARDs[*]				
1 y	748 (1042)	686 (840)	856 (1219)	868 (1483)
2 y	1478 (2098)	1417 (1858)	1558 (1534)	1703 (2721)
3 y	2404 (3463)	1955 (2186)	2392 (2761)	1986 (2424)
Oral corticosteroids[†]				
Year 1	30 (41)	27 (40)	26 (36)	35 (54)
Year 2	47 (69)	50 (77)	46 (72)	68 (109)
Year 3	64 (100)	64 (100)	64 (110)	92 (155)
NSAIDs[‡]				
Year 1	172 (271)	190 (253)	190 (235)	194 (264)
Year 2	300 (453)	314 (391)	408 (492)	306 (466)
Year 3	423 (618)	396 (459)	603 (648)	438 (632)
Self-injection management fee/outpatient chemotherapy premium				
Year 1	352 (363)[a, b]	205 (188)	206 (287)	325 (334)
Year 2	666 (713)[c]	370 (336)	412 (532)	508 (576)
Year 3	1013 (1029)[c, d]	506 (455)	425 (676)	736 (874)
Medical practice cost[§]				
Year 1	224 (118)[c, e]	215 (110)[f, g]	252 (115)	314 (256)
Year 2	413 (238)	414 (217)	459 (204)	506 (293)
Year 3	625 (332)	573 (307)	691 (302)	783 (540)
Medication cost for pneumonic diseases[‖]				
Year 1	7 (49)	27 (181)	16 (106)	43 (205)
Year 2	10 (49)	50 (334)	12 (52)	33 (92)
Year 3	29 (151)	82 (389)	7 (18)	47 (110)
Antimicrobials cost[¶]				
Year 1	50 (124)	68 (260)	38 (82)	111 (239)
Year 2	91 (207)	114 (364)	97 (172)	178 (351)
Year 3	151 (282)	167 (450)	126 (199)	334 (729)
Antidiabetic medication costs[#]				
Year 1	19 (117)	28 (146)	39 (254)	55 (207)
Year 2	29 (201)	57 (304)	54 (369)	84 (318)
Year 3	21 (220)	70 (338)	46 (232)	148 (435)

ADA = adalimumab; ETN = etanercept; IFX = infliximab; TCZ = tocilizumab; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; ATC = Anatomical Therapeutic Chemical.

[a]ETN vs IFX, $P < 0.01$.

[b]ETN vs ADA, $P < 0.01$.

[c]ETN vs ADA, $P < 0.05$.

[d]ETN vs IFX, $P < 0.05$.

[e]ETN vs TCZ, $P < 0.001$.

[f]IFX vs ADA, $P < 0.05$.

[g]IFX vs TCZ, $P < 0.001$.

[*]csDMARDs include actarit, auranofin, salazosulfapyridine, bucillamine, lobenzarit disodium, sodium aurothiomalate, D-penicillamine, tacrolimus, mizoribine, leflunomide, and methotrexate.

[†]ATC code H02A2 or H02B.

[‡]ATC code M01A (excluding leflunomide) or M02 (excluding prednisolone farnesylate).

[§]Medical practice cost includes medical consultation fee (chronic painful disease management fee); rheumatology-related tests (autoantibody test, immunological test interpretation fee, erythrocyte sedimentation rate); rheumatology-related surgery (synovectomy).

[‖]ATC code R03.

[¶]ATC code J01.

[#]ATC code A10.

The switching rates (95% CI) at month 36 were 12.5% (7.6%–17.3%) in the ETN group, 27.1% (19.5%–34.7%) in the IFX group, 31.0% (17.4%–44.6%) in the ADA group, and 16.7% (2.0%–31.4%) in the TCZ group. (Figure 5**B**). From the log-rank test, the unadjusted switching rate was less with ETN compared with ADA ($P = 0.003$) and IFX ($P = 0.006$) and with TCZ versus ADA ($P = 0.016$). HRs (95% CI) of the switching rates adjusted for age, sex, and methotrexate dose versus ETN (reference) were significantly greater for ADA and IFX (2.369 [1.358–4.131] and 1.972 [1.201–3.238]), and the HR versus ADA (reference) was significantly less for TCZ (0.363 [0.147–0.892]) (Table III).

Relative Dose Intensity Analysis

The estimated mean initial doses of ETN in the 25- and 50-mg dose groups were 27.4 and 56.1 mg/wk, respectively (Figure 6). Estimated mean initial doses appeared greater than the approved doses due to the method used for allocating patients into the 2 dosing categories (eg, patients receiving 17.5–37.5 mg/wk between months 2 and 3 were assigned to the ETN 25-mg dose group). Some patients may also have received 5 doses of ETN 50 mg in a 30-day period. The mean (95% CI) RDIs of the ETN 25 mg, ETN 50 mg, IFX, ADA, and TCZ groups until discontinuation were 1.02 (0.95–1.10), 0.82 (0.79–0.85), 1.16 (1.12–1.20), 0.95 (0.90–0.99), and 0.96 (0.93–1.00), respectively (Figure 6).

DISCUSSION

In this retrospective analysis of data from a Japanese claims database, the rate of discontinuation of ETN was the lowest among 3 TNF inhibitors and 1 interleukin-6 receptor inhibitor when used as the first-line biologic treatment. Direct biologic costs and cumulative medical costs were also lowest with ETN over all 3 years, despite the self-injection and outpatient chemotherapy-management fees being the greatest, which were thought to be offset by the lesser biologic cost. Administration costs were likely greater with ETN versus IFX owing to the ways that costs are recorded; self-injection management or outpatient chemotherapy premiums are physicians' management fees, which do not include the administration costs or transportation costs incurred with IFX administration.

Adherence to treatment has been associated with a reduction in overall medical costs in RA patients,[24] which could help to explain the lesser medical costs incurred with ETN use. The main reasons for poor adherence to TNF inhibitors in RA are lack of efficacy and AEs,[19,25] which implies that ETN is perceived as relatively efficacious and well-tolerated. Several studies support greater adherence rates with ETN compared with other TNF inhibitors.[25,26]

ETN is scored higher than IFX on the LUNDEX index, which is used for comparing the long-term efficacy and tolerability of biologic therapies for RA patients treated in clinical practice, mainly because of the greater rate of adherence to ETN therapy.[21] A review of the medical records of Japanese patients enrolled in the Osaka University Biologics for Rheumatic Diseases registry found that rates of continuation of TCZ and ETN were greater than those of IFX and ADA, and that discontinuation due to lack of efficacy was less in TCZ-treated patients.[27] When adjusting for baseline age, sex, and methotrexate dose, our Cox proportional hazards model showed similar results with the previous reports; risk for discontinuation was significantly greater in patients using ADA and IFX versus ETN.

The risk for drug discontinuation due to AEs was assessed in a group of patients enrolled in the Registry of Japanese RA Patients for Long-term Safety database.[22] In their Cox proportional hazards model, patients were significantly more likely to discontinue treatment with IFX (HR [95% CI] = 1.69 [1.14–2.51]) or TCZ (1.98 [1.04–3.76]) due to AEs than they were with ETN.[22] The risk for discontinuation due to AEs was also significantly greater in patients with increasing age by decade (HR [95% CI] = 1.64 [1.38–1.97]) and with the use of ≥ 3 previous conventional synthetic disease-modifying antirheumatic drugs (1.86 [1.30–2.67]).[22]

In our Cox proportional hazards model, among the variables included, the risk for discontinuation was significantly less for increasing methotrexate dose by 1 mg (HR [95% CI] = 0.969 [0.943–0.997]). The risk for discontinuation was significantly less for age ≥ 40 years, age < 60 years (0.661 [0.504–0.867]), and age ≥ 60 years (0.591 [0.395–0.885]) compared with age < 40 years. The greater risk for discontinuation in younger patients was inconsistent with findings from previous reports,[22,28] possibly owing to the small number of patients aged > 60 years and no data for those aged > 75 years in the JMDC database. There may also be an undetected cofounding factor for nonadherence to biologics treatment in patients aged < 40 years in this JMDC population. In a study of the

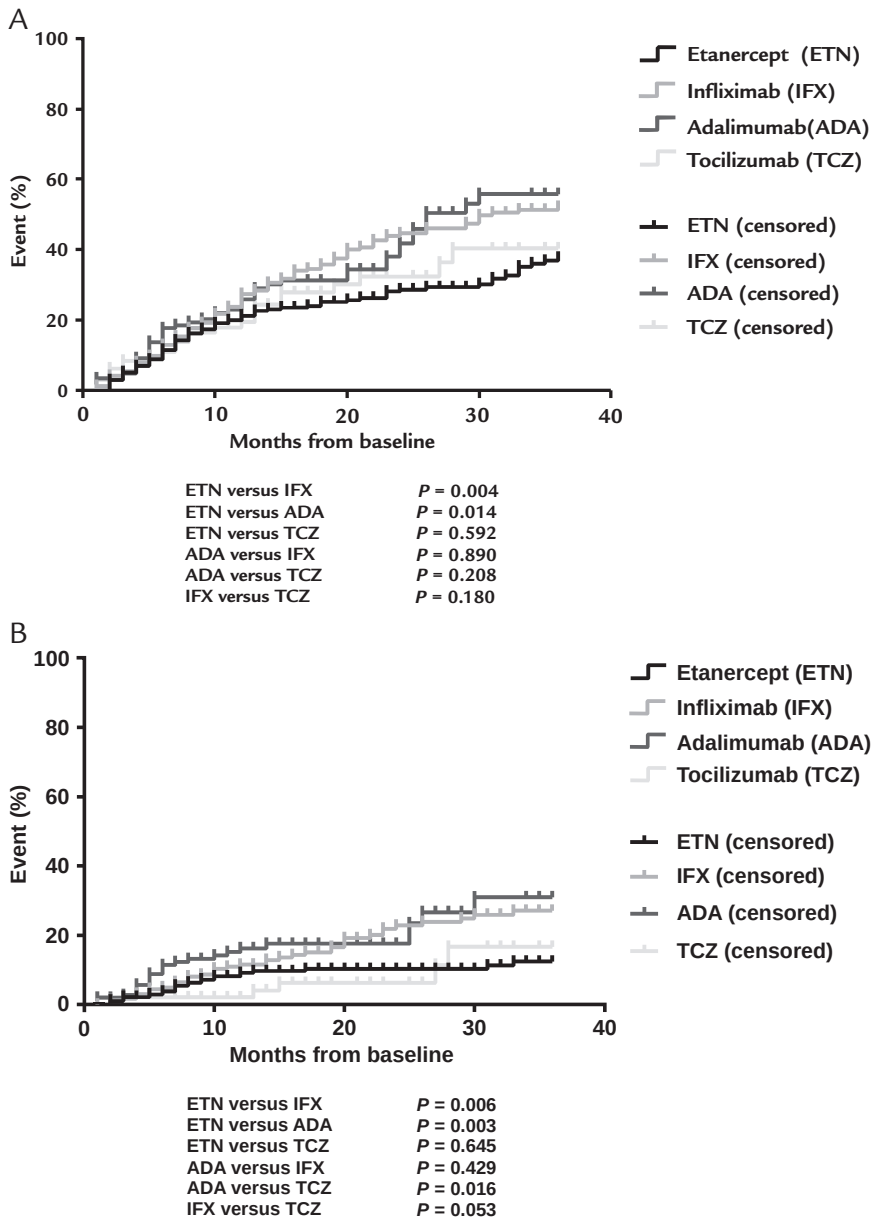

Figure 5. A, Biologic discontinuation event rate. B, Switching event rate. Discontinuation and switching rates in each group were estimated using Kaplan-Meier survival analysis. A *discontinuation* occurred when a drug was not prescribed for an administration interval longer than can be explained by the dosing schedule for each biologic (etanercept, 4 months; infliximab, 5 months; adalimumab, 4 months; tocilizumab, 4 months) or when one biologic was switched to another. Pairwise comparisons of discontinuation rates between treatment groups were analyzed by log-rank (Mantel-Cox) tests. A *switch* occurred when the first biologic prescribed was changed to an alternative biologic agent.

persistent use of glaucoma therapy in Japanese patients in the JMDC database, younger age was also associated with reduced persistence with treatment.[29]

It has been shown that health care resource utilization costs, mainly attributed to RA-related hospitalizations, are reduced when patients with RA

Table III. Cox proportional hazards regression results for biologic discontinuation* event rate and switching† event rate.

Variable	Hazard Ratio (95% CI)
End point = discontinuation rate	
ADA vs ETN	1.618 (1.132–2.313)
IFX vs ETN	1.534 (1.138–2.068)
TCZ vs ETN	1.153 (0.734–1.812
IFX vs ADA	0.948 (0.670–1.343)
TCZ vs ADA	0.713 (0.438–1.159)
IFX vs TCZ	1.331 (0.851–2.080)
Age ≥40–<60 y vs age <40 y	0.661 (0.504–0.867)
Age 60 y vs age <40 y	0.591 (0.395–0.885)
Male vs female	0.860 (0.634–1.167)
MTX dose (increase by 1 mg)	0.969 (0.943–0.997)
End point = switching rate	
ADA vs ETN	2.369 (1.358–4.131)
IFX vs ETN	1.972 (1.201–3.238)
TCZ vs ETN	0.859 (0.352–2.094)
IFX vs ADA	0.833 (0.500–1.386)
TCZ vs ADA	0.363 (0.147–0.892)
IFX vs TCZ	2.296 (0.966–5.455)
Age ≥40–<60 y vs age <40 y	0.732 (0.472–1.137)
Age 60 y vs age <40 y	0.653 (0.342–1.249)
Male vs female	0.885 (0.545–1.437)
MTX dose (increase by 1 mg)	0.996 (0.954–1.039)

ADA = adalimumab; ETN = etanercept; IFX = infliximab; MTX = methotrexate; TCZ = tocilizumab.

*An event was considered a *discontinuation* when the drug was not prescribed for an administration interval longer than can be explained by the dosing schedule for each biologic (etanercept, 4 months; infliximab, 5 months; adalimumab, 4 months; tocilizumab, 4 months) or when one biologic was switched to another.

†An event was considered a *switch* when the first biologic prescribed was changed to an alternative biologic agent.

achieve sustained remission.[30] Sustained remission and improved cost-effectiveness are better achieved when patients adhere to the treatment-to-target strategy.[31,32] In another study, while it was reported that treatment persistence was greater with IFX plus methotrexate compared with ADA plus methotrexate or ETN plus methotrexate, lesser nonpharmacy costs were associated with high persistence.[33] We observed that discontinuation rates were greatest with ADA, but that direct medical costs were greatest with IFX, suggesting that nonadherence is only one of the drivers of increased costs.

The cost of IFX treatment could be greater due to dose escalation in the early stages of treatment. In the literature, greater rates of dose escalation have been associated with higher related costs.[34–36] In this study, RDI analysis of IFX until discontinuation showed the actual dose to be 1.16-fold greater than the expected dose, which supports the practice of dose escalation. Systematic literature reviews and analyses of claims data have revealed that dose escalation is more common with IFX and ADA and less frequent with ETN.[34,35,37,38] It is important to acknowledge that the approval of dose escalation in the product labeling for IFX[39] and ADA[40] could result in more frequent dose escalation compared with ETN. However, if prescribers were more likely to avoid dose escalation with ETN in cases of insufficient efficacy, one might expect to observe greater rates of discontinuation or switching with ETN. This was not the case in our study, in which rates of discontinuation and switching when ETN was used as the first-line biologic were the lowest. In the Cox proportional hazards model, adjusted HRs for switching were significantly greater for ADA and IFX versus ETN, and the risk for switching from TCZ was significantly less versus ADA.

Dose reduction while maintaining efficacy has also been shown for ETN in the PRESERVE (Maintenance, Reduction, or Withdrawal of Etanercept After Treatment With Etanercept and Methotrexate in Patients With Moderate Rheumatoid Arthritis),[41] PRIZE (Sustained Remission With Etanercept Tapering in Early Rheumatoid Arthritis),[42] DOSERA (Full Dose, Reduced Dose or Discontinuation of Etanercept in Rheumatoid Arthritis)[43] clinical studies but has not been fully confirmed in Japanese clinical

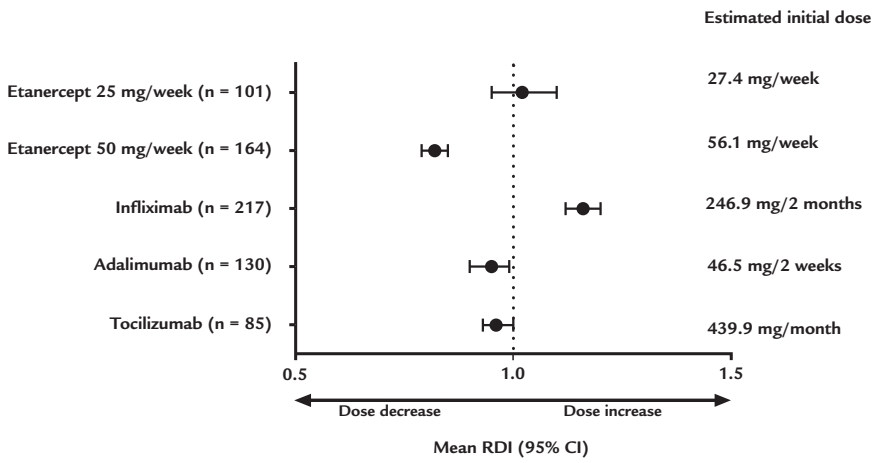

Figure 6. Mean relative dose intensity (RDI) for each drug until discontinuation. RDI = (Actual cumulative dose)/(Initial dose · Period until discontinuation).

settings. Here, we demonstrate that the RDI of ETN 50 mg was 0.82-fold less than that of the recommended highest dose, yet drug retention was the greatest of all of the biologics. Together with low discontinuation and switching rates, this finding suggests maintained efficacy at a reduced dose. It is also important to acknowledge that low-dose ETN (25 mg) is often prescribed as the first-line dose in Japan, to reduce economic and/or AE burden and/or to compensate for the generally lesser weight of Japanese individuals versus those from Western countries.[44] The tendency to reduce the dose of ETN during treatment, or to initially prescribe a lower dose, could also contribute to the lesser cost of ETN observed compared with other drugs.

Effective disease control achieved through intensive escalations of biologics in patients with nonresponse to conventional synthetic disease-modifying antirheumatic drugs is thought to be a justified use of societal resources.[15] Proactive control of disease activity has also been associated with lesser medical and nonmedical costs in a large-scale Japanese cohort.[45] However, rather than escalating the dose, it may be more cost-effective to switch to a biologic with a different mechanism of action if TNF inhibitors have failed.[15,46,47] An analysis from the Netherlands demonstrated that starting patients on biologics with a lesser risk for developing neutralizing antibodies (eg, ETN rather than ADA or IFX) increased drug retention and cost-effectiveness in the treatment of RA.[48] This finding is in agreement with those from this study, which showed that cumulative biologic costs and total costs were lowest when ETN was used as the first-line biologic agent but greatest when IFX and ADA were used first.

It is recognized that economic approaches differ among countries, so cost-effectiveness analyses cannot be generalized.[49,50] However, annual costs per treated patient with RA in a multistate Medicaid population were less with ETN ($18,466) than with ADA ($20,983) or IFX ($26,516).[51] ETN was also associated with the lowest drug and outpatient costs compared with IFX and ADA in a retrospective study of health plan costs.[52] In an analysis of data from >5000 patients with RA from the Optum Research Database, ETN was the most effective and had the lowest biologic cost per effectively treated patient with RA, compared with ADA, IFX, abatacept, and golimumab.[53] Some studies have suggested that TCZ may be more cost-effective than ADA monotherapy[54] and ADA or ETN when used in combination with methotrexate.[55] Cumulative medical costs of TCZ were similar to those of ADA but were greater than those of ETN in our study; however, further research is needed to determine the cost-effectiveness of the TCZ therapeutic strategy in this population.

This study may be limited by the retrospective nature of the analysis and the lack of randomization

of patients to treatment groups, leading to channeling bias. Also, first-line biologic use in biologic-naive patients was defined as that in patients who had no record of a biologic prescription in the 3 months before the first known prescription of the biologic in the JMDC database. It is therefore possible that some of the patients included in the study were actually prevalent users of biologics. The study is, however, representative of the prescribing situation in clinical practice in Japan. Efficacy data were also not available from the JDMC. While drug discontinuation rates can be used as a surrogate for therapeutic response, it should be considered that several other factors, such as drug tolerability, availability, and cost, may affect biologic-discontinuation rates. Assessments of clinical disease activity in each treatment group would inform a more thorough cost-effectiveness analysis. The ADA and IFX groups included more males (23.8%–29.8%) and fewer females (76.2%–70.2%) compared with the ETN group (19.6% vs 80.4%), which could have influenced therapeutic response[56] and adherence to treatment.[57] The JMDC database includes relatively few elderly individuals as a consequence of a separate medical insurance system for those aged >75 years in Japan. In addition, JMDC includes beneficiaries covered by an employee's health insurance system, so most beneficiaries are those of working age or their families. This analysis was therefore limited to patients aged <75 years, which may bias our findings. Medical costs may be expected to be greater in the elderly, so our data should be interpreted with this in mind. Finally, this study cannot estimate the total cost of RA because information on indirect costs was not included, and direct RA-related costs (excluding those of comorbidities) could not be estimated from the JMDC data.

CONCLUSIONS

Our retrospective analysis suggests that in Japan, if ETN is used as the first-line biologic, direct biologic and direct medical costs are less than those of other biologics, in part owing to the high therapeutic retentiveness of ETN. Low drug costs could be partially explained by the practice of ETN dose reduction and the preferred use of low-dose ETN in patients in Japan. We anticipate that our findings will help to guide prescribing decisions as well as support payers and/or government decision making with regard to medical costs. However, further research or prospective clinical studies are necessary to confirm our findings.

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CONFLICTS OF INTEREST

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SUPPLEMENTARY MATERIAL

Supplemental figure accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.03.022.

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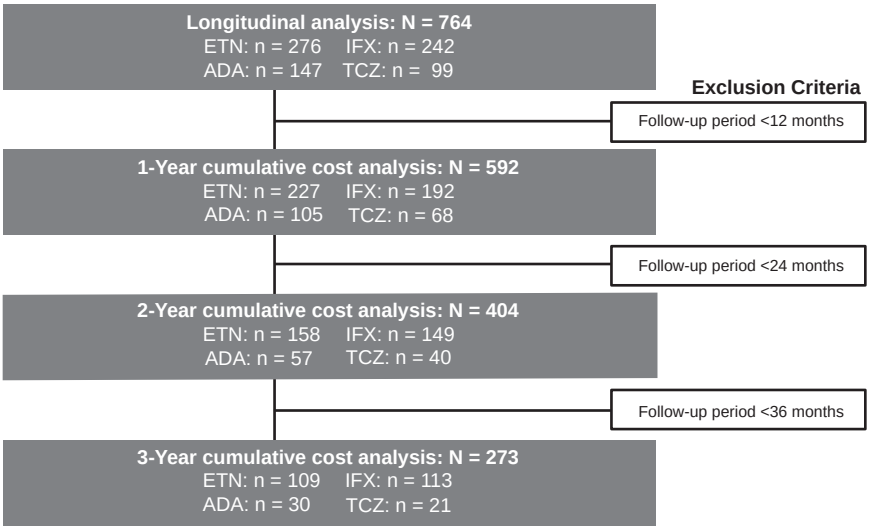
SUPPLEMENTARY MATERIAL

Figure. S1



Supplemental Figure. Cross-sectional cumulative cost analysis. The 1-, 2-, and 3-year cumulative cost for patients with rheumatoid arthritis followed up for >1, >2, or >3 years, respectively, after the initial prescription of biologics. Data from treatment groups were compared with those from a group of biologic-naive patients. ADA = adalimumab; ETN = etanercept; IFX = infliximab; TCZ = tocilizumab.