Biologic retention rate and efficacy in patients with cluster-based phenotypes of ankylosing spondylitis: data from a Korean national biologics registry

H.K. Min[1], H.-R. Kim[2], S.-H. Lee[2], K.Y. Kang[3], S.-H. Park[4], K. Shin[5], J. Kim[6], S.-K. Kwok[4]

[1]Division of Rheumatology, Department of Internal Medicine, Konkuk University Medical Center, Seoul, South Korea; [2]Division of Rheumatology, Department of Internal Medicine, Research Institute of Medical Science, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, South Korea; [3]Division of Rheumatology, Department of Internal Medicine, Incheon Saint Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, South Korea; [4]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [5]Division of Rheumatology, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [6]Division of Rheumatology, Department of Internal Medicine, Chungnam National University Hospital, Daejeon, Republic of Korea.

Abstract

Objective

Patients with ankylosing spondylitis (AS) have a heterogenic disease course and treatment response. Cluster-based phenotypes are useful for predicting AS disease course. Here, we compared drug retention and clinical efficacy of biologic disease-modifying anti-rheumatic drugs (bDMARDs) in AS patients with cluster A and cluster B phenotypes.

Methods

AS patients enrolled in the Korean College of Rheumatology BIOlogics registry were divided into cluster A (axial symptoms predominant) and cluster B (both axial and peripheral symptoms). Retention of bDMARDs was measured using Kaplan-Meier curve and Cox regression analyses. Clinical efficacy (BASDAI50, ASAS20, ASAS40, ASDAS inactive state, and clinically important improvement/major improvement of ASDAS) at 1-year follow-up was measured by logistic regression analysis. Also, propensity score (PS)-matched analyses were conducted.

Results

1600 AS patients (1468 for cluster A, 132 for cluster B) were included. Kaplan-Meier curve analysis revealed that the drug retention rate was lower in cluster B patients (p=0.03). PS-matched analyses showed that the hazard ratio (HR) for drug discontinuation was significantly higher in cluster B patients (HR=1.568; 95% confidence interval =1.055–2.329). The odds ratio for BASDAI50 at 1-year was comparable between cluster A and cluster B patients in PS-matched and multivariate logistic regression analyses. A similar result was obtained in other clinical efficacy assessments.

Conclusion

The drug retention rate was lower in cluster B patients than in cluster A patients; clinical efficacy was comparable between the two groups at 1-year follow-up. These results may help predict drug retention and clinical efficacy in AS patients.

Key words

ankylosing spondylitis, cluster-based phenotype, biologic disease-modifying anti-rheumatic drug, drug retention, efficacy

Hong Ki Min, MD
Hae-Rim Kim, MD, PhD
Sang-Heon Lee, MD, PhD
Kwi Young Kang, MD, PhD
Sung-Hwan Park, MD, PhD
Kichul Shin, MD, PhD
Jinhyun Kim, MD, PhD
Seung-Ki Kwok, MD, PhD

Please address correspondence to:
Seung-Ki Kwok,
Division of Rheumatology,
Department of Internal Medicine,
Seoul St. Mary's Hospital,
College of Medicine,
The Catholic University of Korea,
222 Banpo-daero, Seocho-gu,
Seoul 06591, Republic of Korea.
E-mail: seungki73@catholic.ac.kr

Received on August 26, 2021; accepted in revised form on October 25, 2021.

ORCID iD
H.K. Min: 0000-0003-1147-1046
K.Y. Kang: 0000-0003-0059-119X
S.-K. Kwok: 0000-0002-6142-8364

Competing interests: none declared.

Introduction

Ankylosing spondylitis (AS) is the prototype form of axial spondyloarthritis (axSpA), a type of inflammatory-mediated arthritis (1). AxSpA can be divided into several subtypes, and clinical, laboratory, and radiographic progression differ according to the subtypes (2, 3). The incidence rate range from 3.4 to 9.7 cases per 100,000 person-years according to the subtypes of SpA (4). The disease course and treatment response are heterogeneous; therefore, identifying predictors of drug retention and clinical efficacy will aid treatment decisions. A heterogeneous disease course and treatment response are seen in all types of inflammatory arthritis and autoimmune-mediated diseases. Recent studies in patients with systemic sclerosis and primary Sjögren's syndrome showed that cluster-based phenotyping could predict treatment response and prognosis (5, 6). Some recent studies aim to discriminate subtypes of axSpA to predict treatment response and radiographic progression (2, 7). A French cohort study of patients with early axSpA disease demonstrated the existence of two cluster-based phenotypes of axSpA: cluster A, which had only axial joint symptoms and cluster B, which had both axial and peripheral symptoms (7). Cluster B patients had higher disease activity and a higher prevalence of peripheral arthritis, enthesitis, and dactylitis than cluster A patients (7).

The Korean College of Rheumatology (KCR) formed a national registry of biologic disease-modifying antirheumatic drug (bDMARD) users, named KCR BIOlogics (KOBIO). The KOBIO registry enrolled AS patients from 58 university-based tertiary hospitals; these patients were bDMARD naïve, or were previously exposed to one or more bDMARDs. Patients with non-radiographic axSpA were not enrolled in the KOBIO registry. There are several differences between non-radiographic axSpA and AS, including gender distribution, drug response, and severity of inflammation (8). Therefore, combining non-radiographic axial SpA and AS into one disease category (*i.e.* axSpA) can impact the results of an observational study substantially. Excluding patients with non-radiographic axSpA from the KOBIO registry enabled analysis of drug retention rate and efficacy in AS patients. Baseline demographic, laboratory, and clinical data were collected at the time of enrolment, after which data were collected performed annually. In addition, drug retention time, the reason for switching or stopping bDMARDs, and clinical efficacy were assessed annually.

In this study, we divided AS patients in the KOBIO registry into two cluster-based phenotypes (4), cluster A and cluster B, and compared drug retention rates. In addition, the clinical efficacy of bDMARDs was compared between cluster A and cluster B patients at 1-year follow-up.

Methods

Study population

Data from patients with AS, who were enrolled in the KOBIO registry from December 2012 to July 2020, were used in the study (ClinicalTrials.gov identifier NCT01965132). Patients who fulfilled the 1984 modified New York criteria for the classification of AS and aged older than 18 years were enrolled in the KOBIO registry. Patients who had data collected at least one follow-up were included in the analyses. The present study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the institutional review boards of each participating hospital. All patients provided informed written consent before enrolment.

Data collection and outcomes

Demographics, laboratory data, disease activity, treatment modality, and comorbidities were collected when each patient was enrolled into the KOBIO registry. After enrolment, the aforementioned information, along with data related to changes in treatment modalities, were collected annually. In addition, whether the bDMARD was continued or stopped, and the reason for stopping bDMARD treatment, were recorded. The treatment choice was decided by the treating physician in each hospital. Patients with AS were divid-

ed into two cluster-based phenotypes, cluster A and cluster B, by considering the initial disease manifestation of each patient according to criteria described in the DESIR (Devenir des Spondyloarthropathies Indifferenciees Recentes) cohort study (7, 9). AS patients with peripheral arthritis with enthesitis or dactylitis (peripheral arthritis + enthesitis or peripheral arthritis + dactylitis) were classified as cluster B, and the remaining patients were classified as cluster A (9). The decision tree for cluster determination is presented in supplementary figure 1 (9). The primary endpoint of the present study was comparison of drug retention rates and duration of bDMARD therapy in AS patients with the cluster A and cluster B phenotypes. Secondary endpoints included several measures of clinical efficacy at 1-year follow-up; these included improvement in the Assessment in Ankylosing Spondylitis Response Criteria (ASAS20), improvement in ASAS40 (10), a 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50) (11), low disease activity based on the Ankylosing Spondylitis Disease Activity Score (ASDAS <2.1) (12), and a clinically important improvement and major improvement in ASDAS (13).

Table I. Baseline characteristics of ankylosing spondylitis patients with the cluster A and cluster B phenotypes.

Variable n (%) or mean (SD)	Total AS patients (n=1600)	Cluster A (n=1468)	Cluster B (n=132)	*p*-value
Age, years	39.0 (13.0)	38.9 (12.8)	39.7 (14.8)	0.541
Male	1230 (76.9%)	1139 (77.6%)	91 (68.9%)	0.032
Disease duration, year	4.9 (6.1)	5.1 (6.1)	3.0 (4.8)	<0.001
BMI, kg/m^2	23.6 (3.5)	23.6 (3.5)	23.9 (3.9)	0.292
Current smoker	448 (28.0%)	424 (28.9%)	24 (18.2%)	0.012
HLA B27-positive	1332/1477 (90.2%)	1219/1350 (90.3%)	113/127 (89.0%)	0.747
Patient global assessment	6.3 (2.1)	6.3 (2.1)	6.9 (2.1)	0.002
BASDAI score (range, 0–10)	6.0 (2.0)	5.9 (2.0)	6.6 (1.8)	<0.001
ESR (mm/h)	37.4 (29.7)	36.4 (29.2)	48.3 (33.4)	<0.001
CRP (mg/mL)	2.2 (2.9)	2.0 (2.7)	3.6 (4.3)	<0.001
ASDAS	3.7 (1.1)	3.7 (1.0)	4.2 (1.1)	<0.001
BASFI score	3.5 (2.6)	3.4 (2.6)	4.1 (2.6)	0.004
Peripheral arthritis	457/1579 (28.9%)	325/1447 (22.5)	132/132 (100%)	<0.001
Enthesitis	253/1582 (16.0%)	128/1451 (8.8%)	125 (94.7%)	<0.001
Dactylitis	25/1583 (1.6%)	7/1451 (0.5%)	18/131 (13.7%)	<0.001
Psoriasis	43/1583 (2.7%)	36/1452 (2.5%)	7/131 (5.3%)	0.145
Inflammatory bowel disease	8/1585 (0.5%)	6/1453 (0.4%)	2/132 (1.5%)	0.116
Number of swollen joints	0.6 (2.3)	0.5 (2.2)	2.0 (2.9)	<0.001
Number of tender joints	1.0 (2.8)	0.7 (2.4)	3.6 (5.4)	<0.001
Current NSAIDs	1351 (84.4%)	1229 (83.7%)	122 (92.4%)	0.012
Current csDMARDs*	162 (10.1%)	137 (9.3%)	25 (18.9%)	0.001
Sulfasalazine	93 (5.8%)	78 (5.3%)	15 (11.4%)	
Methotrexate	85 (5.3%)	69 (4.7%)	16 (12.1 %)	
Others	6 (0.4%)	5 (0.4%)	1 (0.8%)	
Biologics-naïve	1247 (77.9%)	1137 (77.5%)	110 (83.3%)	0.147
Biologics				
TNFi	1586 (99.1%)	1455 (99.1%)	131 (99.2%)	1.000
IL-17i	14 (0.9%)	13 (0.9%)	1 (0.8%)	

SD: standard deviation; BMI: Body Mass Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; NSAIDs: non-steroidal anti-inflammatory drugs; csDMARD: conventional synthetic disease-modifying antirheumatic drug; TNFi: tumour necrosis factor inhibitor; IL-17i: interleukin-17 inhibitor.
* Multiple csDMARD use was presented in 22 patients (15 for cluster A, 7 for cluster B).

Statistical analyses

Continuous data were analysed by independent t-test and presented as the mean ± SD. Categorical variable were compared via χ^2 test and expressed as percentages. Multiple imputation by chained equations was used to account for missing baseline data (status of HLA-B27, psoriasis, inflammatory bowel disease, ESR, CRP, BASFI, and ASDAS). Predictive mean matching and logistic regression imputation method were used to impute continuous variables and categorical variables, respectively. Pooling of model estimates was done according to Rubin's rules.

The baseline characteristics and sample size of cluster A and B groups differed, we used propensity score (PS)-based matching to adjust potential confounders based on these differences. PS-matched analyses were used to reduce the effects of confounding factors when estimating effects of treatment or intervention in non-randomised or observational data. Several methods for PS-matching are available, and among them nearest-neighbouring matching and inverse probability of treatment weighting using the propensity score are recommended when evaluating the relative effect of specific factor (cluster A or B in present study) on time-to-event outcomes (14). We selected 1:1 greedy nearest-neighbour matching within propensity score calipers (capliper width equal to 0.2 of the standard deviation of the logit of the propensity score) (15). This method can produce dataset with matched samples balanced by multiple covariates, and allows for the estimation of time-to-event outcomes with minimal bias. Propensity score matching of 1:1 ratio was conducted by imputing various variables known to influence on drug retention rate, including age, gender, BMI, smoking status, HLA-B27 positive, ASDAS, BASFI, previous bDMARD exposure history (a dichotomous variable [bDMARD naïve *vs*. biologics exposed]). Kaplan-Meier curve and log-ranked test were used to compare drug survival. Cox proportional regression analyses was used to calculate hazard ratio (HR) for drug discontinuation by conventional multivariate (including age, gender, body mass index (BMI), smoking status, HLA-B27 positivity, ASDAS, Bath Ankylosing Spondylitis Functional Index (BASFI), and a history of previous exposure to bDMARDs) in original dataset, and Cox proportional regression analyses was also performed with PS-matched dataset. To compare clinical efficacy at 1-year-follow up, conventional multivariate and PS-matched logistic regression analyses were used. *p*-values less than 0.05 were considered

statistically significant. All statistical analyses were performed by software R (R for Windows 3.3.2; The R Foundation for Statistical Computing, Vienna, Austria), and R package of moonBook, Survival, and MatchIt.

Results

Baseline characteristics of enrolled patients

Among 1930 AS patients who were enrolled in the KOBIO registry, 1600 (1468 for cluster A, and 132 for cluster B) had data collected from at least one follow-up. In terms of baseline characteristics, cluster A contained a higher proportion of males, had a higher prevalence of current smokers, and had longer disease duration than cluster B. Disease activity (BASDAI, ASDAS), BASFI, patient global assessment score, and inflammatory markers (C-reactive protein levels and erythrocyte sedimentation rate) were higher in cluster B. Combined peripheral symptoms (peripheral arthritis, enthesitis, and dactylitis) were more frequent in cluster B, and the swollen/tender joint count was also higher in cluster B. Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) or conventional DMARDs were more frequent in cluster B. In all enrolled patients, NSAIDs were used at least 3 months before bDMARDs were started. The baseline characteristics of the AS patients are summarised in Table I.

Comparison of drug retention rates between AS patients with cluster A and cluster B phenotypes

The mean follow-up duration was 34.4±23.2 months for cluster A patients and 32.5±23.2 months for cluster and B patients. Overall, 521 patients (35.5%) in cluster A and 59 patients in cluster B (44.7%) stopped using bDMARDs during the follow-up period. Kaplan-Meier analysis revealed that the drug retention time was significantly shorter in cluster B patients than in cluster A patients (p=0.03, log-rank test; Fig. 1). In both groups, a clinically inadequate response (*i.e.* a lack of drug efficacy) was the most common reason for bDMARD discontinuation (Table II). In cox regression analyses, cluster B showed significant increased hazard ratio (HR) for drug discontinuation by both PS-matched and conventional multivariate regression analyses (HR=1.568; 95% confidence interval (CI), 1.055–2.329 and HR=1.333; 95% CI, 1.007–1.764, respectively). In addition, female gender (HR=1.347) and current smoker (HR=1.231) showed increased risk, whereas HLA-27 positive (HR=0.659) showed decreased risk for drug discontinuation in multivariate cox regression analyses (Table III). Although clinical inefficacy was the most common cause of drug discontinuation, however, large portion of patients stopped bDMARDs due to other reasons than clinical inefficacy. In subgroup analyses (excluding drug discontinuation due to clinical remission, adverse events, and other miscellaneous reasons, n=1204 [1111 for cluster A, 93 for cluster B]), being cluster B still had higher HR for drug discontinuation in PS-matched analyses (Supplementary Table S1).

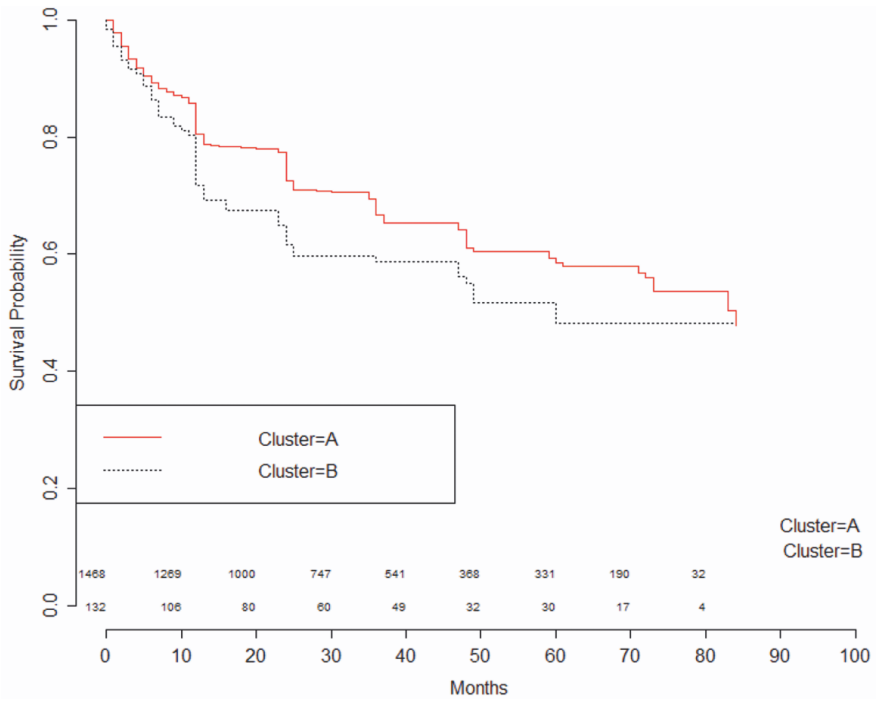

Fig. 1. Kaplan-Meier curve showing drug retention in ankylosing spondylitis patients with the cluster A and cluster B phenotypes.

Table II. Reasons for discontinuation of biologic agents.

Reason for discontinuation, n (%)	Cluster A (n=521, 35.5%)	Cluster B (n=59, 44.7%)
Lack of drug efficacy	164	20
Adverse events	132	13
Clinical remission	65	10
*Others	160	16
Patient's decision	88	11
Follow-up loss	32	2
Cost issue	24	1
Preparing for pregnancy	15	1
Surgery	1	1

Comparison of secondary outcomes (clinical efficacy) at 1-year follow-up

Clinical efficacy data collected at 1-year follow-up were compared in cluster A and cluster B patients. The odds ratio (OR) of patients achieving BASDAI50 were comparable between the two groups both in PS-matched and multivariate logistic regression analyses (O =1.01; 95% CI=0.90–1.13 and OR=1.01; 95%=CI 0.93–1.10, respectively). Other measurements of clinical efficacy, including ASAS20, ASAS40, ASDAS inactive state (ASDAS <2.1),

Table III. Cox regression analysis of drug discontinuation between AS patients with the cluster A and cluster B phenotypes.

Method	Variable	Hazard ratio	95% CI	*p*-value
Propensity score-based	Cluster B (compared to cluster A)	1.568	1.055–2.329	0.026
Covariate adjustment	Cluster B (compared to cluster A)	1.333	1.007–1.764	0.045
	Age	1.004	0.997–1.011	0.234
	Female *vs*. male sex	1.347	1.090–1.666	0.006
	BMI (kg/m^2)			
	<18.5	1.204	0.799–1.813	0.375
	18.5–22.9	1.000 (reference)		
	23.0–24.9	0.951	0.759–1.192	0.663
	≥25.0	1.106	0.899–1.360	0.342
	Current smoker	1.231	1.011–1.499	0.039
	HLA B27 (+) *vs*. HLA B27 (-)	0.659	0.511–0.850	0.001
	ASDAS	0.965	0.881–1.058	0.451
	BASFI score	0.984	0.948–1.022	0.406
	Previous exposure to biologics *vs*. biologics-naïve	1.031	0.838–1.270	0.771
	IL-17i (compared with TNFi)	0.772	0.244–2.446	0.660

TNFi: tumour necrosis factor inhibitor; BMI: Body Mass Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index.

Table IV. Comparison of response rates in AS patients with the cluster A phenotype *versus* the cluster B phenotype after 1-year of treatment.

Measures	Method	Odds ratio	95% CI	*p*-value
BASDAI50	Propensity score-based	1.01	0.90–1.13	0.896
	Covariate adjustment#	1.01	0.93–1.10	0.821
ASAS20	Propensity score-based	1.01	0.90–1.14	0.861
	Covariate adjustment#	0.99	0.91-1.08	0.847
ASAS40	Propensity score-based	0.98	0.87–1.11	0.758
	Covariate adjustment#	0.97	0.89–1.06	0.504
ASDAS<2.1	Propensity score-based	0.96	0.87–1.05	0.379
	Covariate adjustment#	1.06	0.98–1.15	0.139
ΔASDAS≥1.1	Propensity score-based	1.03	0.94–1.13	0.492
	Covariate adjustment#	1.00	0.93–1.07	0.917
ΔASDAS≥2.0	Propensity score-based	1.06	0.94–1.19	0.339
	Covariate adjustment#	1.03	0.96–1.11	0.424

BASDAI50: 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index; ASAS20: an improvement of at least 20%, and an absolute improvement of at least 10 units, on a 0–100 scale in at least three of the following domains: patient global pain assessment, function (BASFI), and inflammation (last two questions of BASDAI); ASDAS: Ankylosing Spondylitis Disease Activity Score; ASAS40: defined as for ASAS20 above, but with improvements of at least 40%; ASDAS <2.1: achievement of an ASDAS <2.1, representing low disease activity; ΔASDAS ≥1.1: improvement in ASDAS of at least 1.1 points; ΔASDAS ≥2.0: improvement in ASDAS of at least 2.0 points.
#Adjusted for age, gender, BMI, smoking status, HLA B27 positivity, ASDAS, BASFI, previous exposure to biologics (compared with biologics-naïve), and type of biologic (tumour necrosis factor inhibitor versus interleukin-17 inhibitor).

and clinically important and/or major improvement in ASDAS, were also comparable between cluster A and cluster B patients (Table IV).

Discussion

In the present study, we used data from the Korean national biologics registry (KOBIO) to demonstrate that the bDMARD retention rate differed between cluster-based phenotypes of AS patients; cluster B patients had an increased risk of drug discontinuation. However, clinical efficacy at 1-year follow-up (assessed by several methods, including BASDAI50, ASAS20, ASAS40, achievement of inactive state of ASDAS, and clinically important and/or major improvement of ASDAS) were comparable in AS patients with cluster A and cluster B phenotypes. Classifying AS patients according to their AS phenotype may be useful for predicting drug retention times and clinical responses when patients are beginning bDMARD therapy.

There are fewer conventional DMARDs and bDMARDs available for AS patients than for patients with rheumatoid arthritis (16-18). Therefore, treatment options are limited for AS patients; the choice of correct medication, and maintaining treatment for a prolonged period, is important when treating AS. Several inflammatory- and autoimmune-mediated diseases have a heterogenic disease course, and the treatment response varies depending on the individual patient (19). A recent study of patients with primary Sjögren's syndrome divided patients into four subtypes (low symptom burden, high symptom burden, dryness-dominant with fatigue, and pain-dominant with fatigue), and suggested that the treatment strategy should be individualized according to the subtypes (6). A cluster-based subgroup analyses of EUSTAR (European Scleroderma Trials and Research) data revealed that patients with systemic sclerosis could be divided into six subtypes according to organ involvement, laboratory profile (including the presence of autoantibodies), and gender (5). This cluster-based phenotyping could predict the survival and prognosis of patients with systemic sclerosis (5). Recent machine learning based phenotype clustering of axSpA could predict radiographic progression (2). An awareness of the importance of precision medicine in rheumatology is emerging (20), and such phenotype-based clustering could be the first step in performing precision medicine. A large prospective French study that included patients with inflammatory back pain suggestive of SpA, known as the DESIR cohort, suggested two cluster-based phenotypes: cluster A (patients exhibiting axial symptoms predominantly) and cluster B (patients exhibiting both axial and peripheral symptoms) (7). In the DESIR cohort, patients were classified according to the initial disease manifestation; the features of the cluster-based phenotypes were followed-up, and data were collected, for 5 years in the same cohort (9). Axial SpA patients with the cluster B phenotype had a higher prevalence of peripheral arthritis, enthesitis, dactylitis, and psoriasis, and had a higher disease

activity score than axial SpA patients with the cluster A phenotype (7). Initiation of tumour necrosis factor (TNF) inhibitor therapy was more common in SpA patients with the cluster B phenotype, whereas patients with the cluster A phenotype more frequently presented with radiographic sacroiliitis (9). In the present study, we demonstrated for the first time that the bDMARD retention rate was higher in AS patients with the cluster A phenotype than in those with the cluster B phenotype. Although a lack of clinical efficacy was the most common cause of bDMARD cessation in both groups, there were several reasons for discontinuation. This is due to the characteristics of the KOBIO registry, which is an observational inception cohort rather than a strictly controlled clinical trial. However, initiation of bDMARDs was strictly controlled in most cases enrolled in the KOBIO registry because the Korean national insurance system covers all residences in Korea, and the insurance review board strictly restricts the use of bDMARDs to AS patients that have had an insufficient treatment response to conventional therapy for at least 3 months. Therefore, the patient groups in which bDMARD treatment was initiated were tightly controlled, whereas discontinuation was not. The HR for total discontinuation cases was higher in cluster B, a finding confirmed by subgroup analysis that excluded drug discontinuation cases that occurred due to reasons other than a lack of drug efficacy (Table III and Suppl. Table S1).

Several factors are known to impact on drug retention of bDMARDs in patients with AS. Female AS patients showed lower retention rate of bDMARDs (21-23). Patients with HLA-B27 negative showed increased risk for bDMARD discontinuation (23-25). In aspect of smoking, one study demonstrated that current or previous smoker showed shorter retention time for TNF inhibitors (26), whereas another study showed that current smoking status did not affect on discontinuation of TNF inhibitors in patients with axSpA (27). However, smoking promotes radiographic progression in patients with AS (2, 28). In present study, being female gender, current smoker, and HLA-B27 negative showed higher risk for bDMARD discontinuation, and these factors should be considered when bDMARDs are starting in patients with AS.

Although there was a significant difference in drug survival rates between AS patients with the cluster A phenotype and those with the cluster B phenotype, the clinical efficacy was comparable at 1-year follow-up. The severity of disease was higher in AS patients with the B phenotype, and AS patients with the cluster B phenotype had an increased probability of starting TNF inhibitor therapy than those in cluster A (7, 9). Here, conventional multivariate and PS-matched Cox regression analyses demonstrated that cluster B patients had a higher risk of discontinuing bDMARD therapy. This finding suggests that the clinical efficacy of bDMARDs is not inferior in AS patients with the cluster B phenotype; rather, the retention rate of bDMARDs is inferior in cluster B patients.

The present study had several limitations. First, and most importantly, it was based on an observational registry. Although we performed PS-matching to overcome the biases inherent in an observational study, residual undetectable bias may exist. Second, the number of participants in cluster B was relatively small. Constantino *et al*. reported that 46.2% of patients enrolled in the DESIR cohort had a cluster B phenotype, whereas in the present study only 8.3% of AS patients had a cluster B phenotype. This discrepancy may arise from differences in the inclusion criteria of the DESIR and the current KOBIO cohorts. The DESIR cohort included patients who had features suggestive of SpA, and the study included patients with early SpA disease, whereas the KOBIO registry only includes AS patients who fulfil the 1984 modified New York criteria for the classification of AS. Therefore, the results of the present study cannot be generalised to non-radiographic axSpA patients. Third, this study included only a few patients receiving an IL-17 inhibitor. The first approved IL-17 inhibitor, secukinumab, was approved for use in Korea in late 2017. The KOBIO registry is an ongoing prospective cohort; therefore, further studies with a larger sample size and more participants treated with an IL-17 inhibitor will be possible in the future. Forth, the name, dosage, and previous treatment duration of concomitant NSAIDs/conventional DMARDs were not presented in present study. These concomitant medications could affect on retention and efficacy of bDMARDs in patients with AS.

In conclusion, we demonstrated that the bDMARD retention rate was inferior in AS patients with the cluster B phenotype, whereas the clinical efficacy at 1-year was comparable between cluster A patients and cluster B patients. The results of the present study suggest that cluster-based phenotyping of AS patients during initiation of bDMARD therapy will help predict the drug retention time.

Acknowledgements

We thank the Clinical Research Committee of the Korean College of Rheumatology for providing the data and all the participating hospitals. Out thanks go especially to Hyoun-Ah Kim, Jung Hee Koh and So Young Park, who substantially contributed to the KOBIO registry management.

References

1. SIEPER J, RUDWALEIT M, BARALIAKOS X *et al*.: The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009; 68 (Suppl. 2): ii1-44.
2. JOO YB, BAEK IW, PARK KS, TAGKOPOULOS I, KIM KJ: Novel classification of axial spondyloarthritis to predict radiographic progression using machine learning. *Clin Exp Rheumatol* 2021; 39: 508-18.
3. SU J, WANG R, DUAN X *et al*.: Clinical characteristics of axial spondyloarthritis patients in China: results from ChinaSpA, the Chinese Spondyloarthritis Registry. *Clin Exp Rheumatol* 2021 Apr 23; PMID 33938794.
4. ALAMANOS Y, PELECHAS E, VOULGARI PV, DROSOS AA: Incidence of spondyloarthritis and its subtypes: a systematic review. *Clin Exp Rheumatol* 2021; 39: 660-7.
5. SOBANSKI V, GIOVANNELLI J, ALLANORE Y *et al*.: Phenotypes determined by cluster analysis and their survival in the prospective European Scleroderma trials and research cohort of patients with systemic sclerosis. *Arthritis Rheumatol* 2019; 71: 1553-70.
6. TARN JR, HOWARD-TRIPP N, LENDREM DW *et al*.: Symptom-based stratification of patients with primary Sjögren's syndrome: multi-dimensional characterisation of international observational cohorts and reanalyses

of randomised clinical trials. *Lancet Rheumatol* 2019; 1: e85-e94.
7. COSTANTINO F, AEGERTER P, DOUGADOS M, BREBAN M, D'AGOSTINO M-A: Two phenotypes are identified by cluster analysis in early inflammatory back pain suggestive of spondyloarthritis: results From the DESIR Cohort. *Arthritis Rheumatol* 2016; 68: 1660-68.
8. BARALIAKOS X, BRAUN J: Non-radiographic axial spondyloarthritis and ankylosing spondylitis: what are the similarities and differences? *RMD Open* 2015; 1: e000053.
9. COSTANTINO F, AEGERTER P, MOLTO A, SCHETT G, BREBAN M, D'AGOSTINO M-A: Cluster-based spondyloarthritis phenotypes defined at baseline are predictive of different severity outcomes at 5-year in the DESIR cohort. *2019 ACR/ARP Annual Meeting* 2019.
10. VAN DER HEIJDE D, DOUGADOS M, DAVIS J *et al*.: ASsessment in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. *Arthritis Rheum* 2005; 52: 386-94.
11. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK H, GAISFORD P, CALIN A: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91.
12. VAN DER HEIJDE D, LIE E, KVIEN TK *et al*.: ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009; 68: 1811-8.
13. MACHADO P, LANDEWÉ R, LIE E *et al*.: Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis* 2011; 70: 47-53.
14. AUSTIN PC: The performance of different propensity score methods for estimating marginal hazard ratios. *Stat Med* 2013; 32: 2837-49.
15. AUSTIN PC: Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011; 10: 150-61.
16. VAN DER HEIJDE D, RAMIRO S, LANDEWÉ R *et al*.: 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017; 76: 978-91.
17. SMOLEN JS, LANDEWÉ RBM, BIJLSMA JWJ *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020; 79: 685-99.
18. WARD MM, DEODHAR A, GENSLER LS *et al*.: 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol* 2019; 71: 1599-613.
19. CHO JH, FELDMAN M: Heterogeneity of autoimmune diseases: pathophysiologic insights from genetics and implications for new therapies. *Nat Med* 2015; 21: 730-8.
20. PITZALIS C, CHOY EHS, BUCH MH: Transforming clinical trials in rheumatology: towards patient-centric precision medicine. *Nat Rev Rheumatol* 2020; 16: 590-9.
21. GLINTBORG B, OSTERGAARD M, KROGH NS, DREYER L, KRISTENSEN HL, HETLAND ML: Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. *Ann Rheum Dis* 2010; 69: 2002-8.
22. VAN DER HORST-BRUINSMA IE, ZACK DJ, SZUMSKI A, KOENIG AS: Female patients with ankylosing spondylitis: analysis of the impact of gender across treatment studies. *Ann Rheum Dis* 2013; 72: 1221-4.
23. MICHEROLI R, TELLENBACH C, SCHERER A *et al*.: Effectiveness of secukinumab versus an alternative TNF inhibitor in patients with axial spondyloarthritis previously exposed to TNF inhibitors in the Swiss Clinical Quality Management cohort. *Ann Rheum Dis* 2020; 79: 1203-9.
24. YAHYA F, GAFFNEY K, HAMILTON L *et al*.: Tumour necrosis factor inhibitor survival and predictors of response in axial spondyloarthritis-findings from a United Kingdom cohort. *Rheumatology* (Oxford) 2018; 57: 619-24.
25. KIM HA, LEE SK, OH S, PARK EH, PARK YB, SHIN K: Comparison of retention rates between tumor necrosis factor-α inhibitors in patients with ankylosing spondylitis: data from the Korean College of Rheumatology Biologics Registry. *Front Med* (Lausanne) 2021; 8: 689609.
26. GLINTBORG B, HÚJGAARD P, LUND HETLAND M *et al*.: Impact of tobacco smoking on response to tumour necrosis factor-alpha inhibitor treatment in patients with ankylosing spondylitis: results from the Danish nationwide DANBIO registry. *Rheumatology* (Oxford) 2016; 55: 659-68.
27. ZHAO SS, YOSHIDA K, JONES GT *et al*.: Smoking status and cause-specific discontinuation of tumour necrosis factor inhibitors in axial spondyloarthritis. *Arthritis Res Ther* 2019; 21: 177.
28. PODDUBNYY D, HAIBEL H, LISTING J *et al*.: Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. *Arthritis Rheum* 2012; 64: 1388-98.