



Available Alternative Biologics and Disease Groups Influence Biologic Drug Survival in Patients with Psoriasis and Psoriatic Arthritis

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Background: Factors other than efficacy and safety could influence the survival of biologics in patients with psoriasis. Little is known about whether different disease groups affect drug survival of biologics or not.

Objective: This study aimed to investigate whether the availability of alternative biologics and disease groups could influence drug survival of biologics approved for psoriasis and psoriasis arthritis (PsA).

Methods: A nationwide population-based retrospective cohort study was conducted using the Health Insurance and Review Assessment data in Korea between January 2009 and August 2019.

Results: The drug survival analysis included 5,634 biologic episodes. Ustekinumab was the most frequently prescribed drug (n=2,488, 44.2%). Multivariable time-dependent Cox regression analysis showed that higher age, female sex, no comorbidity, concomitant cyclosporine or acitretin use, biologic-experienced and use of tumor necrosis factor (TNF)- α inhibitors were predictors of drug discontinuation. PsA was a predictor of drug persistence, particularly for TNF- α inhibitors. Ustekinumab and adalimumab discontinuation significantly increased after introducing secukinumab and ustekinumab, respectively.

Conclusion: The availability of alternative biologics and disease groups affect biologic drug survival in patients with psoriasis and PsA.

Keywords: Arthritis, psoriatic, Biological products, Interleukin inhibitors, Psoriasis, Survival analysis, Tumor necrosis factor inhibitors

INTRODUCTION

The introduction of biologic agents over the past two decades has led to a significant shift in psoriasis and psoriatic arthritis (PsA) treatment paradigm¹. However, biologic treatment costs have been increasing as biologic therapies became the standard of care for these patients².

Better and more comprehensive methods to measure biologic drug effectiveness are needed to evaluate their cost-effectiveness. Improvement in clinical outcomes, such as the psoriasis area and severity index (PASI), has been the most

frequently used effectiveness measure. However, considering only the clinical outcomes as a measure of biologic agent effectiveness in daily practice might not reflect the patients' perception of treatment success³.

Drug survival is an increasingly used measure in daily practice to access biologic therapy effectiveness for psoriasis³. Drug survival was defined as the time interval between treatment initiation and discontinuation⁴. Drug survival is considered an overall marker for treatment success, as it informs on the effectiveness and safety of biologics in the real world³.

There are still significant gaps in understanding the long-



term efficacy of biologics. Open-label extension studies have indicated that most patients are likely to maintain the effect for years⁵⁻⁷. However, patients treated with biologic agents in the real world often have to discontinue treatment or switch biologic agents over time due to loss of effectiveness or the development of adverse events⁸.

Dermatologic drug survival studies were used for head-to-head comparisons between biologic agents for psoriasis treatment^{5,9}. Head-to-head comparisons are still a major target of drug survival studies; however, the results should be carefully interpreted because many factors affecting drug survival could change over time⁴. For example, introducing new drugs superior to old ones might influence drug survival. With limited treatment options to switch to, physicians maximize their efforts to keep patients on the current treatment⁴. However, the presence of better alternatives might make physicians less hesitant to switch to other drugs. Nevertheless, this hypothesis has not been investigated clearly.

Additionally, it is unknown whether biologic drug persistence differs between treatments for PsA and psoriasis. Comorbid PsA is usually associated with biologic persistence in patients with psoriasis¹⁰. However, a comparison between PsA and psoriasis as the primary diseases for prescription has not been investigated yet. In Korea, interleukin (IL)-23/IL-17A and tumor necrosis factor (TNF)- α inhibitors received insurance benefits for PsA and psoriasis.

This study used the Health Insurance and Review Assessment (HIRA) data in Korea to investigate whether alternative availability and different disease groups could influence the drug survival of biologic agents approved for psoriasis and PsA.

MATERIALS AND METHODS

Data source

We conducted a nationwide population-based retrospective cohort study using the HIRA data in Korea from January 2009 to August 2019 (HIRA research data M20200121233). The HIRA data are health insurance claims data, also known as the National Health Insurance (NHI) data, as they are generated in the process of reimbursing claims for healthcare services under the NHI system in Korea¹¹. The HIRA data contain information about all medical utilizations covered by the NHI for the entire Korean population. It includes information about age, sex, type of health insurance, type of medical

institutions, department, diagnostic codes based on the tenth revision of the International Classification of Diseases (ICD-10), and prescriptions¹². This study was exempt from the need for Institutional Review Board approval because the dataset consisted of deidentified secondary data (07-2020-3).

Study population

We first extracted all individuals who had an outpatient visit or admission history with an ICD-10 diagnostic code for plaque psoriasis (L40.* except for L40.1, L40.2, and L40.3) or PsA (M07.3, L40.5). Next, we identified patients with psoriasis and PsA prescribed biologics, including etanercept (ETA), adalimumab (ADA), infliximab (IFX), ustekinumab (UST), secukinumab (SEC), guselkumab (GUS), and ixekizumab (IXE). These biologics have been approved in Korea to treat both diseases. We did not include golimumab and certolizumab because golimumab did not receive insurance reimbursement for psoriasis, and certolizumab did not receive insurance benefits for either disease in Korea. Patients with a single visit per biologic episode during the follow-up period were excluded from the analysis because it was impossible to evaluate the biologic treatment persistence.

Insurance benefits were approved after the study start date (January 1, 2009) for UST (June 2012), SEC (August 2017), IXE (August 2018), and GUS (September 2018). Therefore, the first claim of these drugs was considered the start date of the biologic episode. ETA, ADA, and IFX received insurance benefits for diseases other than psoriasis or PsA even before the start date of our study. When the gap between January 1, 2009 (the study start date) and the first claim of ETA, ADA, or IFX met the definition of treatment discontinuation (as defined below), the first claim of the biologic was considered the biologic episode start date. Otherwise, we excluded those patients from the drug survival analyses as it was impossible to determine the treatment continuity before the study period or the start of a new treatment cycle after the study period.

Outcome and definitions

The biologic treatment persistence was defined as the time from initiation to discontinuation of the biologic prescription. To consider the dosing regimens and previous studies^{9,13}, treatment discontinuation (event) was defined as switching to other biologic or any gap in the treatment of >90 days for ETA, ADA, SEC, and IXE, >120 days for IFX and GUS, and >180

days for UST. Same drug treatment sequences were merged if used in two consecutive series.

Covariables

We recorded the age at the index date (the date of inclusion in the study cohort), age at the initiation date of each biologic episode, sex, number of biologic episodes, concomitant systemic treatment, and comorbidities for each patient. All included biologics were approved for treating both diseases; therefore, we categorized the patients based on disease groups as psoriasis alone, psoriasis with PsA, and PsA alone according to the principal diagnostic code of each biologic episode. Concomitant conventional systemic treatments included acitretin, methotrexate (MTX), and cyclosporine.

A patient was considered being with comorbidity other than PsA based on the principal diagnostic code during the follow-up period as follows: inflammatory bowel disease (K50, K51), ankylosing spondylitis (M45), rheumatoid arthritis (M05, M06, M08), hypertension (I10), diabetes mellitus (E10~E14), dyslipidemia (E78), major adverse cardiovascular events (I20~I25, I60~I69), hepatic disease (B18, I85, K70~K76), renal disease (N18), chronic obstructive pulmonary disease, and asthma (J40~J47, J96 except for J96.0, J98), tuberculosis (A15~A19), and cancer (C00~C97, D00~D09).

Statistical analysis

Categorical variables are presented as numbers (%), and continuous variables are shown as mean±standard deviation or median (interquartile range [IQR]).

The Kaplan-Meier method and log-rank test estimated the drug survival and assessed the differences in drug continuation for all biologics together and for each biologic separately. The Bonferroni correction was applied to correct for multiple comparisons. Univariable and multivariable time-dependent Cox regression analyses evaluated the association between drug survival and independent variables at the start date of each biologic episode. The independent variables included age, sex, disease groups, the biologic type, the number of previously used biologics, concomitant systemic treatment, and comorbidities. An interaction term between the modes of action of biologics (TNF- α inhibitors vs. non-TNF- α inhibitors) and disease groups was included in Cox regression to evaluate the effect of disease groups on drug survival according to the mode of action. Additionally, we compared drug survival rates

for the periods before and after the introduction of UST (June 2012) for ADA and SEC (August 2017) for UST. We selected these biologics because they had enough data (patients and follow-up) for the analysis.

Analyses were performed using SAS Enterprise Guide Version 6.1 (SAS Institute Inc., Cary, NC, USA) and R, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided, and statistical significance was set at $p < 0.05$.

RESULTS

We identified 4,852 patients with 6,053 biologic episodes of psoriasis or PsA during the study period. For ETA, ADA and IFX, 59 biologic episodes were excluded from the drug survival analysis because they had already received biologic treatment before the study period. We also excluded 360 biologic episodes with a single visit during the follow-up period. Finally, 5,634 biologic episodes were included in the drug survival analysis.

Patient characteristics

Table 1 presents the baseline characteristics of the 5,634 biologic episodes. UST was the most frequently prescribed biologic ($n=2,488$, 44.2%), followed by ADA ($n=1,049$, 18.6%). The overall mean age of the cohort was 44.8 ± 13.8 years and males predominated ($n=3,843$, 68.2%). Three TNF- α inhibitors (ETA, ADA, and IFX) were prescribed to treat PsA more frequently than UST, SEC, GUS, and IXE. UST had the longest follow-up, with a median of 87.0 weeks (IQR 40.3~177.0 weeks), followed by ADA with a median of 66.0 weeks (22.1~136.6 weeks).

Predictive factors of biologic drug survival

Of the total 5,634 biologic episodes, 1,642 were terminated during the follow-up period. Table 2 presents the results of the univariable and multivariable analyses investigating predictors of drug survival. UST was considered the reference standard to which the other biologics were compared because it was the most frequently prescribed biologic in our cohort.

The univariable time-dependent Cox regression analysis showed that female sex, patients with psoriasis alone, concomitant systemic therapy (cyclosporine, MTX, or acitretin), previous experience with biologics, no comorbidity, and be-

Table 1. Demographics based on biologic episodes at the time of biologic therapy

Demographic	Etanercept	Adalimumab	Infliximab	Ustekinumab	Secukinumab	Guselkumab	Ixekizumab	All
No. of patients	369	1,049	195	2,488	738	679	116	5,634
Age (yr)	43.4±13.7	43.9±14.3	41.7±13.8	45.1±13.8	45.8±13.2	45.4±13.7	47.7±12.5	44.8±13.8
Male	234 (63.4)	702 (66.9)	124 (63.6)	1,720 (69.1)	511 (69.2)	475 (70.0)	77 (66.4)	3,843 (68.2)
Indication for biologics								
Psoriasis alone	198 (53.7)	593 (56.5)	105 (53.8)	1,780 (71.5)	539 (73.0)	495 (72.9)	91 (78.4)	3,801 (67.5)
Psoriasis+PsA	88 (23.8)	272 (25.9)	45 (23.1)	699 (28.1)	163 (22.1)	182 (26.8)	25 (21.6)	1,474 (26.2)
PsA alone	83 (22.5)	184 (17.5)	45 (23.1)	9 (0.4)	36 (4.9)	2 (0.3)	0 (0.0)	359 (6.4)
Concomitant systemic therapy								
Cyclosporine	77 (20.9)	119 (11.3)	33 (16.9)	207 (8.3)	34 (4.6)	12 (1.8)	3 (2.6)	485 (8.6)
Methotrexate	230 (62.3)	512 (48.8)	118 (60.5)	297 (11.9)	88 (11.9)	12 (1.8)	2 (1.7)	1,259 (22.3)
Acitretin	37 (10.0)	55 (5.2)	15 (7.7)	102 (4.1)	8 (1.1)	5 (0.7)	2 (1.7)	224 (4.0)
Phototherapy	3 (0.8)	11 (1.0)	1 (0.5)	16 (0.6)	1 (0.1)	0 (0.0)	0 (0.0)	32 (0.6)
Type of medical center								
Tertiary referral hospital	269 (72.9)	730 (69.6)	123 (63.1)	1,591 (63.9)	480 (65.0)	402 (59.2)	84 (72.4)	3,679 (65.3)
General hospital	86 (23.3)	299 (28.5)	61 (31.3)	864 (34.7)	254 (34.4)	236 (34.8)	32 (27.6)	1,832 (32.5)
Private clinic and others	14 (3.8)	20 (1.9)	11 (5.6)	33 (1.3)	4 (0.5)	41 (6.0)	0 (0.0)	123 (2.2)
Insurance type								
Health insurance	349 (94.6)	1,003 (95.6)	182 (93.3)	1,382 (95.7)	688 (93.2)	657 (96.8)	109 (94.0)	5,370 (95.3)
Medical aid	20 (5.4)	46 (4.4)	13 (6.7)	106 (4.3)	50 (6.8)	22 (3.2)	7 (6.0)	264 (4.7)
Total number of comorbidities* (excluding psoriasis and PsA)								
No comorbidities	118 (32.0)	396 (37.8)	47 (24.1)	1,192 (47.9)	411 (55.7)	454 (66.9)	74 (63.8)	2,692 (47.8)
1	148 (40.1)	392 (37.4)	91 (46.7)	750 (30.1)	245 (33.2)	180 (26.5)	30 (25.9)	1,836 (32.6)
2	74 (20.1)	169 (16.1)	32 (16.4)	349 (14.0)	63 (8.5)	37 (5.4)	8 (6.9)	732 (13.0)
3 or more	29 (7.9)	92 (8.8)	25 (12.8)	197 (7.9)	19 (2.6)	8 (1.2)	4 (3.4)	374 (6.6)
Previous biologic therapies								
0 (naïve)	341 (92.4)	882 (84.1)	158 (81.0)	2,309 (92.8)	420 (56.9)	387 (57.0)	71 (61.2)	4,568 (81.1)
1	23 (6.2)	149 (14.2)	29 (14.9)	151 (6.1)	239 (32.4)	236 (34.8)	25 (21.6)	852 (15.1)
2 or more	5 (1.4)	18 (1.7)	8 (4.1)	28 (1.1)	79 (10.7)	56 (8.2)	20 (17.2)	214 (3.8)
No. of events	232 (62.9)	456 (43.5)	121 (62.1)	723 (29.1)	101 (13.7)	4 (0.6)	5 (4.3)	1,642 (29.1)
Follow-up time (wk)								
Median	61.0	66.0	62.0	87.0	37.4	12.7	16.1	52.0
Interquartile range	12.0~154.7	22.1~136.6	17.5~154.2	40.3~177.0	15.9~61.9	4.2~21.0	8.0~28.0	19.7~127.1

Values are presented as mean±standard deviation or number (%). PsA: psoriatic arthritis. *Comorbidities include any of the following: inflammatory bowel disease, ankylosing spondylitis, rheumatoid arthritis, hypertension, diabetes mellitus, dyslipidaemia, major adverse cardiovascular event, hepatic disease, renal disease, chronic obstructive pulmonary disease or asthma, tuberculosis, and cancer.

ing treated with a TNF- α inhibitor (ETA, ADA, or IFX) were significantly associated with discontinuation of the biologic treatment (Fig. 1). In the multivariable analysis, female sex, concomitant systemic therapy (cyclosporine or acitretin), treatment with a TNF- α inhibitor (ETA, ADA, or IFX), previ-

ous experience with biologics, and no comorbidity were still predictors of biologic discontinuation. Higher age was a predictor of biologic discontinuation and PsA (PsA alone, psoriasis with PsA) was a predictor of drug survival after adjusting for covariates. Concomitant MTX use was not associated with

Table 2. Univariable and multivariable analyses for biologic drug discontinuation

Demographic	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.002 (0.999~1.006)	0.2144	1.010 (1.006~1.015)	<0.0001
Sex				
Male	1 (reference)		1 (reference)	
Female	1.134 (1.017~1.265)	0.0241	1.131 (1.017~1.259)	0.0233
Indication for biologics				
Psoriasis alone	1 (reference)		1 (reference)	
Psoriasis+PsA	0.793 (0.702~0.896)	0.0002	0.713 (0.626~0.811)	<0.0001
PsA alone	1.057 (0.878~1.272)	0.5562	0.659 (0.543~0.800)	<0.0001
Insurance type				
Medical aid	1 (reference)		1 (reference)	
Health insurance	0.943 (0.755~1.178)	0.6053	0.870 (0.696~1.087)	0.2195
Concomitant systemic therapy				
Cyclosporine	2.382 (2.052~2.766)	<0.0001	1.989 (1.715~2.306)	<0.0001
Methotrexate	1.438 (1.290~1.604)	<0.0001	1.058 (0.921~1.214)	0.4270
Acitretin	1.902 (1.563~2.315)	<0.0001	1.341 (1.084~1.660)	0.0070
Previous biologic therapies				
0 (naïve)	1 (reference)		1 (reference)	
1	1.805 (1.539~2.117)	<0.0001	1.820 (1.535~2.160)	<0.0001
2 or more	2.122 (1.573~2.863)	<0.0001	2.492 (1.804~3.443)	<0.0001
Number of patients with comorbidities (excluding psoriasis and PsA)				
No comorbidities	1 (reference)		1 (reference)	
1	0.963 (0.853~1.086)	0.5362	0.822 (0.726~0.930)	0.0019
2	0.841 (0.724~0.977)	0.0237	0.671 (0.568~0.793)	<0.0001
3 or more	0.594 (0.487~0.726)	<0.0001	0.427 (0.343~0.531)	<0.0001
Biologic therapy				
Ustekinumab	1 (reference)		1 (reference)	
Etanercept	2.354 (1.990~2.784)	<0.0001	2.537 (2.088~3.082)	<0.0001
Adalimumab	1.810 (1.608~2.036)	<0.0001	1.900 (1.656~2.181)	<0.0001
Infliximab	2.466 (1.992~3.052)	<0.0001	2.824 (2.264~3.523)	<0.0001
Secukinumab	1.230 (1.003~1.509)	0.0469	0.942 (0.765~1.161)	0.5778
Guselkumab	0.115 (0.043~0.306)	<0.0001	0.091 (0.034~0.245)	<0.0001
Ixekizumab	0.718 (0.295~1.748)	0.4649	0.528 (0.218~1.277)	0.1561

CI: confidence interval, HR: hazard ratio, PsA: psoriatic arthritis.

drug discontinuation after adjusting for covariates, although concomitant cyclosporine or acitretin use was associated with drug discontinuation. The insurance type was insignificant in the univariable and multivariable analyses in our cohort.

We compared the drug survival of biologics in association with the disease groups in search of a difference in drug

survival among diseases (Fig. 2). ADA showed longer drug survival in psoriasis with PsA ($p<0.0001$; hazard ratio [HR], 0.567; 95% CI, 0.444~0.726) and PsA alone ($p<0.0001$; HR, 0.555; 95% CI, 0.428~0.720) than in psoriasis alone (Fig. 2B). ETA and IFX showed similar results (Fig. 2A, C). UST showed higher drug discontinuation in PsA alone ($p=0.0016$; HR,

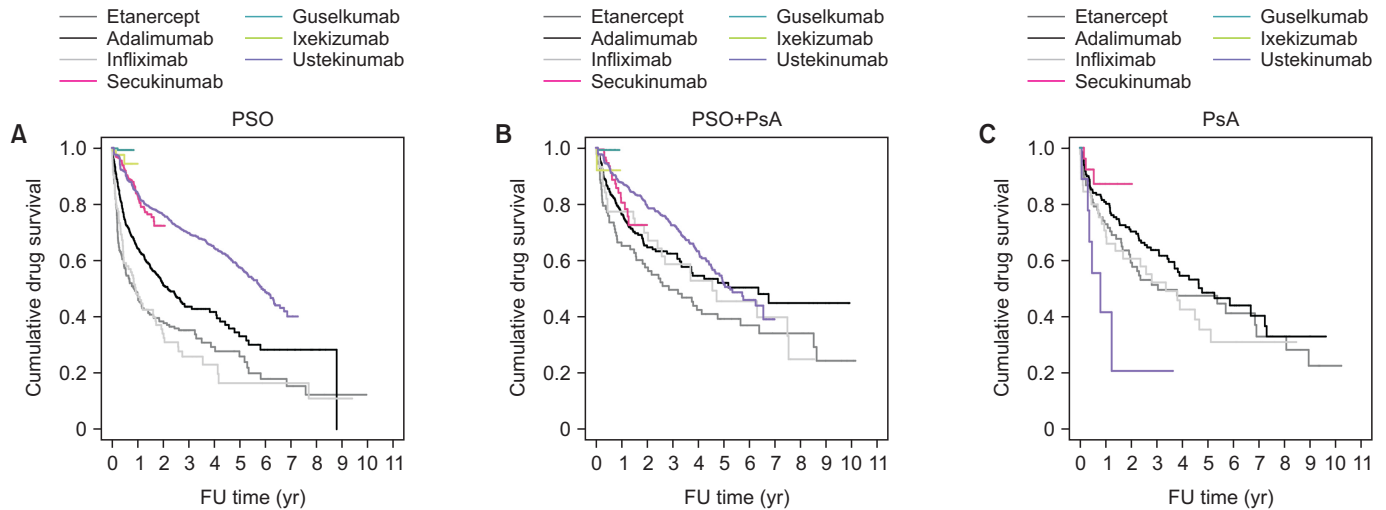


Fig. 1. Biologic drug survival in patients with psoriasis (PSO) or psoriatic arthritis (PsA). (A) Crude biologic drug survival in patients with PSO alone. (B) Crude biologic drug survival in patients with PSO and PsA. (C) Crude biologic drug survival in patients with PsA alone. FU: follow-up.

5.833; 95% CI, 2.160~15.751) than in psoriasis alone (Fig. 2D); although, the number of patients with PsA alone in UST was sparse ($n=9$). In contrast, SEC, GUS, IXE showed no significant differences in drug survival among disease groups (Fig. 2E~G). These findings suggested that the effects of disease groups might be different according to the different modes of action (TNF- α inhibitor vs. non-TNF- α inhibitor). Next, we analyzed data adding an interaction term, mode of action (TNF- α inhibitor [ETA, ADA, IFX] vs. non-TNF- α inhibitor [UST, SEC, GUS, IXE]) $\times$ disease group. There was a significant interaction effect of mode of action $\times$ disease group after adjusting for covariates ($p<0.0001$). For non-TNF- α inhibitors, there was no significant difference in drug survival according to disease groups ($p=0.1569$). For TNF- α inhibitors, psoriasis with PsA (HR, 0.550; 95% CI, 0.452~0.670; $p<0.0001$) and PsA alone (HR, 0.591; 95% CI, 0.483~0.724; $p<0.0001$) were associated with longer drug survival compared with psoriasis alone.

Effects of alternatives' availability on adalimumab and ustekinumab drug survival

We compared the ADA drug survival rate between before and after the availability of UST (June 2012) and the UST drug survival between before and after the availability of SEC (August 2017). The discontinuation rate of ADA started after the introduction of UST was higher than ADA started before UST became available (log-rank test, $p=0.0097$). The difference in ADA drug survival according to the availability of

UST was insignificant at one year ($p=0.3431$; difference 6.2%; 95% CI, -6.6%~19.0%), but significant at two years ($p=0.0377$; difference 15.5%; 95% CI, 0.8%~30.2%).

We found the same trend in UST drug survival when comparing the periods before and after SEC became available (Fig. 3B). SEC is the first IL-17A inhibitor and superior to UST in efficacy¹⁴. The UST drug survival rate after the introduction of SEC was lower than before SEC introduction (log-rank test, $p=0.0001$). This trend was sustained for one year ($p=0.0082$; difference 5.1%; 95% CI, 1.3%~8.9%) and two years ($p=0.0273$; difference 6.8%; 95% CI, 0.8%~12.8%).

DISCUSSION

This study investigated drug survival of biologics for psoriasis or PsA using the HIRA data in Korea. We found that higher age, female sex, no comorbidity, concomitant cyclosporine or acitretin use, biologic-experienced, and use of TNF- α inhibitors were predictors of drug discontinuation. PsA was a predictor of drug persistence, particularly for TNF- α inhibitors. Drug discontinuation of UST and ADA significantly increased after the introduction of superior alternatives.

ADA and UST drug survival rates were compared in this study according to the availability of alternatives. We found that drug survival dropped after the introduction of a superior alternative. A recent meta-analysis of biologic drug survival suggested that UST showed a longer drug survival than SEC

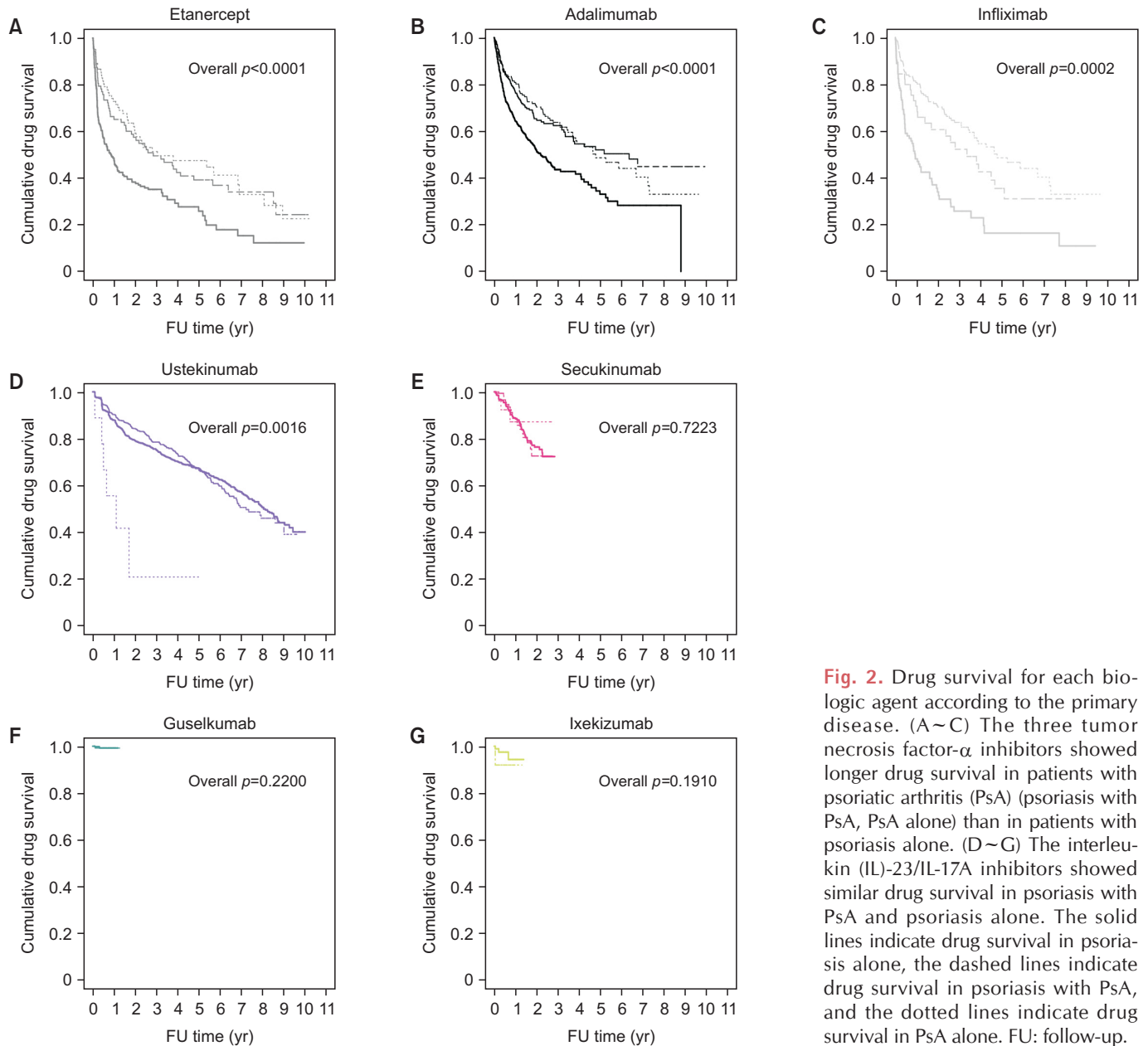


Fig. 2. Drug survival for each biologic agent according to the primary disease. (A~C) The three tumor necrosis factor- α inhibitors showed longer drug survival in patients with psoriatic arthritis (PsA) (psoriasis with PsA, PsA alone) than in patients with psoriasis alone. (D~G) The interleukin (IL)-23/IL-17A inhibitors showed similar drug survival in psoriasis with PsA and psoriasis alone. The solid lines indicate drug survival in psoriasis alone, the dashed lines indicate drug survival in psoriasis with PsA, and the dotted lines indicate drug survival in PsA alone. FU: follow-up.

and TNF- α inhibitors¹⁵. UST was the first biologic to directly inhibit the IL-23/IL-17A pathway that received the US FDA approval (September 2009)¹⁶, followed by SEC (January 2015)¹⁶. In other words, UST was the only biologic targeting the IL-23/IL-17A pathway available for psoriasis for more than five years. This suggests that UST drug survival in previous reports might have been overestimated.

Comparisons of drug survival between biologics are the main purpose of drug survival analysis⁴. We found that TNF- α inhibitors had a lower drug survival rate than UST, consistent

with previous studies^{8,17}. However, it was difficult to compare the drug survival of GUS and IXE because their follow-up was relatively short than that of other biologics. When biologics are switched in Korea, continuous treatment for over 6 months is strongly recommended under the insurance coverage.

We found an association between female sex and biologic discontinuation as in previous studies^{8,10}. A recent meta-analysis compared males and females and showed that the female sex had a pooled HR of 1.22 for discontinuation¹⁰. The reason for lower drug persistence rates in female patients is currently

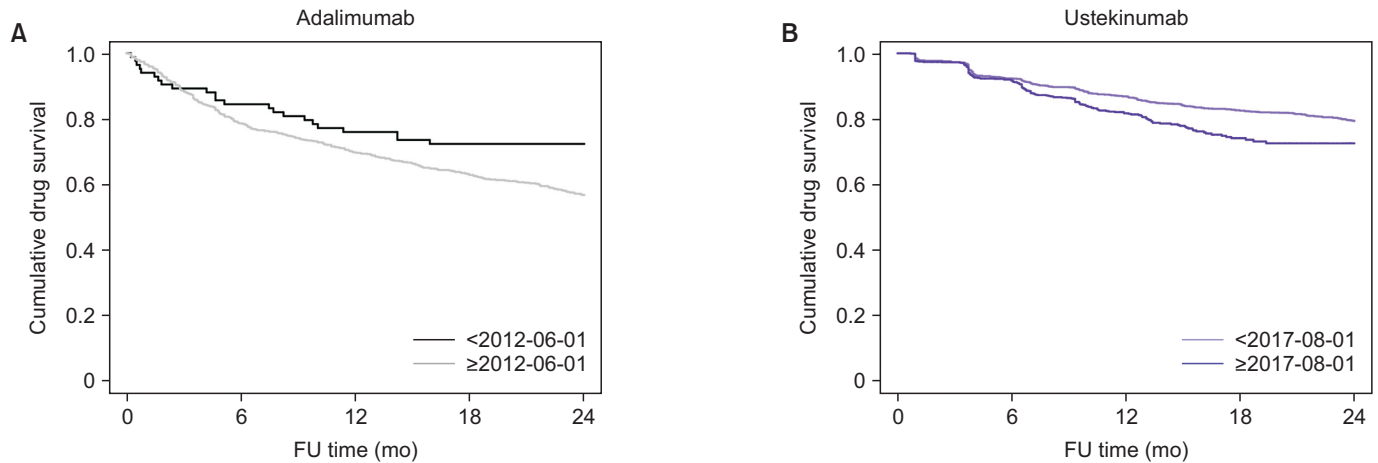


Fig. 3. The effect of alternative availability on biologic drug survival. (A) Adalimumab drug survival before and after the introduction of ustekinumab (June 2012) were compared. (B) Ustekinumab drug survival was evaluated according to the availability of secukinumab (as of August 2017). FU: follow-up.

unknown, although adverse events seem to play a role in biologic discontinuation in female patients⁹.

Our results showed that concomitant MTX use was not associated with drug discontinuation although concomitant cyclosporine or acitretin use was associated with biologic drug discontinuation. Physicians may prescribe nonbiologic systemic agents during biologic therapy when they believe the patients are particularly recalcitrant. Unlike cyclosporine or acitretin, concomitant use of MTX is known to be a positive predictor for drug survival in patients with psoriasis probably due to its ability to reduce the immunogenicity of biologic agents¹⁸⁻²⁰.

To the best of our knowledge, this study was the first to compare drug survival between patients with psoriasis and PsA. Previous studies on biologic drug survival were performed independently in patients with psoriasis or PsA. We only included biologics approved to treat both diseases in Korea and compared their drug survival rates. Little is known about the comparative drug effectiveness in different disease groups. Comparing drug survival between disease groups could provide insight into whether knowledge could be exchanged between those groups⁴.

Our results demonstrated that patients with PsA (PsA alone, psoriasis with PsA) showed longer biologic drug survival than patients with psoriasis alone. These findings were distinct in TNF- α inhibitors. It can be explained by the fact that non-TNF- α inhibitors were classified as second-line drugs for PsA during the study period. However, the patterns differed depending on individual biologics although all non-

TNF- α inhibitors were second-line drugs during the study period. UST showed higher drug discontinuation in PsA alone, whereas the biologic survival rates of SEC, GUS, and IXE among disease groups were not significantly different.

PsA might influence drug survival of biologics because only some of the biologics were more efficient in PsA than psoriasis. A recent meta-analysis found few statistically significant differences between most biologic treatments of PsA²¹, while TNF- α inhibitors consistently showed a higher drug discontinuation rate than UST in patients with psoriasis^{15,22}. Additionally, patients with PsA might be more frequently motivated by their physicians for treatment persistence or recognize the importance of treatment persistence better than patients with psoriasis in whom only the skin is involved¹⁰.

Our results showed that age and number of comorbidities predicted biologic drug persistence, in contrast to previous studies^{5,9}. This difference could be partly explained by differences in the biologics included in the analysis. Previous studies included only TNF- α inhibitors and UST, whereas our cohort primarily consisted of IL-23/IL-17A inhibitors rather than TNF- α inhibitors. Comorbidities such as hypertension, renal disease, and hepatic disease are contraindications for conventional systemic therapy²³. Thus, patients with comorbidities and their physicians would adhere to biologic therapy unless serious adverse events occur. The incidence of severe adverse effects in patients with psoriasis receiving IL-23/IL-17 inhibitors is lower than in patients with psoriasis receiving TNF- α inhibitors²⁴. Therefore, patients with comorbidities

receiving IL-23/IL-17A inhibitors might be less likely to stop biologic therapy due to adverse events than those treated with TNF- α inhibitors.

Similar to other studies using claims data, this study had some limitations. First, we did not know the reasons for discontinuation. However, previous studies showed that most biologic drug discontinuations in patients with psoriasis were due to a lack of efficacy^{5,9}. Second, the data used in this study did not include information about disease severity, such as PASI or the Disease Activity Score-28. However, biologics receive reimbursement benefits for patients with severe and recalcitrant psoriasis or PsA. For example, to be eligible for the benefits, patients with psoriasis must have a body surface area of $\geq 10\%$ and PASI of ≥ 10 , even after a 12-week continuous treatment with systemic therapy or phototherapy. The situation is similar for PsA. In other words, the prescription of biologics for patients with psoriasis or PsA covered by the NHI in Korea means that these patients have severe and recalcitrant disease.

Finally, biological naivety in our cohort may have been different from actual biological naivety. Some biologic-experienced patients with PsA may have been misclassified as biologic-naïve because our operational definition of naivety was patients who had not been prescribed biologics since 2009. This misclassification may have occurred only for PsA because the insurance coverage of biologics for psoriasis in Korea started after 2009. Patients with PsA treated with biologics before 2009 were classified as biologic-naïve. However, the proportion of such patients was minimal in this study, and misclassification of biologic-experienced as biologic-naïve would have decreased the statistical difference between the groups. Thus, misclassification did not alter our primary results.

We found that drug survival in patients with PsA was longer than in patients with psoriasis, particularly for TNF- α inhibitors, and the availability of alternatives decreased drug survival of biologics. Drug survival is a representative real-world outcome measure of the use of biologics for psoriasis. However, a comparison of drug survival between biologics should be carefully considered if their introduction times differ. Our results also suggested that attitudes toward treatment persistence might affect drug survival.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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