



Persistence with Biological Disease-modifying Antirheumatic Drugs and Its Associated Resource Utilization and Costs

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Abstract

Objective The study assessed persistence rates of biological disease-modifying antirheumatic drugs (bDMARDs) for the treatment of rheumatoid arthritis in Japan and compared resource utilization and treatment costs between persistence and non-persistence groups.

Methods Data were extracted from a Japanese claims database between 2009 and 2015. bDMARD-naïve patients were identified and included in the final analysis. Survival analysis was used to estimate 1-year persistence rates for current bDMARDs. Propensity score matching was applied to control for potential treatment selection bias. Resource utilization and healthcare costs were calculated 1 year before and after initiation of bDMARDs and compared between persistence and non-persistence groups.

Results A total of 6153 bDMARD-naïve patients were identified and the overall 1-year persistence rate was 85% (95% CI 84–86). Overall, 1-year outpatient visits increased from 10 at baseline to 16 after bDMARD treatment, while the number of hospital admissions declined from 3.3 to 1.6. The non-persistence group had a larger increase in outpatient visits after bDMARD initiation compared with the persistence group (8–16 vs. 10–16, respectively) and a smaller decrease in hospital admissions (3.1–1.9 vs. 3.5–1.4, respectively). Persistence was associated with a reduction in total healthcare costs of US\$760.

Conclusions Japanese bDMARD-naïve patients with RA have a high persistence rate with those treatments. The reduction in medication costs in non-persistent patients is offset by higher hospitalization costs, making non-persistence more expensive.

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Key Points

In general, drug survival of biological agents in Japanese patients with rheumatoid arthritis is high, indicating that relatively few patients discontinue their treatment.

Patients who discontinued their treatment or switched to another treatment caused higher costs to the healthcare system compared to patients who were persistent with their initial treatment.

1 Introduction

Rheumatoid arthritis (RA) is defined as a systemic autoimmune inflammatory disease characterized by chronic synovitis in multiple joints resulting in severe pain and deformity. The estimated prevalence of RA in Japan in 2011 was 1.24 million corresponding to 1.0% of the population [1].

Biological disease-modifying antirheumatic drugs (DMARDs) have improved the lives of many patients with RA and have been reported to delay and even halt the clinical progression of the disease [2]. Furthermore, biological DMARDs (bDMARDs) are not only effective in reducing symptoms [3], their use is also associated with a decrease in mortality [4].

Despite these documented benefits of bDMARDs in the treatment of RA, persistence rates, which refers to the duration of time from initiation to discontinuation of therapy [5], have been shown to vary considerably depending on the country, types of health centres as well as the specific drug being investigated. A systematic review of 52 studies reported 1-year persistence rates that ranged from 32.0 to 90.9% [6].

Few studies have evaluated persistence rates for bDMARDs in a Japanese population. One claims data analysis found that the overall 1-year persistence rate in Japan of 86% was higher than international rates. Of note, persistence rates for the bDMARD-naïve subpopulation were above 95%. Persistence was also higher for older patients and lower for patients with a high co-morbidity score [7]. A prospective cohort study evaluated patients who were treated with the bDMARDs infliximab (IFX), etanercept (ETN) or tocilizumab (TCZ) [8]. Compared with ETN, patients who took infliximab and tocilizumab were significantly more likely to discontinue treatment because of adverse events. Lastly, results from a Japanese Rheumatic Diseases registry suggested 1-year drug continuation rates between 73% for infliximab and 89% for tocilizumab [9].

With one notable exception from Sweden, few studies have calculated the cost implications of low persistence rates [10]. In the Swedish study, the authors compared the cost for patients who reliably took their medication over a 1-year period with that of patients who discontinued their treatment. Although patients who were non-persistent had lower drug costs, the authors found that this reduction in medication costs was counterbalanced by higher hospitalization costs, making non-persistence more costly than persistence. Another study using a US managed-care administrative claims database found that patients with a treatment persistence of > 80% had higher mean total healthcare costs compared with those with a treatment persistence of < 80%. This difference was largely due to higher pharmacy costs. However, non-pharmacy costs were lower in the persistence cohort [11]. Evidence also suggests that switching medications during treatment impacts healthcare costs. A US database study revealed that both first-line and second-line switchers had significantly higher monthly total healthcare costs after the switch than non-switchers (\$3759 vs. \$2343) and (\$3956 vs. \$2616), respectively [12].

While numerous factors have been found to impact persistence with bDMARDs and its impact on healthcare costs,

these results are not transferrable across countries and cultures. Therefore, we aimed to identify persistence rates for bDMARDs in a Japanese population of bDMARD-naïve patients, using a similar approach to that employed in the Swedish study. In addition, to broaden the scope of our investigation, we also evaluated RA-related drug costs since previous studies did not evaluate drug costs.

2 Methods

2.1 Data Source

We utilized commercially available hospital claims data from Medical Data Vision Co., Ltd. (MDV) This is an administrative database for inpatients and outpatients that includes approximately 4,400,000 patients and represents around 3% of the total Japanese population. The age distribution in the database is 13.5% 0–14 years old, 52.4% 15–64 years old, and 34.1% 65 years and older, and resembles that of the general population [13]. The data were obtained from hospital electronic information systems derived from 147 acute-phase hospitals throughout Japan. The hospitals operate 40,000 beds and are registered as Diagnosis Procedure Combination (DPC) hospitals. The DPC is a Diagnosis-Related Group (DRG)-like flat fee system that was introduced in 2003 for big hospitals in Japan [14]. Costs that occur outside this hospital network are not captured. The database had been used in health economic or epidemiological analyses of many different indications such as schizophrenia [15], influenza [16], infectious diseases [17], RA [18, 19], cardiovascular disease [20], diabetes [21], and prostate cancer [22, 23]. The time span of our analysis was from March 2009 to September 2015.

2.2 Study Population and Study Design

The study population was identified based on the International Classification of Diseases, 10th revision (ICD-10). Patients with RA were diagnosed as ICD 10: M05, M06.0, M06.2–M06.9. bDMARD-naïve patients were defined as patients who had received no prescriptions for biological agents during the first 3 months of their observation period. The 3-month ‘washout’ period is common in database analysis [24] and we choose this time period to ensure comparability across results of different database studies. Patients were required to have at least two diagnoses of RA and to have received at least two prescriptions for treatment of RA (DMARDs including bDMARDs). The following conventional DMARDs were identified for treatment in Japan: sulfasalazine (SSZ), methotrexate (MTX), leflunomide (LEF), tacrolimus (TAC), penicillamine (PNC), actarit, lobenzarit, iguratimod, bucillamine and gold salts.

Biological agents included infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira), golimumab (Simponi), abatacept (Orencia), tocilizumab (Actemra), certolizumab pegol (Cimzia), tofacitinib (Xeljanz). The index date was defined as the first claim for a bDMARD medication. At least 24 months of follow-up data in the database were also required for all eligible patients to determine healthcare utilization and cost (12 months prior to bDMARD initiation and 12 months after bDMARD treatment). We excluded children and patients < 18 years of age. In addition, because some bDMARDs are indicated in the treatment of certain diseases such as Crohn’s disease, psoriasis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis, we also excluded patients with the following diagnoses: Crohn’s disease, ankylosing spondylitis, juvenile idiopathic arthritis, psoriasis, ulcerative colitis and/or Behçet’s disease.

A total of six matched cohorts were created: golimumab (GOL) versus etanercept (ETN), GOL versus adalimumab (ADL), GOL versus infliximab (IFX), GOL versus certolizumab pegol (CTZ), GOL versus tocilizumab (TCZ) and GOL versus abatacept (ABT). GOL served as the anchor point in this analysis because a recent review concluded that GOL might be associated with higher persistence rates in a real-world setting [25].

2.3 Outcomes

2.3.1 Persistence Rates

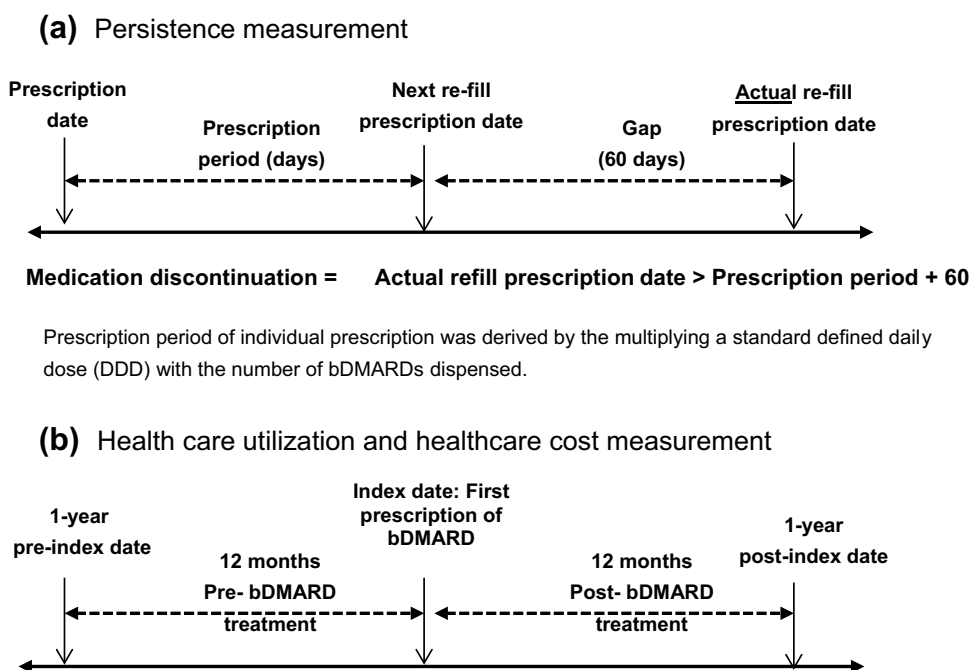
We used survival analysis to estimate 6-, 12-, and 18-month persistence rates for the bDMARDs GOL, ETN,

IFX, TCZ, ADL, ABT and CTZ. The persistence rate was defined as the time from treatment initiation (index date) until discontinuation of the index bDMARDs (Fig. 1a). This definition of persistence was consistent with that employed in other claims data-based studies of RA [10, 26] and other indications [27, 28].

In addition, a sensitivity analysis was performed with alternative gap definitions of 30 and 90 days. We defined the index date as the first bDMARD prescription in the database. Patients were categorized as discontinuing the index bDMARD treatment if either of the following occurred first: (1) a gap in the days’ supply of the index biological agent that exceeded the medication gap was encountered, or (2) the patient switched from the index bDMARD to other treatment(s) during the follow-up. In the base case, we used a medication gap of 60 days to define medication discontinuation. We also assessed the sensitivity of our results by using alternative gap definitions, namely 30 and 90 days.

To estimate the days’ supply of index medication, we referred to the standard recommended dose for RA treatment [29] for each bDMARD multiplied by the number of bDMARDs per prescription. We use the recommended dose and not the maximum dose that can be used for heavy patients. The prescription period of individual prescriptions was derived by multiplying a standard defined daily dose (DDD) with the number of bDMARDs dispensed (Online Supplementary material, Appendix 1).

Fig. 1 Persistence measurement and healthcare utilization measurement



2.3.2 Resource Utilization

Patients were allocated into two groups, a persistence and a non-persistence group, over a 12-month period and compared in terms of their resource utilization. Healthcare resource utilization was determined after at least 24 months of follow-up. [12 months before the index date (first initiation of bDMARD and 12 months after index date)] (Fig. 1 b). Healthcare resource utilization and associated costs included the following items:

- number of outpatient visits,
- number of all cause-hospitalizations,
- number of re-hospitalizations (re-hospitalization was defined as all-cause hospitalization within 30 days after a hospital discharge),
- length of stay (per hospitalization),
- cost accrued for specific treatments,
- overall cost of treatment.

All costs were converted to US dollars based on the exchange rate on 30 September 2016 (US\$1 = 101.08 Japanese Yen) [30] and adjusted for inflation using the consumer price index [31].

2.4 Statistical Analysis

Descriptive statistics were used to analyse demographic characteristics and treatment persistence with bDMARDs. Chi square and Wilcoxon rank sum tests were used to assess the difference between bDMARDs among bDMARD-naïve patients. A Kaplan–Meier analysis was used to calculate the persistence of bDMARD treatment. Differences in persistence were tested for significance using the Log Rank tests. A *p* value of ≤ 0.05 was considered statistically significant.

Propensity score matching: To control for potential confounders that could influence treatment initiation with a specific bDMARD, giving rise to selection bias, we employed a 1:1 propensity score-matching method, where patients not selected as a match are dropped from subsequent analyses. Matching attributes were age, gender and the Charlson co-morbidity index (CCI) score [32], using the previously described algorithms by Quan et al. [33].

The propensity score was derived from a logit model as the predicted probability of initiating treatment with a bDMARD given the baseline characteristics with a simple nearest-neighbour matching without replacement, conditional on the common support [34]. To compare the persistence rate of different bDMARDs, pairwise comparisons were performed using the bDMARD with the highest persistence rate as an anchor. Equality and balancing of covariates before and after matching was evaluated by the approach suggested by Rosenbaum and Rubin [35], in which

standardized bias before and after matching should be less than 5% after matching. The analysis was undertaken using STATA (StataCorp LP, College Station, TX, USA).

3 Results

3.1 Study Population

Based on the inclusion criteria, we identified 6153 bDMARD-naïve patients (Fig. 2).

Table 1 shows the patient characteristics of the bDMARD-naïve persistence and non-persistence groups. The mean age for the total sample was 59 years. The majority of patients were female with an average CCI score of 5 indicating a rather morbid population [20]. In addition, Online supplementary material, Appendix 2 provides an overview of the study population stratified by prescribed bDMARD.

3.2 Persistence

Figure 3 presents the Kaplan–Meier curve for the baseline case using a gap definition of 60 days. Overall, the 1-year persistence rate was 85% (95% CI 84–86).

For the base case, persistence rates ranged from 82% for ETN and IFX to 92% for GOL (Online supplementary material, Appendix 3). Online supplementary material, Appendix 3 also shows Kaplan–Meier curves using alternative gap definitions of 30 and 90 days as the sensitivity analysis. All values are also reported in Table 2. The results are robust towards the gap definition of 120 days, while a 30-day gap definition led to a stark decrease in persistence rates.

The results using propensity score adjusted survival rates and comparing GOL patients pairwise with GOL, ADL, IFX, CTZ, TCZ and ABT are plotted in Appendix 4.

3.3 Healthcare Utilization and Cost

Table 3 outlines the healthcare resource utilization before and after bDMARD treatment initiation stratified by persistence status. The overall sample had about ten outpatient visits at baseline and 16 visits after starting bDMARD treatment. The number of hospital admissions on the other hand declined from 3.3 to 1.6. Additionally, the number of days in hospital decreased from 17 to 12. The non-persistence group had a significantly higher increase in outpatient visits after bDMARD initiation compared with the persistence group (from 8 to 16 vs. 10 to 16, respectively) and a significantly lower decrease in hospital admission (from 3.1 to 1.9 vs. 3.5 to 1.4, respectively).

The associated costs are listed in Table 4. Overall, there was an annual increase in cost from US\$6747 to

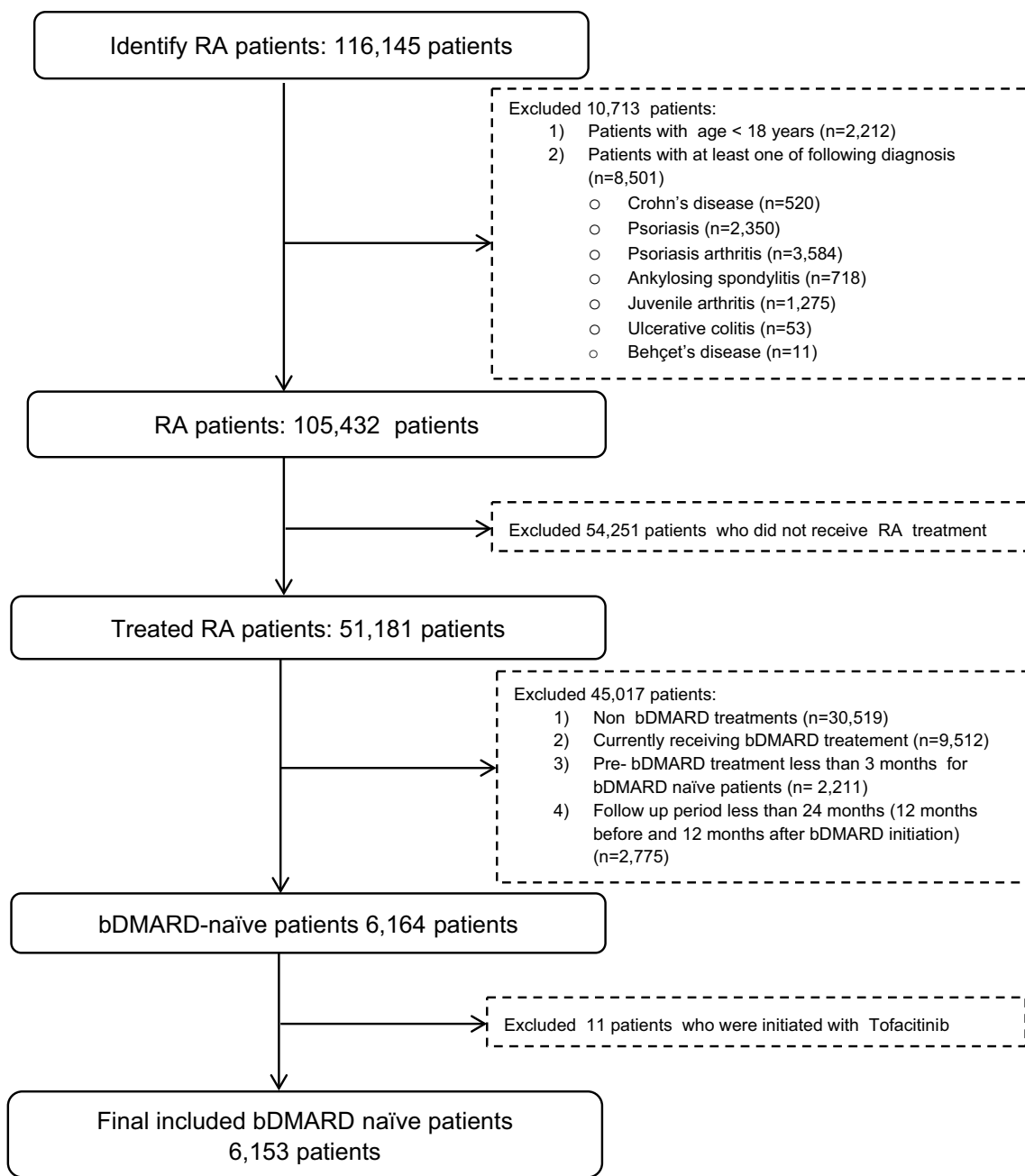


Fig. 2 Patient flow

US\$14,337 after starting bDMARD treatment. The cost increase was due to RA-related medication costs that increased from US\$3161 to US\$12,076. This increase in cost was partially offset by a decrease in hospitalization costs from US\$3072 to US\$1657. The cost increase was lower in the persistence group (US\$7397) than in the

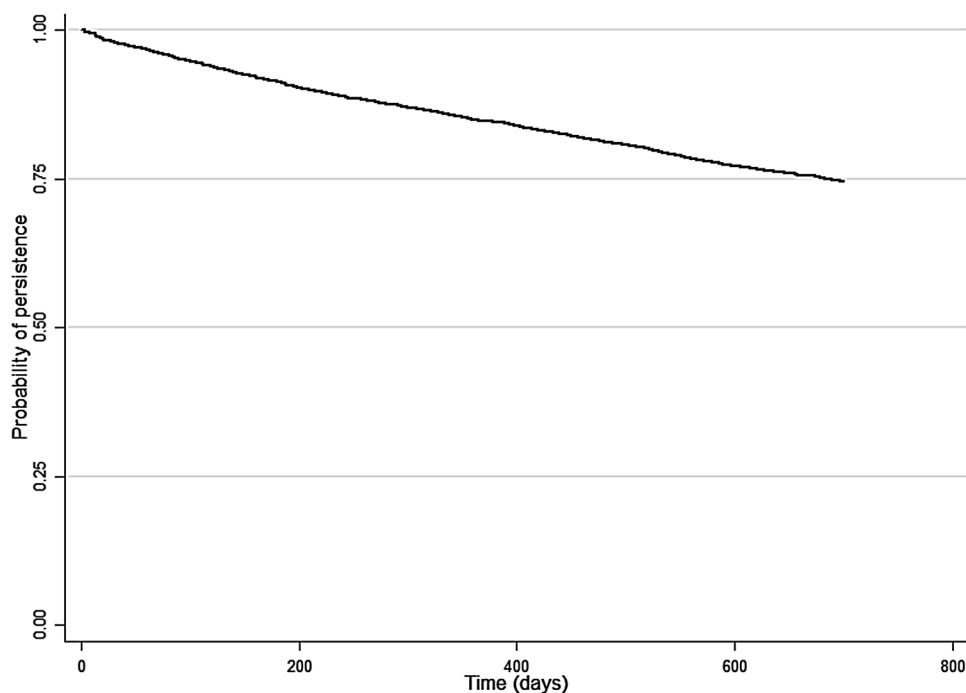
non-persistence group (US\$8157). Although RA-related medication costs increased by US\$9106 in the persistence group compared with US\$8629 in the non-persistence group, the reduction in hospitalization cost was greater in the persistence group (US\$-1814 vs. US\$-681).

Table 1 Patient characteristics of persistence vs. non-persistence in bDMARD-naïve groups

Characteristic, <i>N</i> (%)	bDMARD-naïve patients			<i>P</i> value
	Total	Persistence	Non-persistence	
RA patients	6153	4867 (79)	1286 (21)	
Age (mean ± SD)	59.20 ± 14.20	59.34 ± 14.29	58.69 ± 13.82	0.131
≤ 60 years	2882 (47)	2254 (46)	628 (49)	
61–70 years	1905 (31)	1505 (31)	400 (31)	
> 70 years	1366 (22)	1108 (23)	258 (20)	
Gender				0.198
Male	1398 (23)	1123 (23)	275 (21)	
Female	4755 (77)	3744 (77)	1011 (79)	
CCI score (mean ± SD)	5.01 ± 3.15	5.03 ± 3.16	4.97 ± 3.08	0.579
≤ 2	1341 (22)	1064 (22)	277 (22)	
3–5	2663 (43)	2094 (43)	569 (44)	
> 5	2149 (35)	1709 (35)	440 (34)	

Value present: persistence rate in percent and 95% confidence intervals by time point

bDMARDs biological disease-modifying antirheumatic drugs, CCI Charlson Co-morbidity Index, CI confidence interval, RA rheumatoid arthritis

Fig. 3 Persistence rate of all included patients

4 Discussion

4.1 Persistence Rates

Compared to the results from international studies of medication persistence, Japanese bDMARD-naïve patients have a higher persistence rate in the use of bDMARDs for the treatment of RA. The baseline rate of 85% for bDMARD-naïve patients is at the upper end of that reported in a

recent systematic review of 52 studies [6]. The Swedish study by Dalen et al. reported rates of 55–58%. Most other studies from other countries using real-world databases have also reported persistence rates only slightly above 50% [26].

This is not the first study to report high bDMARDs persistence and adherence in Japanese compared with Western patients across different indications [7]. This phenomenon has been attributed to both cultural beliefs and the authority status attributed to physicians in Japan [36]. Cultural

Table 2 Unadjusted persistence rates by prescribed bDMARDs

Time points (months)	Total RA patients (95% CI)	ETN (95% CI)	ADL (95% CI)	IFX (95% CI)	GOL (95% CI)	CTZ (95% CI)	TCZ (95% CI)	ABT (95% CI)
Base-case analysis (gap 60 days)								
6	91 (90–92)	88 (87–90)	93 (91–95)	90 (89–92)	95 (92–96)	97 (90–99)	92 (90–93)	93 (91–95)
12	85 (84–86)	82 (80–84)	88 (85–90)	82 (80–84)	92 (89–94)	91 (81–96)	86 (83–88)	87 (83–90)
18	79 (78–80)	76 (73–78)	82 (79–85)	76 (73–78)	88 (84–92)	87 (75–93)	81 (78–84)	79 (75–83)
Sensitivity analysis (gap 30 days)								
6	78 (76–78)	70 (68–73)	84 (81–86)	81 (79–83)	87 (84–90)	76 (65–83)	71 (68–74)	81 (77–84)
12	63 (62–65)	58 (55–60)	74 (70–77)	65 (62–67)	80 (76–84)	42 (30–53)	52 (48–56)	69 (65–73)
18	51 (49–52)	48 (45–51)	66 (62–70)	48 (46–51)	72 (66–77)	25 (14–38)	39 (35–43)	58 (53–63)
Sensitivity analysis (gap 90 days)								
6	95 (95–96)	93 (91–94)	95 (93–96)	96 (95–97)	98 (96–99)	98 (92–99)	95 (94–97)	96 (93–97)
12	92 (91–92)	88 (86–90)	91 (89–93)	93 (91–94)	96 (94–98)	97 (87–99)	92 (89–94)	92 (90–95)
18	88 (87–89)	84 (82–86)	86 (83–89)	90 (84–88)	92 (88–95)	90 (77–96)	89 (86–91)	90 (86–92)

Value present: persistence rate in percent and 95% confidence intervals by time point

ABT abatacept, ADL adalimumab, bDMARDs biological disease-modifying antirheumatic drugs, CI confidence interval, CTZ certolizumab pegol, ETN etanercept, GOL golimumab, IFX infliximab, RA rheumatoid arthritis, TCZ tocilizumab

attributes might also explain the high number of observed outpatient visits (9.6 per year in the overall sample), which is a direct consequence of a high persistence that results in a high frequency of monitoring and doctor's visits. This finding confirms OECD data that show Japan and Korea having the highest number of doctors' consultations within the OECD countries, with numbers being twice as high as for some Scandinavian countries [37].

Although we did not explore the reasons for the observed differences in persistence between different bDMARDs, potential explanations might be differences in efficacy and safety profiles [25, 38]. Another factor that is associated with persistence is the administration frequency: Patients using the monthly administration period had better adherence than those using more frequent dosing schedules [39].

A third explanation might be the so-called channelling bias that is defined as an "allocation bias, where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences" [40]. During our observation period new bDMARDs have been introduced to the Japanese market and possibly new drugs are prescribed to patients with pre-existing morbidities that would also influence the treatment persistence.

4.2 Healthcare Utilization and Costs

The Swedish study reported that persistence was associated with a cost savings of US\$987, while non-persistence led to a cost increase of US\$793 [10]. Of note, the cost of the bDMARDs was not included in this analysis. We found that, when the cost of medications was included, the increase in cost was actually smaller in the persistence compared with

the non-persistence group (US\$7397 vs. US\$8157, respectively). Therefore, persistence was associated with a cost savings of US\$760 per year, which translates into approximately two hospital admissions per year and 6 days in the hospital. While these findings suggest at first glance that persistence with bDMARDs for patients with RA leads to better outcomes in terms of costs and resource utilization, other factors must be taken into consideration. Patients in the non-persistence groups who discontinue their treatment because of severe side effects, for instance, may subsequently require additional treatments and/or hospitalizations. In such cases, the increase in cost and resource utilization is more directly related to adverse reactions to the bDMARD treatment per se. From a clinical perspective, the choice of bDMARDs should therefore be based not only a high continuation rate but also on a good side-effect profile.

Although we did not include indirect costs in our analysis, it is worth mentioning that the observed avoidance of one hospitalization for the persistent group likely corresponds with a smaller burden for patients and their families and less productivity costs for the total economy as a whole. Previous studies found that productivity costs in Japanese RA patients are indeed significant [41].

4.3 Limitations

There are several limitations to this study. Claims data analyses in general can only utilize a very limited set of medical parameters. As a result, we were unable to control for RA-specific disease severity, disease activity and disease duration at the time of bDMARD treatment initiation. We were also unable to determine the reasons for treatment

Table 3 Healthcare utilization before and after initiation of bDMARD treatment

Healthcare resource utilization	Overall (<i>n</i> =6153)	Persistence (<i>n</i> =4867)	Non-persistence (<i>n</i> =1286)	<i>P</i> value (persistence vs. non-persistence)
(1) 12 months prior to bDMARD initiation				
Number of OPD visits				
Mean ± SD	9.6 ± 9.2	10.1 ± 9.6	8.1 ± 9.7	<0.001
Median (IQR)	8 (3–13)	8 (4–13)	6 (2–11)	
Number of hospitalizations				
Mean ± SD	3.3 ± 3.0	3.5 ± 2.8	3.1 ± 2.8	0.510
Median (IQR)	3 (3–5)	3 (3–5)	3 (3–5)	
Length of stay				
Mean ± SD	17.2 ± 39.9	18.4 ± 21.8	16.9 ± 23.5	0.733
Median (IQR)	8 (3–29)	8 (4–30)	8 (3–27)	
Number of re-hospitalizations				
Mean ± SD	0.6 ± 0.4	0.7 ± 0.8	0.5 ± 0.8	0.205
Median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	
(2) 12 months post-bDMARD treatment initiation				
Number of OPD visits				
Mean ± SD	16.4 ± 13.99	16.4 ± 13.3	16.3 ± 13.9	0.757
Median (IQR)	13 (9–20)	14 (9–20)	13 (8–18)	
Number of hospitalizations				
Mean ± SD	1.6 ± 0.7	1.4 ± 0.7	1.9 ± 0.6	0.075
Median (IQR)	2 (1–3)	2 (1–3)	2 (1–4)	
Length of stay				
Mean ± SD	12.2 ± 19.1	12.5 ± 18.7	11.8 ± 21.0	0.198
Median (IQR)	12 (8–20)	12 (8–20)	12 (7–18)	
Number of re-hospitalizations				
Mean ± SD	0.3 ± 0.1	0.3 ± 0.6	0.2 ± 0.4	0.467
Median (IQR)	1 (0–1)	1 (0–1)	1 (0–1)	
Difference in healthcare resources prior to vs. post bDMARD initiation				
Number of OPD visits	6.7 (0.2), <0.001	6.3 (0.2), <0.001	8.2 (0.5), <0.001	– 1.9 (0.6), 0.072
Number of hospitalizations	–2.0 (0.2), <0.001	–2.1 (0.1), <0.001	–1.2 (0.2), <0.001	–0.9 (0.3), 0.042
Length of stay	–5.0 (1.1), <0.001	–5.9 (1.8), <0.001	–5.1 (1.1), 0.001	–0.9 (0.9), 0.653
Number of re-hospitalizations	–0.3 (0.1), <0.001	–0.4 (0.2), <0.001	–0.3 (0.1), <0.001	–0.1 (0.3), 0.411

bDMARDs biological disease-modifying antirheumatic drugs, *IQR* interquartile range, *OPD* Outpatient Department, *SD* standard deviation

discontinuation, which could have encompassed adverse events, lack of efficacy or even clinical remission. Also, the persistence rates might be biased downwards if Japanese patients use lower dosages due to weight differences. In that case, the medication supply would be longer for any prescribed drug. This implies that patients who do not refill their prescription might still be under treatment, and our analysis would classify them as being non-persistent. Our inclusion criteria of at least 24 months of coverage in the database might also give rise to a bias if we would have excluded a higher fraction of non-persistent patients relative to persistent patients. In addition, the matching algorithm that was employed to compare persistence rates of different bDMARDs accounts only for age, gender and CCI score. Further research should include other variables that

potentially influence persistence rates as well. Examples are concomitant use of MTX that was identified with a better treatment persistence [42].

Regarding medical costs and resource utilization, our analysis is limited to the costs that accrues within the hospital network and do not capture other health service utilization and costs that occur outside this network. Therefore, the estimates in this study provide only a lower bound and true costs might be even higher. However, as we have no reason to believe that either the persistent or the non-persistent group systematically differ in the utilization of external healthcare services, we do not think that this confounds our results.

Last, generalizability of these findings should be approached with caution. Because our data were generated

Table 4 Healthcare costs before and after initiation of bDMARD treatment

Healthcare resources	Overall		Persistence		Non-persistence		<i>P</i> value (persistence vs. non-persistence)
	12 months prior	12 months post	12 months prior	12 months post	12 months prior	12 months post	
Healthcare cost (US\$) (mean ± SD)							
Total OPD cost	3675 ± 1632	12,720 ± 1704	3664 ± 1657	12,874 ± 1691	3702 ± 1794	12,540 ± 1765	0.063/0.960
Laboratory cost	55 ± 16	54 ± 18	58 ± 17	52 ± 18	35 ± 406	60 ± 21	<0.001/0.233
Radiology cost	49 ± 16	38 ± 15	47 ± 16	34 ± 14	55 ± 17	40 ± 19	0.027/<0.001
Management cost (drug, counselling and general management)	151 ± 140	465 ± 244	156 ± 129	458 ± 238	130 ± 184	497 ± 264	0.011/0.036
RA-related medication cost	3161 ± 1257	12,076 ± 6258	3147 ± 1371	12,253 ± 6285	3215 ± 1,2,68	11,844 ± 6123	0.041/<0.001
Non-RA-related medication cost	225 ± 341	51 ± 577	277 ± 368	42 ± 447	215 ± 166	57 ± 975	0.393/0.019
Surgery and other procedure cost	29 ± 519	29 ± 465	25 ± 501	29 ± 474	47 ± 598	38 ± 420	0.921/0.703
Other cost	4 ± 47	6 ± 61	3 ± 49	6 ± 65	5 ± 38	5 ± 38	0.849/0.474
Total hospitalization cost	3072 ± 5194	1657 ± 4723	3283 ± 5024	1469 ± 4669	2950 ± 5925	2269 ± 4947	0.513/0.008
Total healthcare cost	6747 ± 5491	14,337 ± 11,001	6946 ± 5430	14,343 ± 5008	6652 ± 6280	14,809 ± 5440	0.793/0.412
Difference in healthcare costs prior to vs. post biological initiation (US\$) [mean (SE, <i>p</i> value)]							
Total OPD cost	9026 (6689), <0.001		9210 (6242), <0.001		8838 (6271), <0.001		372 (578), 0.010
Laboratory cost	−1 (17), 0.710		−7 (13), 0.07		25 (17), <0.001		−32 (68), 0.011
Radiology cost	−11 (11), 0.001		−13 (22), <0.001		−15 (32), 0.830		2 (6), 0.766
Management cost (drug, counselling and general management)	314 (125), <0.001		303 (270), <0.001		367 (288), <0.001		−65 (44), 0.021
RA-related medication cost	8915 (4834), 0.006		9106 (7582), <0.001		8629 (6343), <0.001		477 (148), 0.032
Non-RA-related medication cost	−174 (226), <0.001		−185 (39), 0.124		−158 (33), 0.018		−27 (11), 0.002
Surgery and other procedure cost	0 (8), 0.962		4 (1), 0.703		−10 (5), 0.451		14 (11), 0.416
Other cost	2 (8), 0.153		3 (0.9), 0.037		0 (174), 0.953		3 (2), 0.342
Total hospitalization costs	−1416 (1020), <0.001		−1814 (1137), <0.001		−681 (516), 0.001		−1132 (721), 0.021
Total healthcare costs	7630 (5057), 0.022		7397 (4549), 0.435		8157 (6101), 0.069		−760 (277), 0.034

bDMARDs biological disease-modifying antirheumatic drugs, *OPD* Outpatient Department, *RA* rheumatoid arthritis, *SD* standard deviation

from large Japanese DPC hospitals, we cannot rule out the existence of a bias towards patients whose RA was more

severe than that of the general patient population. The rather high CCI score in our sample supports this possibility. The

results may therefore not be representative of the daily practice of RA treatment in Japan.

5 Conclusion

Based on an administrative claims data set from large Japanese hospitals we found that Japanese patients with RA who had poor persistence with biological agents do cause higher costs to the healthcare system compared to patients who are persistent with their medications. The higher observed costs are mainly due to differences in the number of hospitalizations. Acknowledging several limitations of database studies, further studies are warranted to validate our findings in a clinical setting. Despite its limitations, this analysis highlights the relevance of defining drug persistence as a treatment goal in RA.

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Authors contributions JM and RS made substantial contributions to the conception and design, the acquisition of data, and the analysis and interpretation of data. JM drafted the manuscript. JM, HK and RS discussed the critical important intellectual content and revised the manuscript accordingly.

Compliance with Ethical Standards

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Conflict of interest JM and RS are affiliated with Janssen Pharmaceutical KK, a company that markets drugs for the treatment of RA. HK received research grants from Abbvie GK, Astellas Pharma, AstraZeneca K.K., Bristol–Myers K.K., Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Co., Novartis Pharma K.K., Takeda Pharmaceutical Co. Ltd.; speaking fees from AbbVie GK, Astellas Pharma, Ayumi Pharmaceutical Corporation, Bristol–Myers K.K., Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Novartis Pharma K.K., and Takeda Pharmaceutical Co. Ltd.; consultant fees from Abbvie GK, Eli Lilly Japan K.K., Novartis Pharma K.K., Nippon Kayaku Co. Ltd, Pfizer Japan Inc, UCB Pharma, Santen Pharmaceutical Co Ltd. and Sanofi K.K.

Availability of data and materials We used the MDV database, which is a third-party database commercially available from Medical Data Vision Co., Ltd., Tokyo Japan: <https://www.mdv.co.jp/company/outline/>, TEL: +81-3-5283-6911, FAX: +81-3-5283-6811, e-mail: ebm_sales@mdv.co.jp. Accessing the data involves a fee.

Ethics statement In the MDV database, the claim records of each patient are anonymously linked using de-identified codes, making it impossible to identify them.

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