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ORIGINAL ARTICLE

The effect of extra-articular manifestations on tumor necrosis factor-α inhibitor treatment duration in patients with ankylosing spondylitis: nationwide data from the Korean College of Rheumatology BIOlogics (KOBIO) registry

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Abstract

Tumor necrosis factor-α inhibitor (TNFi) therapy has shown to be remarkably effective for treating ankylosing spondylitis (AS); however, nearly 30% of AS patients every year either stop TNFi therapy or switch to a different TNFi due to inefficacy or adverse effects. The goal of this study was to identify predictors of TNFi treatment duration, including extra-articular manifestations, using a nationwide registry in Korea. Data obtained from the Korean College of Rheumatology Biologics (KOBIO) registry, a nationwide, multi-center database representing 58 tertiary care hospitals in Korea. Demographics, clinical features, laboratory findings, disease activity indices (BASDAI, ASDAS-ESR, ASDAS-CRP), peripheral arthritis, and extra-articular manifestations (uveitis, enthesitis, dactylitis, psoriasis, and inflammatory bowel disease) were studied in patients with AS during TNFi therapy. We also analyzed treatment duration outcomes for five TNFi agents (etanercept, infliximab, infliximab biosimilar, adalimumab, and golimumab), as well as factors associated with treatment duration, particularly in terms of extra-articular manifestations. Univariable and multivariable Cox regression analyses were performed to verify preliminary results. A total 1482 AS patients starting TNFi drug therapy between Dec. 2012 and Jan. 2017 were included. No differences in demographics, disease activity, or extra-articular manifestations were evident between continued and discontinued TNFi groups at baseline, though baseline differences were detected for gender distribution, CRP, platelet counts, and HLA-B27 positivity. During treatment period, the effects of extra-articular manifestations, including uveitis (unadjusted hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.57 to 1.48, $p = 0.74$), enthesitis, dactylitis, psoriasis, and inflammatory bowel disease, on TNFi treatment duration were not statistically significant. By contrast, the occurrence of peripheral arthritis was significantly associated with shorter TNFi treatment duration (unadjusted HR 2.21, 95% CI 1.66 to 2.95; adjusted HR 1.38, 95% CI 1.01 to 1.88). Among disease activity indices, higher ASDAS-ESR levels were significantly associated with shortening of the TNFi treatment duration (unadjusted HR 1.87, 95% CI 1.73 to 2.03; adjusted HR 2.23, 95% CI 2.00 to 2.63). Among TNFi drugs, golimumab had a lower discontinuation rate than that of etanercept over a 3-year follow-up period (unadjusted HR 0.46, 95% CI 0.31 to 0.68; adjusted HR 0.65, 95% CI 0.43 to 0.99). In a nationwide KOBIO registry, extra-articular manifestations, including uveitis, were not associated with TNFi treatment duration. Among clinical cofactors, the development of peripheral arthritis during TNFi therapy was associated with a higher risk of TNFi treatment discontinuance in AS patients.

Keywords Ankylosing spondylitis · Extra-articular manifestation · Nationwide registry · Peripheral arthritis · Treatment duration

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Introduction

Since the first study investigating the use of tumor necrosis factor-α inhibitor (TNFi) for the treatment ankylosing spondylitis (AS) patients in 2002, TNFi therapy has become the primary option for AS patients who failed to respond to non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) [1, 2]. The effectiveness of TNFi in AS patients has been demonstrated by numerous randomized, placebo-controlled clinical trials [3–6], with overall drug tolerability rates of TNFi ranging from 58 to 75% in AS patients who were previously biologic-naïve [7–9]. However, despite the widespread success of these drugs, the number of patients not responding to therapy, as well as those discontinuing treatment due to side effects or other causes, remains high. Patients who fail their first TNFi treatment are typically switched to a second TNFi agent. Although the response rates and treatment duration are lower among switchers, the overall effectiveness of switching TNFi treatment has been demonstrated in numerous nationwide registry studies [10, 11].

In most cases, patients able to sustain their first round of TNFi therapy typically exhibit better long-term clinical outcomes. Previous studies have shown that disease activity at baseline influences treatment outcome and treatment duration [7, 12]. While the frequency of extra-articular manifestations in patients with AS varies according to the specific disease, higher incidences of these symptoms are typically indicative of uncontrolled systemic inflammation [13]. The one of frequent extra-articular manifestation is anterior uveitis, seen in ~ 20–30% of patients [14]. TNFi has been shown to be effective for both controlling and reducing flares of anterior uveitis in AS patients [15]; however, a recent report has cast doubt on this finding, showing that a new onset of uveitis could occur de novo under TNFi therapy [16]. Therefore, the management of extra-articular manifestations in AS patients, particularly uveitis, remains one of the most important considerations when deciding whether to switch or stop TNFi therapy.

The goal of this study was to identify prognostic risk factors associated with TNFi therapy in terms of extra-articular manifestations, peripheral arthritis, and disease activity indices in AS patients who have switched or stopped TNFi therapy. We also investigate the treatment duration of each TNFi available in South Korea, using real-world data from the Korean nationwide Biologics registry (KOBIO).

Methods

Data sources and collecting method

The KOBIO registry is a nationwide biologics registry conducted by the Korean College of Rheumatology. This registry prospectively records the clinical manifestations, treatment outcomes, and safety profiles of patients with rheumatoid arthritis (RA), AS, and psoriatic arthritis (PsA) treated with one or more biologic agents. Eligible patients are enrolled gradually when they start a biologic therapy or switch from one biologic agent to another. Patients included in this database were selected from the rheumatologic centers of 58 tertiary care hospitals in the Republic of Korea. Data from every patient was collected and transferred by individual investigators into the KOBIO web server (http://www.rheum.or.kr/kobio/). Medical records of each patient were acquired by interview or from the medical charts at the time of enrollment.

Data was collected from all AS patients who started new TNFi treatment and enrolled in the KOBIO registry between December 2012 and January 2017. All patients eligible for the study were classified as having AS by their treating rheumatologists and fulfilled the 1984 modified New York criteria for the diagnosis of AS. AS patients were interviewed using a structured questionnaire that documented socio-demographic data along with current and past concomitant medications. The data include patient age, gender, marital status, disease duration, education level, smoking status, alcohol consumption, blood pressure, body mass index (BMI), familial history of autoimmune disease, and concomitant diseases. Laboratory findings, including human leukocyte antigen B27 (HLA-B27), complete blood count (CBC), chemistry, and inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were also measured. The assessment was recorded using Spondyloarthritis International Society (ASAS) classification criteria for axial spondyloarthropathy. To assess disease activity, tender and swollen joints were recorded to evaluate peripheral joint involvement. The visual analog scale (VAS) for patient global assessment (PGA) was recorded on a 0 to 10 scale. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), ESR, and CRP were evaluated at the time of initial biologic agent administration. The TNFi agent (etanercept, infliximab, infliximab biosimilar, adalimumab, or golimumab) used at the initial registration and the start date were registered in the database. A combination of NSAIDs or conventional DMARD treatment was also checked. Extra-articular features and peripheral arthritis were identified during each follow-up period. After the initial registration, follow-up evaluations were performed every 12 months with a 3-month grace period before and after. During each follow-up period, the KOBIO registry identified treatment outcomes, including treatment duration and adverse events. Our registry is ongoing and using real-world data, some

patients were not eligible to register between initial and follow-up registration. Similarly, between every follow-up registration, some patients were not eligible to register and be analyzed, too.

Study design

We analyzed the treatment duration of the five TNFi agents (etanercept, infliximab, infliximab biosimilar, adalimumab, and golimumab) as well as the factors affecting treatment duration, particularly extra-articular manifestations. The "continued" group was defined as those maintaining TNFi treatment and reached at least one follow-up period, while the "discontinued" group included all patients either stopping or switching TNFi treatment. Treatment duration was calculated as the number of days an individual patient continued treatment with the initial TNFi agent. Start date was the date of the first given dose, and discontinuation date was the date on which the patient stopped or switched TNFi therapy for any reason. Reasons for stopping drug treatment were registered as clinical remission, inefficacy, adverse events, and other. Reasons for switching TNFi were also registered as inefficacy, adverse events, and other. If the patient stopped or switched again after discontinuation of another TNFi, the case was again counted as part of the discontinued group. Therefore, the case of discontinued group is greater than the number of discontinued persons.

This research complied with the Helsinki Declaration. Informed consent was obtained from all enrolled participants. The same informed consent form (ICF) and study protocol were provided to the independent institutional review boards/ethics committees (IRB/EC) at each medical center, and each IRB/EC reviewed the appropriateness of the protocol, risks, and benefits to the study participants. Ultimately, the IRB/EC independently approved this study without revision of the ICF or study protocol.

Statistics

Statistical analyses were performed using SPSS for Windows (V.16.0, SPSS Inc., Chicago, IL, USA). Demographic and descriptive data were presented by means ± standard deviations (SDs) and percentages. Demographic and baseline data were analyzed using the independent sample t test and the χ^2 test between the discontinued and continued groups. The Kaplan-Meier plots and the log-rank test were used to analyze treatment duration. Unadjusted/univariate and adjusted/multivariate Cox regression analyses with hazard ratios (HRs) were used to identify factors associated with the treatment duration of the initial TNFi treatment. In all statistical tests, a p value < 0.05 was considered statistically significant.

Results

Baseline demographics and characteristics of patients

A total of 1482 AS patients were treated with their first TNFi between December 2012 and January 2017. Of these patients, 409 patients who did not have matched to evaluation for the first follow-up registration were deemed not eligible, leaving 1073 patients suitable for baseline comparisons. Patients maintaining TNFi treatment were defined as the continued group, while those stopping or switching TNFi therapy were defined as the discontinued group. An overview of patient screening and treatment grouping throughout the course of the study is presented in Fig. 1. After the initial registration period, annual interval registration periods were applied, with a 3-month grace period before and after. Following initial registration, 781 patients continued their first TNFi treatment, with the remaining 292 patients either switching or stopping their first TNFi treatment during the 3 years of follow-up.

Baseline demographics and disease characteristics at the initial registration of patients are summarized in Table 1. Between the discontinued and continued groups, there were no significant differences in age, BMI, smoking history, DMARD use, or NSAID use. By contrast, the discontinued group was disproportionately female and exhibited shorter disease duration on average. Among extra-articular manifestations and peripheral arthritis, there were no significant differences between these two groups. Disease activity indices showed broad similarity between groups, with the exception of CRP, which was lower in discontinued patients. Among clinical laboratory findings, HLA-B27 positivity and platelet counts were lower in the discontinued group.

Reasons for discontinuation

The discontinuation included all patients either stopping or switching TNFi treatment. The number of patients switching or stopping TNFi therapy and the reasons for these changes are shown in Table 2. Five patients discontinued their TNFi treatment, but the reason for this discontinuation was not specified. An additional 46 patients switched therapy more than once, as reflected in the numbers of patients reported in Tables 1 and 2. Inefficacy was the most common reason for switching TNFi therapy (n = 86, 61%), followed by adverse events (n = 44, 31.2%). Adverse event and clinical remission were the two main reasons for stopping TNFi therapy (n = 44, 22.7%, and n = 31, 16.1%, respectively). Other reasons for stopping TNFi therapy (n = 90, 46.9%) included follow-up loss of 22 patients, patient's will to stop treatment of 20 patients, and planned pregnancies of 13 patients.

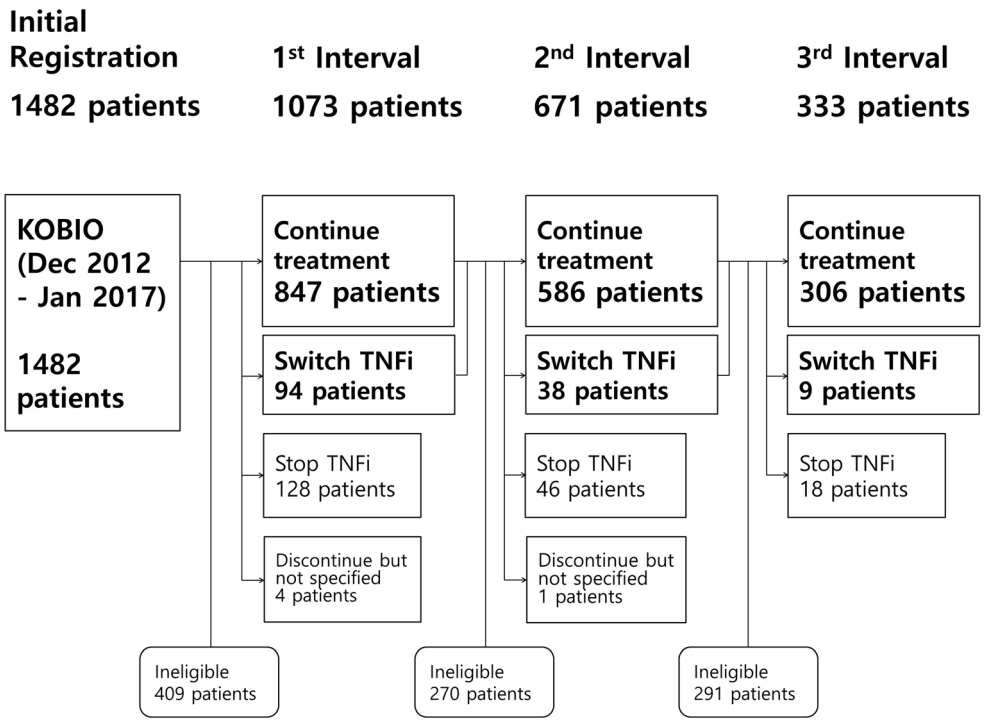

Fig. 1 Patient flow chart from initial registration to third interval registration. 1st interval registration is 9 to 15 months away from initial registration; 2nd interval registration is 21 to 27 months away from initial registration; 3rd interval registration is 33 to 39 months away from initial registration. KOBIO Korean College of Rheumatology Biologics, TNFi tumor necrotic factor alpha inhibitor

Treatment duration and retention rate of TNFi drugs

TNFi treatment duration and its associated symptoms (peripheral arthritis, extra-articular manifestations, and disease activity indices) are shown in Table 3. The occurrence of peripheral arthritis means the both new onset and reactivated peripheral arthritis in follow-up period. In univariate Cox regression analysis, peripheral arthritis (HR 2.21, $p < 0.001$), enthesitis (HR 1.94, $p = 0.005$), and psoriasis (HR 2.22, $p = 0.003$) were the most common clinical outcomes associated with discontinuation of TNFi. All standard disease activity indices, including BASDAI, VAS for PGA, ESR, CRP, ASDAS-ESR, and ASDAS-CRP, were significantly associated with treatment duration in univariate analysis, although only peripheral arthritis (HR 1.38, $p = 0.04$) and ASDAS-ESR (HR 2.23, $p < 0.001$) were found to be significantly associated with treatment duration when analyzed by multivariate Cox regression analysis.

Cumulative treatment duration rates for TNFi therapy are shown in Fig. 2. Adalimumab was the most frequently used drug among patients both switching and stopping treatment ($n = 131$, 38.8%; $n = 287$, 36.7%). Further analysis of treatment duration was performed for infliximab, infliximab biosimilar, adalimumab, and golimumab using etanercept as a reference. Golimumab showed the lower discontinuation rate compared with etanercept by both univariate and multivariate Cox regression (HR 0.46, $p < 0.001$, and HR 0.65, $p = 0.04$, respectively).

Effect of peripheral arthritis and extra-articular manifestations on TNFi treatment duration

The Kaplan-Meier treatment duration curves for peripheral arthritis and each extra-articular manifestation are shown in Fig. 3. For patients with peripheral arthritis, enthesitis, and psoriasis, the cumulative probability of continuing treatment was significantly lower than that of unaffected patients after 1 year. Other incidence of symptoms, including uveitis, dactylitis, and inflammatory bowel disease, was not associated with treatment duration.

Discussion

The presence of extra-articular manifestations is a significant determinant of the health-related impact of AS on quality of life [17]. The efficacy of TNFi for treatment of extra-articular manifestations and other comorbidities appears to vary from agent to agent. Although there have been no randomized controlled trials or meta-analyses assessing the effect of extra-articular manifestations on TNFi treatment duration, monoclonal antibodies, such as infliximab and adalimumab, do appear to be better for treating extra-articular manifestations and other comorbidities compared with etanercept [13]. By contrast, a similar meta-analysis found etanercept to be more effective than placebo for treating uveitis, with no efficacy seen for monoclonal TNFi therapies [18]. Given these divergent

Table 1 Baseline demographics and disease activity at the time of starting the first tumor necrosis factor alpha inhibitor

	Discontinued group $N = 292$ (persons)	Continued group $N = 781$ (persons)	p value
Demographic characteristics			
Age, years, mean ± (SD)	42.0 (13.8)	41.3 (12.4)	0.414
Disease duration, years, mean ± (SD)	7.3 (5.4)	8.0 (6.0)	0.072
Treatment duration, days, mean ± (SD)	281.4 (246.3)	728.0 (299.0)	< 0.001**
BMI, mean ± (SD)	23.2 (3.3)	23.5 (3.5)	0.220
Men, *n* (%)	210 (72.2)	624 (79.8)	0.008*
Cigarette smoking, *n* (%)	143 (49.1)	391 (50.0)	0.802
Use of DMARDs, *n* (%)	3 (1.0)	14 (1.8)	0.582
Use of NSAIDs, *n* (%)	246 (84.5)	672 (85.9)	0.563
Extra-articular manifestations, *n* (%)			
Enthesitis	63 (21.6)	163 (21.0)	0.803
Uveitis	58 (19.9)	164 (21.1)	0.687
Dactylitis	4 (1.4)	12 (1.5)	1.000
Psoriasis	9 (3.1)	20 (2.6)	0.638
Inflammatory bowel disease	3 (1.0)	13 (1.7)	0.578
Peripheral arthritis, *n* (%)	113 (38.8)	262 (33.7)	0.116
Disease activity indices, mean ± (SD)			
BASDAI (0–10)	6.2 (1.9)	6.0 (2.0)	0.127
VAS for PGA (0–10)	6.4 (2.1)	6.3 (2.1)	0.626
ESR (mm)	34.5 (29.2)	37.5 (30.0)	0.143
CRP (mg/dl)	1.8 (2.4)	2.3 (2.8)	0.015*
ASDAS-ESR (0–10)	3.6 (1.0)	3.7 (1.1)	0.586
ASDAS-CRP (0–10)	3.5 (1.1)	3.6 (1.1)	0.060
Laboratory tests			
HLA-B27 positivity, *n* (%)	234 (84.8)	647 (91.4)	0.002*
White blood cell (/mm^3)	8408 (6404)	8441 (6867)	0.942
Hemoglobin (g/dl)	13.6 (1.7)	13.6 (1.7)	0.719
Platelet (/mm^3)	290,703 (78,290)	303,065 (77,312)	0.021*
AST (U/l)	21.7 (9.2)	21.8 (9.2)	0.798
ALT (U/l)	22.6 (16.1)	22.6 (14.6)	0.999
Creatinine, (mg/dl)	0.82 (0.21)	0.83 (0.33)	0.550

Independent sample *t* test and chi-squared test. Values are mean (standard deviation) unless otherwise indicated

BMI body mass index, *DMARDs* disease-modifying antirheumatic drugs, *NSAIDs* nonsteroidal anti-inflammatory drugs, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *VAS for PGA* Visual Analogue Scale for Patient Global Assessment, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *HLA* human leukocyte antigen, *AST* aspartate transaminase, *ALT* alanine transaminase

*$p < 0.05$, **$p < 0.001$

findings, we hypothesized that uveitis flare-ups are likely to affect TNFi treatment duration in AS patients. Our registry showed similar baseline presence of uveitis in both the continued (21.1%) and discontinued (19.9%) groups [14], although these incidences of flare-ups and new-onset AS were lower in our study (5.5% in the discontinued group vs. 6.2% in the continued group). This relatively low incidence of new-onset uveitis during TNFi treatment in AS patients implies a durable effect of TNFi, consistent with the low detection rate of new-onset uveitis in the KOBIO registry. This result might be the result of lower prevalence of extra-articular manifestations among Asians [14]. All data in this study were collected by a rheumatologist, with the presence of uveitis based on either patient statements or ophthalmic records. This suggests that there are likely more flare-ups of uveitis that remain either undetected or are simply not recorded. As a result, our study was not able to identify any effects of extra-articular manifestations, including uveitis, on treatment duration.

In this study, we were unable to identify specific extra-articular manifestations, including uveitis, predictive of

Table 2 Reason for discontinuation cases of TNFi

Switch, *n* (%)	141	Stop, *n* (%)	192
Inefficacy	86 (61.0)	Clinical remission	31 (16.1)
Adverse events	44 (31.2)	Inefficacy	27 (14.1)
Others	10 (7.1)	Adverse events	44 (22.9)
Not mentioned	1 (0.7)	Others	90 (46.9)

Total case number of discontinuation was 338. There were 5 cases who discontinued their TNFi treatment, but they were not specified of reason to discontinuation

discontinuous TNFi treatment in AS. However, AS patients with higher ASDAS-ESR scores, as well as those experiencing peripheral arthritis during TNFi treatment, tended to switch or stop their TNFi treatment more frequently. Other factors were also found to be significant, despite inconsistencies across studies. An observational study conducted by the South Swedish Arthritis Treatment Group (SSATG) concluded that the presence of peripheral arthritis among AS patients could be the positive predictor for treatment continuation [19]. By contrast, our study found that peripheral arthritis was strongly associated with the discontinuation of TNFi therapy by univariate analysis (HR 2.21, $p < 0.001$). After adjusting for other extra-articular manifestations, peripheral arthritis was still predictive of discontinuation of TNFi therapy (HR 1.38, $p = 0.04$). A similar result was observed in a single tertiary center study in South Korea. In this study, incidence of peripheral arthritis was significantly associated with TNFi discontinuation rate by univariate analysis (HR 2.079, $p = 0.035$) [20]. Such discrepancies between these studies and the SSATG study suggest that these results should be interpreted

Table 3 Cumulative comparison between discontinued and continued groups with univariate and multivariate Cox regression analyses of TNFi, peripheral arthritis, extra-articular manifestations, and disease activity indices

	Discontinued	Continued	Univariate		Multivariate	
	N = 338 (cases)	*N* = 781 (cases)	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Tumor necrosis factor-α inhibitor, *n* (%)						
Etanercept	58 (17.2)	110 (14.1)	Reference		Reference	
Infliximab	41 (12.1)	52 (6.7)	1.30 (0.87–1.94)	0.21	1.48 (0.97–2.28)	0.07
Infliximab biosimilar	62 (18.3)	121 (15.5)	0.94 (0.54–1.35)	0.74	0.84 (0.56–1.26)	0.40
Adalimumab	131 (38.8)	287 (36.7)	0.84 (0.61–1.15)	0.29	1.06 (0.75–1.51)	0.73
Golimumab	46 (13.6)	211 (27.0)	0.46 (0.31–0.68)	< 0.001**	0.65 (0.43–0.99)	0.04*
Peripheral arthritis, *n* (%)	57 (17.3)	77 (8.7)	2.21 (1.66–2.95)	< 0.001**	1.38 (1.01–1.88)	0.04*
Extra-articular manifestations, *n* (%)						
Enthesitis	19 (5.7)	31 (3.5)	1.94 (1.22–3.09)	0.005*		
Uveitis	18 (5.5)	55 (6.2)	0.92 (0.57–1.48)	0.74		
Dactylitis	3 (0.9)	2 (0.2)	2.05 (0.66–6.39)	0.22		
Psoriasis	19 (5.7)	22 (2.5)	2.22 (1.39–3.53)	0.003*		
Inflammatory bowel disease	2 (0.6)	9 (1.0)	0.55 (0.34–2.19)	0.392		
Disease activity indices, mean ±(SD)						
BASDAI (0–10)	4.2 (2.8)	2.3 (1.7)	1.36 (1.30–1.42)	< 0.001**		
VAS for PGA (0–10)	4.6 (2.8)	2.7 (2.1)	1.30 (1.25–1.35)	< 0.001**		
ESR (mm)	21.8 (25.1)	12.0 (13.7)	1.02 (1.02–1.03)	< 0.001**	0.99 (0.98–1.00)	0.001**
CRP (mg/dl)	1.10 (2.33)	0.45 (0.77)	1.14 (1.10–1.19)	< 0.001**		
ASDAS-ESR (0–10)	2.6 (1.3)	1.7 (0.8)	1.87 (1.73–2.03)	< 0.001**	2.23 (2.00–2.63)	< 0.001**
ASDAS-CRP (0–10)	2.4 (1.4)	1.5 (0.9)	1.74 (1.61–1.89)	< 0.001**		

If the patient stopped or switched again after discontinuation of another TNFi, the case was again counted as part of the discontinued group. Therefore, the case of discontinued group is greater than the number of discontinued persons. Our registry checked the patient's peripheral swollen and tender joint count, BASDAI, ESR, CRP, and VAS for PGA at initial and every follow-up evaluation. Based on these records, we calculated ASDAS-ESR and ASDAS-CRP. ASDAS-ESR = 0.08 × Back pain + 0.07 × Duration of morning stiffness + 0.11 × Patient global + 0.09 × Peripheral pain/swelling + 0.29 × Square root ESR; ASDAS-CRP = 0.12 × Back pain + 0.06 × Duration of morning stiffness + 0.11 × Patient global + 0.07 × Peripheral pain/swelling + 0.58 × Ln(CRP + 1)

Cox regression analysis with hazard ratios. *HR* hazard ratio, *CI* confidence interval, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *VAS for PGA* Visual Analogue Scale for Patient Global Assessment, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ASDAS* Ankylosing Spondylitis Disease Activity Score

*$p < 0.05$, **$p < 0.001$

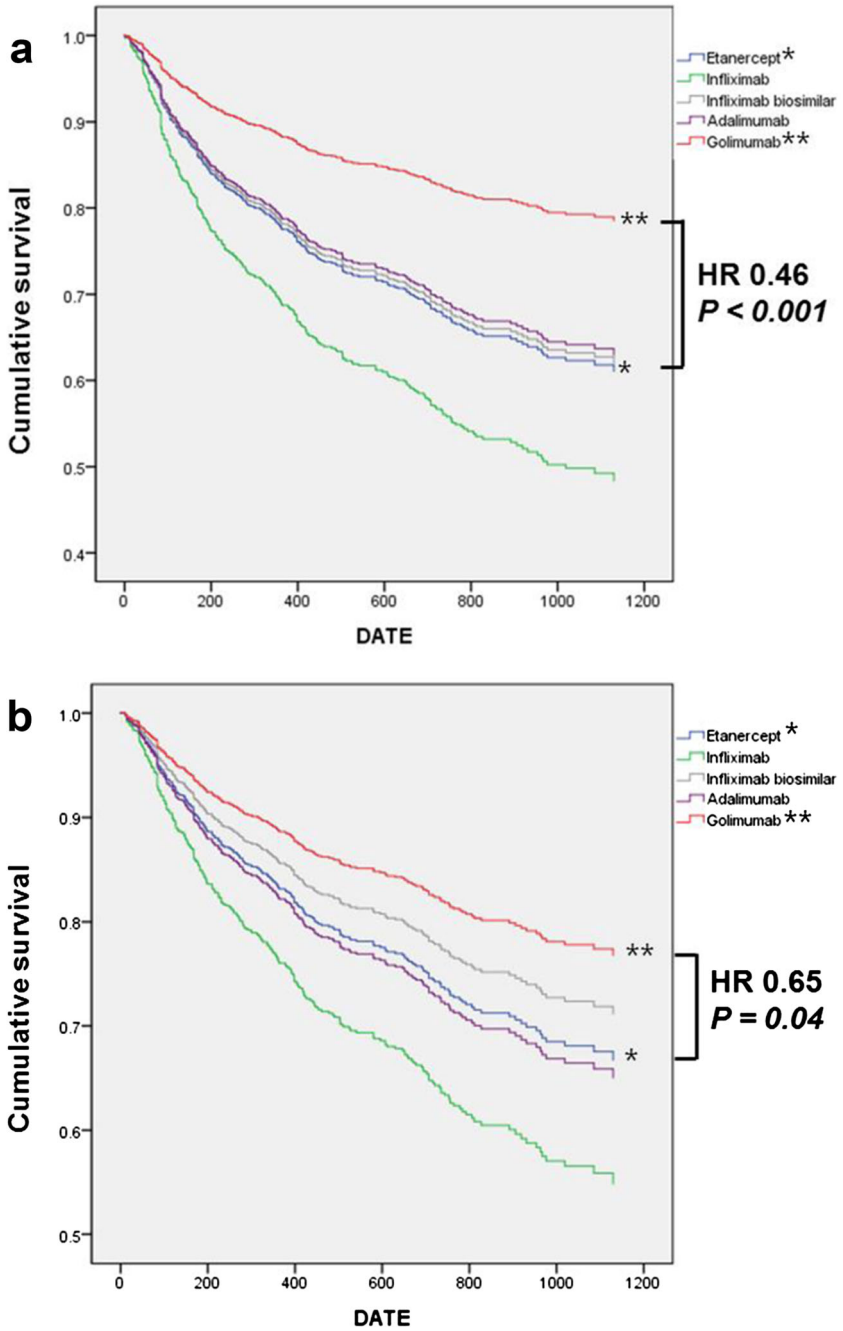

Fig. 2 Univariate and multivariate Cox regression curve of the five TNFi drugs. Etanercept is used as the reference compound. In the univariate analysis (**a**), golimumab had a longer drug retention rate (HR 0.46, $p < 0.001$). In the multivariate analysis (**b**), golimumab also exhibited a longer drug retention rate (HR 0.65, $p = 0.04$). All the variables in Table 2 were included for the multivariable analysis: peripheral arthritis, five of extra-articular manifestations, and disease activity indices

with caution. Together, these results highlight the need for additional investigations from other nationwide registries.

The discontinued group was disproportionately female, with lower rates of HLA-B27 positivity than the continued group. This result is consistent with other registry studies, which showed the same gender distribution among switchers [7, 8, 11]. A prospective longitudinal observational cohort study from the Netherlands also found female gender to be significantly associated with discontinuation of TNFi treatment in AS patients [21]. It is unclear why females are more likely to discontinue TNFi treatment, but this sex-related factor is useful for predicting TNFi treatment duration in AS patients. There were no differences in age, disease duration, disease activity indices except CRP, or concomitant use of DMARDs and NSAIDs between the continued and discontinued groups. Although broadly consistent with other studies, the DANBIO registry study did find that switchers typically experienced shorter disease duration and higher concomitant DMARD use compared with non-switchers [7, 11].

Switching to an alternative TNFi has been shown to be associated with lower response and/or treatment duration rates in patients with AS [22]. A recent study by the Swiss Clinical

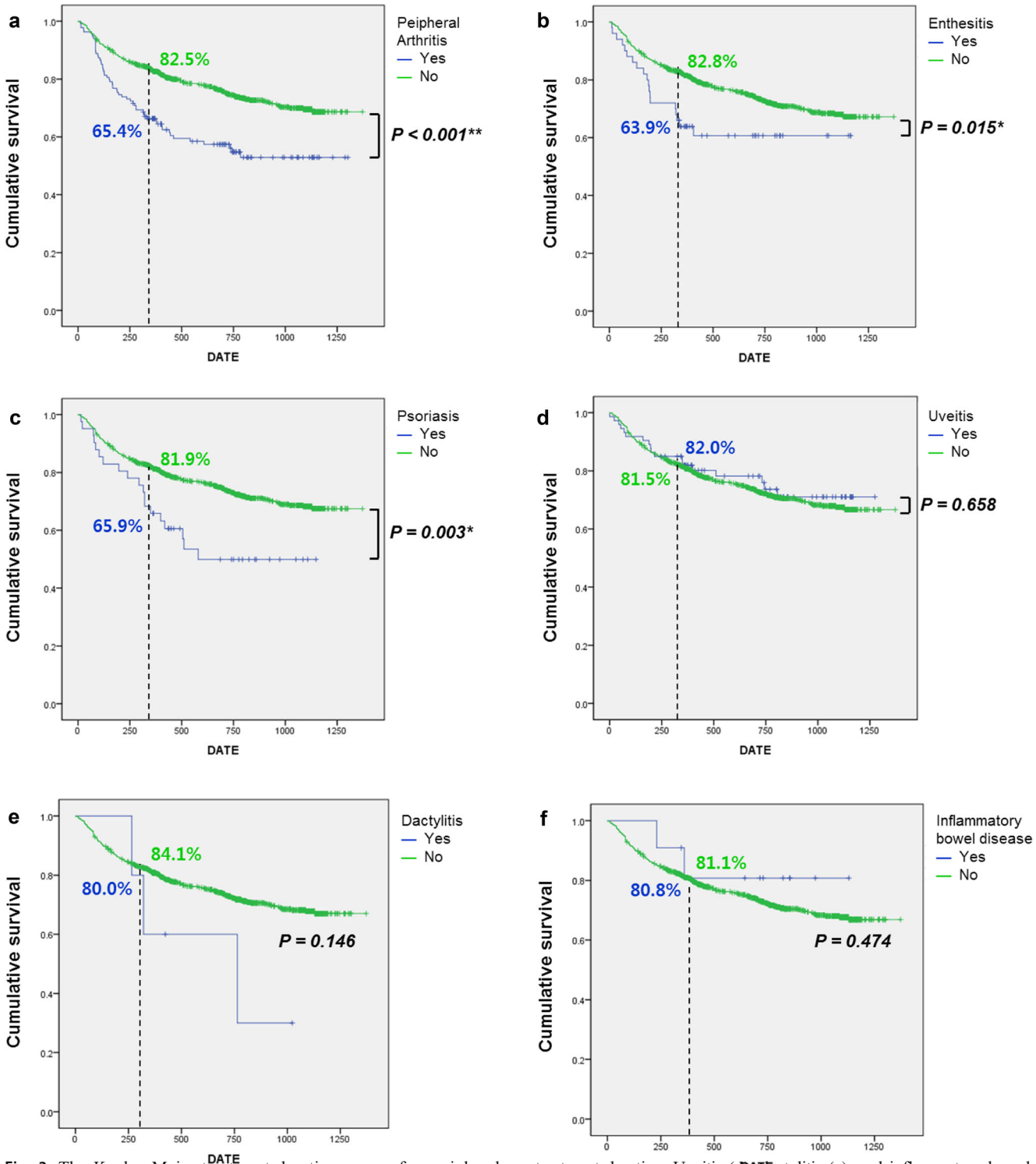

Fig. 3 The Kaplan-Meier treatment duration curves for peripheral arthritis and each extra-articular manifestation. Patients who do not have peripheral arthritis (**a**), enthesitis (**b**), and psoriasis (**c**) show longer treatment duration. Uveitis (**d**), dactylitis (**e**), and inflammatory bowel disease (**f**) do not affect treatment duration. *$p < 0.05$, **$p < 0.001$

Quality Management cohort found effectiveness of a second TNFi is significantly lower in AS patients who failed to respond to a first TNFi during the first 6 months of treatment [23]. Given this predictive power for failed TNFi therapy, drug retention rate in AS patients may imply the effectiveness of treatment among TNFi agents. However, drug retention rate cannot be interpreted as efficacy alone. A recent meta-analysis comparing discontinuation of TNFi in RA patients found substantial heterogeneity in studies estimating head-to-head HRs due to differences in the type of data, location, and order of

treatment [24]. Therefore, there are likely more factors influencing TNFi retention rate beyond effectiveness alone. Here, we evaluated retention rates of four TNFi drugs (infliximab, etanercept, adalimumab, and golimumab) and one TNFi biosimilar (infliximab). Golimumab showed significantly longer treatment duration compared with etanercept after adjustment (HR 0.65, $p = 0.04$). While treatment with etanercept led to a lower percentage of discontinuations than treatment with infliximab and adalimumab in RA [25], similar studies in AS remain scarce. A systematic review and economic evaluation conducted by the National Institute for Health and Care Excellence (NICE) in the UK concluded that all TNFi drugs were effective equally for the treatment of AS [26]. Although our results showed golimumab had longer drug retention compared with etanercept, it cannot be concluded that golimumab has superior efficacy than that of etanercept in real world. However, given the nature of registry-based research, our data have a few important limitations. As the data collection was not performed by the researcher, all the necessary information may not be available, including relevant confound factors or other missing information, which may affect data quality [27]. Further nationwide studies and meta-analyses combined with practical convenience and efficacy are needed to evaluate drug retention in patients with AS.

To our knowledge, this is the first study investigating the effect of extra-articular manifestations on TNFi treatment duration in patients with AS using data from the nationwide KOBIO registry. Although we were unable to identify conclusive differences in extra-articular manifestations between the continued and discontinued groups, the development of peripheral arthritis during TNFi therapy was higher in the discontinued group in Korea. Peripheral arthritis was shown to be predictive of treatment duration in Korean AS patients on TNFi treatment. We also found golimumab had longer treatment retention rates compared with that of etanercept.

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Compliance with ethical standards

This research complied with the Helsinki Declaration. Informed consent was obtained from all enrolled participants. The same informed consent form (ICF) and study protocol were provided to the independent institutional review boards/ethics committees (IRB/EC) at each medical center, and each IRB/EC reviewed the appropriateness of the protocol, risks, and benefits to the study participants. Ultimately, the IRB/EC independently approved this study without revision of the ICF or study protocol.

Disclosures None.

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