Effectiveness and safety of biologic and targeted synthetic disease-modifying anti-rheumatic drugs in elderly patients with rheumatoid arthritis: real-world data from the KOBIO Registry

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Abstract

Objective

We aimed to evaluate the clinical outcomes and safety of biologic and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) and to identify predictors of treatment responses to b/tsDMARDs in elderly patients with rheumatoid arthritis (RA).

Methods

Data from the nationwide cohort of elderly (≥ 65 years) patients enrolled in the KOBIO Registry were analysed. Clinical outcomes were assessed, including changes in the Simplified Disease Activity Index, after treatment. Adverse events and reasons for drug discontinuation were assessed. Multivariable logistic regression analyses were performed to determine which baseline variables affected treatment responses and adverse events (AE).

Results

Elderly patients treated with b/tsDMARDs (n=355) or conventional synthetic DMARDs (csDMARDs) (n=104) were included. The median age was 70 years and 77% were female. After 1 year, 63% of patients in the b/tsDMARD group and 68% in the csDMARD group achieved remission or low disease activity (LDA). Overall, 27% of patients in the b/tsDMARDs group and 24% in the csDMARDs group experienced AE. A total of 43.4% of patients on b/tsDMARDs discontinued therapy due to lack of effectiveness (27%), AE (34%), or other reasons (35%). The estimated median retention of b/tsDMARDs was 2.5 years. Male sex and non-exposure to tobacco at baseline were independent factors associated with achieving remission or LDA after 1 year. Interstitial lung disease (ILD) was the most prominent comorbidity associated with AE.

Conclusion

Treatment with b/tsDMARDs is effective and well tolerated in elderly patients with RA; nonetheless, ILD is a key comorbidity that should be monitored carefully.

Key words

rheumatoid arthritis, elderly, anti-rheumatic agents, treatment outcome

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by destructive synovitis. The disease affects 0.5–1% of the general population; however, the prevalence in the geriatric population is approximately 2% (1-4). The cumulative lifetime risk of developing RA escalates from the age of 60 to 80 years (5). In fact, the mean age at RA onset has increased from 50 years in the 1970s to 55–65 years in 2000–2013 (6-9). As the life expectancy in the general population is rising, so too is the number of elderly patients with RA. The treatment of patients with RA has changed dramatically over the last several decades. The era of biologic treatment emerged in the late 1990s, and new drugs with different mechanisms of action, as well as biosimilars, have followed (10, 11). As elderly onset RA patients have more radiographic damage than those with young-onset RA (12, 13), intensive treatment to achieve treatment targets should be considered. However, elderly RA patients are less often treated with methotrexate (MTX), or with biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), than younger RA patients, despite having equivalent or even greater disease activity (13-17). Intensive management of RA in elderly patients is challenging due to their comorbidities; furthermore, the benefits of treatment are often weighed against the potential harm from drug-related adverse events (AE).

The risk of AE, especially infection, is a concern in elderly patients treated with b/tsDMARDs. Data from randomised controlled trials are limited owing to exclusion criteria based on age, comorbidities, or co-medication (18). Meanwhile, real-world clinical outcomes and safety data regarding b/tsDMARDs therapy are scarce in elderly patients, other than those treated with tumour necrosis factor (TNF)-α inhibitors.

Therefore, the aim of this study was to investigate the effectiveness and safety of b/tsDMARDs in a large cohort of elderly patients with RA in South Korea, and to identify factors associated with a good treatment response and drug retention.

Methods

Patient population and data collection

The Korean College of Rheumatology Biologics and Targeted Therapy (KOBIO) Registry is a nationwide, multicenter cohort that aims to evaluate the clinical outcomes and AE of b/tsDMARDs treatment in Korean patients (19). Patients with RA were enrolled from 58 hospitals in South Korea from December 2012 (KOBIO-RA). The KOBIO-RA Registry collects longitudinal data from RA patients aged ≥18 years and consists of two treatment cohorts: one comprises patients who initiated b/tsDMARDs as a first- or further-line therapy (b/tsDMARD cohort) and the other comprises patients treated with conventional synthetic DMARDs as the comparator group (csDMARD cohort). If a patient in the csDMARD cohort began b/tsDMARDs treatment, then that patient was moved to the b/tsDMARD cohort. In this study, eligible participants were aged 65 years or older, and were registered in the KOBIO-RA Registry between December 2012 and December 2018 (Supplementary Fig. S1).

The b/tsDMARD cohort included patients who started or switched new b/tsDMARDs. Thus, most patients showed moderate-to-high disease activity at baseline. For the csDMARD cohort, no patient was excluded based on their disease activity score at the time of enrolment.

To compare the effectiveness and safety between csDMARDs and b/tsDMARDs in elderly patients, all patients who achieved remission based on the Simplified Disease Activity Index (SDAI) (SDAI score of ≤3.3) at baseline were excluded (Suppl. Fig. S1) (20).

The KOBIO-RA Registry data include demographics, previous or current use of medications, comorbidities, extra-articular manifestations, and laboratory tests. These data are collected by rheumatologists and from patient questionnaires completed during routine clinical practice. Treatment is chosen at the discretion of each clinician. In Korea, the health care reimbursement system permits use of b/tsDMARDs for RA patients who show an inadequate response to at least two csDMARDs for

more than 6 months. Since 2013, all bDMARDs, except rituximab, can be prescribed as first-line therapy. Before 2013, TNF-α inhibitors were the accepted first-line agents, and abatacept and tocilizumab could be used as second-line agents after failure of TNF-α inhibitors. Tofacitinib was released as a second-line agent in Korea in 2015; it was approved as a first-line agent from July 2017.

Drug retention was evaluated as the time until definitive treatment interruption. Reasons for discontinuation were analysed and classified into the following four categories: (1) lack of effectiveness; (2) disease remission; (3) AE, including infections, skin or systemic reactions, haematologic, pulmonary, renal, or cardiovascular complications, and malignancies; and (4) other reasons, including patient preference, change of hospital, and financial reasons.

De-escalation of b/tsDMARDs can be considered in patients who achieve remission (21). The dose and interval of each b/tsDMARD are recorded in the KOBIO-RA Registry. Standard doses are as follows: etanercept and Brenzys™, 50 mg weekly; adalimumab, 40 mg every other week; infliximab and Remsima™, 5 mg /kg every 8 weeks; tocilizumab, 8 mg/kg every 4 weeks (intravenous) or 162 mg every other week (subcutaneous); abatacept, 500 mg (body weight <60 kg) or 750 mg (body weight >60 kg) every 4 weeks (intravenous) or 125 mg weekly (subcutaneous); and tofacitinib, 5 mg twice daily.

Ethical approval for the use of data from the KOBIO Registry was provided by the Institutional Review Boards (IRB) of all 58 participating institutions. Written informed consent was obtained from participants at each hospital at the time of enrolment in the registry. This study was approved by the IRB of Bucheon St. Mary's Hospital (approval number: H19OCSI0081).

Assessment of disease activity

The disease activity of all patients was evaluated using validated composite measures at every evaluation, which included the disease activity score in 28 joints (DAS28) using the erythrocyte sedimentation rate (ESR), the SDAI, and the clinical disease activity index (CDAI). Trained investigators at each institution performed the joint assessments. Disease activity was categorised as remission or high, moderate, or low disease activity (LDA) based on the American College of Rheumatology (ACR) recommendations (22).

Treatment response

The effectiveness of treatment was assessed using the European League Against Rheumatism (EULAR) treatment response criteria for DAS28 (23, 24) and on the proportion of patients achieving remission or LDA based on the SDAI (20, 25). The former reflects the magnitude of changes in disease activity and the latter reflects whether disease activity is well controlled. If the patient achieved remission or LDA, then the therapeutic goal was achieved (26). The functional capacity of patients with RA was determined using the Routine Assessment of Patient Index Data 3 (RAPID3) (27).

Statistical analysis

Categorical variables are expressed as numbers and percentages, and continuous variables are expressed as medians and interquartile ranges (IQR). The Kruskal-Wallis test and the Mann-Whitney U-test were used for group comparisons. The chi-squared test or Fisher's exact test were used to compare categorical variables.

Logistic regression was used to predict good EULAR treatment responses to b/tsDMARDs, achievement of the therapeutic goal at the first-year follow-up, and occurrence of AE during the observation period. The results of these analyses are presented as odds ratios (ORs) with 95% confidence intervals (CI). ORs for a good treatment response in b/tsDMARDs patients at the first-year follow-up were analysed after adjustment for potential confounders that may influence drug responses or AE.

The survival curves for each b/tsDMARD were constructed using the Kaplan–Meier method and compared using the log-rank test. The observation time was from the start of b/tsDMARDs treatment to an event. An event was defined as any discontinuation of b/tsDMARDs. If patients were lost midway or the cause of death was unknown, then they were censored. If death was related (directly or indirectly) to treatment, these cases were considered to be events. The retention rates of each b/tsDMARD were analysed at 1, 2, and 3 years. Statistical analyses were performed using SAS software, v. 9.4 (SAS Institute, Cary, NC, USA). $p<0.05$ was considered statistically significant.

Results

Baseline characteristics

In total, 449 patients aged 65 years or older were assigned to the b/tsDMARD cohort, and 136 patients to the csDMARD cohort, by December 2018. Among them, 347 patients in the b/tsDMARD cohort and 131 patients in the csDMARD cohort had at least 1 year of follow-up data available. In the csDMARD cohort, 27 patients in SDAI remission at baseline were excluded; 104 patients were finally selected for this study (Suppl. Fig. S1).

The median age of enrolled patients was 70 years (IQR, 67–73), 77% (n=346) were female, and the median disease duration was 6.6 years (IQR, 2.0–13.7). In total, 211 patients (47%) were diagnosed with RA at the age of 65 years or older. The median follow-up duration was 22 months (IQR, 12–36).

The baseline demographic and clinical features of the two groups, and between each b/tsDMARD, were compared (Table I). Eighty percent of patients were never-smokers; however, more patients in the b/tsDMARD group than in the csDMARD group were current smokers ($p=0.018$). For patients with available serologic data, 88% were rheumatoid factor-positive and 87% were anti-citrullinated protein antibody-positive. Fewer tofacitinib users were positive for rheumatoid factor than TNF-α inhibitor users ($p=0.014$).

Patients using b/tsDMARDs were more likely to have a history of tuberculosis (TB) and interstitial lung disease (ILD) than those using csDMARDs. Abatacept was prescribed for 42.9% of patients with ILD; tocilizumab and TNF-α inhibitors were prescribed for 13% and 11% of these patients, respectively (Table I).

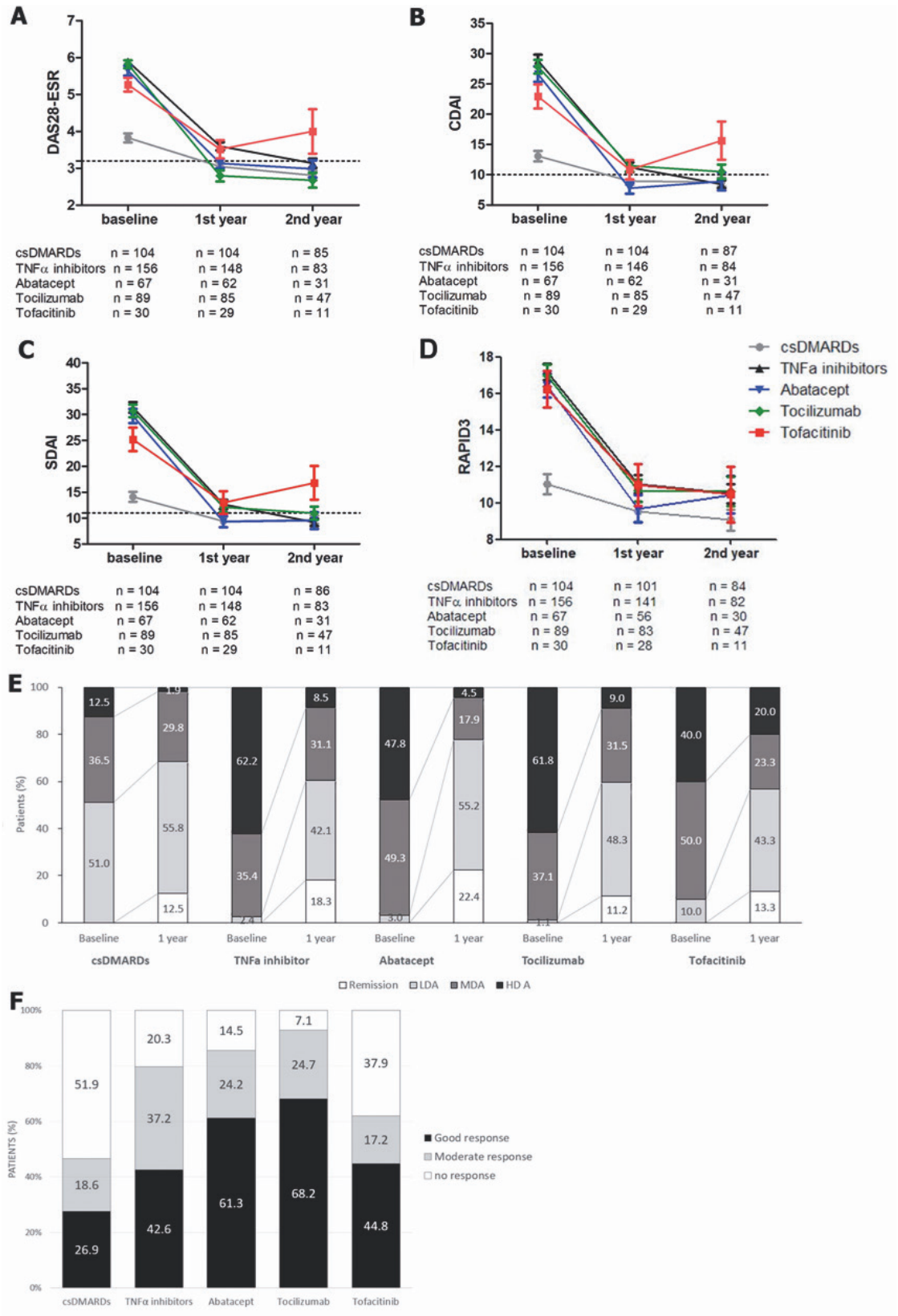

Fig. 1. Time course of disease activity scores over 2 years and the percentage of patients with different disease activity categories at the baseline and 1-year follow-up visits. Points and bars represent the means and standard deviations, respectively. Time course of disease activity scores in 28 joints using erythrocyte sedimentation rate (DAS28-ESR) **(A)**, the Clinical Disease Activity Index (CDAI) **(B)**, the Simplified Disease Activity Index (SDAI) **(C)**, and the Routine Assessment of Patient Index Data 3 (RAPID3) **(D)**. the percentage of patients with different disease activity categories according to SDAI, categorised as follows: SDAI ≤3.3 (remission), 3.3 <SDAI ≤11 (low disease activity, LDA), 11 <SDAI ≤26 (moderate disease activity, MDA), and SDAI >26 (high disease activity, HDA) **(E)**. The percentage of patients showing different European League Against Rheumatism (EULAR) treatment responses at the first-year follow-up **(F)**.

Table I. Baseline characteristics of elderly RA patients at the time of enrolment in the KOBIO-RA registry

	csDMARDs (n=104)	b/tsDMARDs (n=347)	TNF-α inhibitors (n=156)	Abatacept (n=67)	Tocilizumab (n=89)	Tofacitinib (n=30)	P†	P‡
Age, yr	70 (67–73)	70 (67–73)	70 (67–73)	74 (70–79)	70 (67–73)	69 (66–73)	0.398	0.108
Female, n (%)	85 (81.7)	261 (75.2)	117 (75.0)	47 (70.2)	67 (75.3)	25 (83.3)	0.168	0.584
Elderly onset, n (%)	48 (46.2)	163 (47.0)	69 (44.2)	32 (47.8)	50 (56.2)	11 (36.7)	0.883	0.189
Duration of RA, yr	6.8 (2.0–12.4)	6.6 (2.0–14.1)	6.8 (2.3–15.4)	6.6 (2.1–14.1)	5.5 (1.6–11.1)	8.5 (4.5–11.4)	0.372	0.403
BMI, kg/m^2	23 (22–25)	23 (20–25)	23 (20–25)	23 (20–26)	23 (21–25)	22 (19–25)	0.249	0.504
Smoking status								
Never smoker	84 (80.8)	285 (80.7)	127 (81.4)	52 (77.6)	72 (80.9)	24 (80.0)		
Ex-smoker	12 (11.5)	17 (4.9)	8 (5.1)	3 (4.5)	4 (4.5)	2 (6.7)		
Currently smoker	8 (7.7)	50 (14.4)	21 (13.5)	12 (17.9)	13 (14.6)	4 (13.8)	0.016	0.985
RF-positive, n (%)	86/103 (83.5)	294/330 (89.1)*	135/148 (91.2)	57/64 (89.1)	77/86 (89.5)	20/27 (74.1)*	0.130	0.076
ACPA-positive, n (%)	61/70 (87.1)	241/278 (86.7)	103/119 (86.6)	50/57 (87.7)	67/78 (85.9)	17/20 (85.0)	0.921	0.987
Comorbidity, n (%)								
T2 DM	27 (26.0)	80 (23.1)	36 (23.1)	14 (20.9)	22 (24.7)	6 (20.0)	0.541	0.927
Hypertension	59 (56.7)	177 (51.0)	82 (52.6)	32 (47.8)	44 (49.4)	15 (50.0)	0.305	0.917
ILD	5 (4.8)	40 (11.5)	10 (6.4)	18 (26.9)*	11 (12.4)	1 (3.3)	0.045	<0.001
Osteoporosis	47 (45.2)	157 (45.2)	69 (44.2)	30 (44.8)	42 (47.2)	13 (43.3)	0.993	0.970
History of TB, n (%)	6/95 (6.3)	49/327 (15.0)	25/147 (17.0)	10/62 (16.1)	9/85 (10.6)	4/29 (13.8)	0.024	0.601
Concomitant	**csDMARDs**	**Treatment**						
MTX	83 (79.8)	217/336 (64.6)	116/153 (75.8)**	39/61 (63.9)	46/87 (52.9)**	13/30 (43.3)**	0.004	<0.001
LEF	43 (41.4)	48/334 (14.4)	23/151 (15.2)	6/61 (9.8)	13/87 (14.9)	3/30 (10)	<0.001	0.675
HCQ	33 (31.7)	30/334 (9.0)	10/151 (6.6)	9/61 (14.8)	10/87 (11.5)	1/30 (3.3)	<0.001	0.153
SSZ	12 (11.5)	12/334 (3.6)	4/151 (2.6)	4/61 (6.6)	2/87 (2.3)	1/30 (3.5)	0.002	0.551
Tacrolimus	18 (17.3)	20/334 (6.0)	8/151 (5.3)	5/61 (8.2)	5/87 (5.8)	1/30 (3.3)	<0.001	0.789
Glucocorticoids	78 (75.0)	246/337 (73.0)	116/153 (75.8)	46/62 (74.2)	60/87 (69.0)	19/30 (63.3)	0.686	0.432
- PD equivalent dose, mg/day	5.0 (2.5–5.0)	5.0 (4.5–7.5)	5.0 (5.0–7.5)	5.0 (5.0–7.5)	5.0 (2.5–7.5)	5.0 (5.0–6.3)	<0.001	0.371

†csDMARDs group compared with the b/tsDMARDs group. ‡Comparing each b/tsDMARDs using the Kruskal-Wallis test or χ^2 test.
*Significantly different (p<0.05) and **(p<0.01) after *post-hoc* analysis.
ACPA: anti-citrullinated protein antibody; b/tsDMARDs: biologic or targeted synthetic disease modifying anti-rheumatic drugs; BMI: body mass index; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; DM: diabetes mellitus; ILD: interstitial lung disease; HCQ: hydroxychloroquine; LEF: leflunomide; MTX: methotrexate; PD: prednisolone; RA: rheumatoid arthritis; SSZ: sulfasalazine; TB: tuberculosis.

Table II. Prescription of biologic and targeted synthetic DMARDs and causes of treatment discontinuation in elderly RA patients in the KOBIO registry.

n (%)	b/tsDMARDs (n=347)	TNF-α inhibitors (n=156)	Abatacept (n=67)	Tocilizumab (n=89)	Tofacitinib (n=30)	*p*-value
Prior bDMARDs	85 (24.5)	34 (21.8)	16 (23.9)	25 (28.1)	5 (16.7)	0.555
One bDMARD	63 (74.1)	29 (85.3)	12 (75.0)	16 (64)	3 (60)	
Two or more	22 (25.9)	5 (14.7)	4 (25.0)	9 (36)	2 (40)	0.332
Starting dose						
Standard dose	310 (89.3)	133 (85.3)	67 (100)	83 (93.3)	24 (80.0)	
Less than standard dose	37 (10.7)	23 (14.7)	0	6 (6.7)	6 (20.0)	0.001
Dose at the last visit						
Standard dose	242 (69.7)	121 (77.6)¶§	39 (58.2)¶	55 (61.8)§	23 (76.7)	
Less than standard dose	105 (30.3)	35 (22.4)¶§	28 (41.8)¶	34 (38.2)§	7 (23.3)	0.007
Discontinuation	149 (43.4)	74 (47.4)	29 (43.9)	37 (42.5)	8 (27.6)	0.274
Reason for discontinuation						
Remission	6 (4.0)	4 (5.4)	2 (6.9)	0	0	
Insufficient effectiveness	40 (26.9)	22 (29.7)	6 (20.7)	10 (27.0)	2 (25.0)	
All adverse event	51 (34.2)	25 (33.8)	10 (34.5)	11 (29.6)	5 (62.5)	
Other reasons*	52 (34.9)	23 (31.1)	11 (37.9)	16 (43.2)	1 (12.5)	

*Other reasons include patient preference, change in hospital, and financial problems. ¶, § Significantly different after *post-hoc* analysis
b/tsDMARDs: biologic or targeted synthetic disease-modifying anti-rheumatic drugs; TNF-α: tumour necrosis factor α.

Prescription of b/tsDMARDs in elderly patients

In the b/tsDMARDs group, 262 patients (75.5%) were biologic-naïve, whereas 63 patients (18.2%) had a history of using one bDMARD; 22 patients (6.3%) had used two or more b/tsDMARDs (Table II).

Regarding concomitant use of csDMARD, a higher proportion of patients taking TNF-α inhibitors received MTX than those taking tocilizumab or

tofacitinib (75.8% *vs*. 52.9% or 43.3%, respectively; $p<0.001$) (Table I). Similar proportions of patients received glucocorticoids.

Overall, b/tsDMARDs were started at the standard dose/interval in 89% of patients. Tofacitinib was started at less than the standard dose more often than bDMARDs. At the last follow-up (median, 15 months [IQR, 8–32]), 27% of patients using b/tsDMARDs were using less than the standard dose. Of the remaining patients, 63% continued therapy at the standard dose, 3% continued at less than the standard dose, and 7% started therapy at less than the standard dose but increased to the standard dose. A higher percentage of patients using abatacept and tocilizumab reduced the drug dose than did those using TNF-α inhibitors (Table II). Of patients using b/tsDMARDs at less than the standard dose at the last follow-up, 13% were in remission and 65% were in LDA, whereas of those at the standard dose, 15% were in remission and 46% were in LDA.

Treatment responses

At baseline, the median DAS28-ESR, CDAI, SDAI, and RAPID3 values were 3.8 (IQR, 2.9–4.7), 10.0 (IQR, 7.0–18.5), 10.8 (IQR, 7.4–18.7), and 10.5 (IQR, 6.5–14.7), respectively in the csDMARD group, and 5.7 (IQR, 5.1–6.5), 26 (IQR, 20–35), 28.4 (IQR, 21.5–38.1), and 17.0 (IQR, 13.0–21.0), respectively, in the b/tsDMARD group (Fig. 1A-C). Among patients using b/tsDMARDs, those using tofacitinib had significantly lower baseline median DAS28-ESR, CDAI, and SDAI values than those using other bDMARDs. After 1 year, DAS28-ESR, CDAI, SDAI, and RAPID3 values were significantly lower in patients using b/tsDMARDs (Fig. 1A-D).

Overall, the proportion of patients who achieved LDA or remission at the first-year follow-up (based on DAS28-ESR, CDAI, and SDAI scores) was not different between the csDMARD and b/tsDMARD cohorts. Comparison of each b/tsDMARD revealed that a higher proportion of patients using abatacept achieved SDAI-based LDA or remission than those using TNF-α inhibitors, tocilizumab, or tofacitinib ($p=0.038$) (Fig. 1E). In addition, the proportion of patients who achieved SDAI-based LDA or remission after 1 year was greater for biologic-naïve patients than for patients who switched from other bDMARDs (67% *vs*. 53%, respectively; $p=0.019$).

Overall, 53% of elderly patients in the b/tsDMARD group achieved a good EULAR treatment response during the first year, whereas only 27% of patients using csDMARDs did. The percentage of patients using abatacept or tocilizumab who showed a good EULAR treatment response was greater than that of patients taking TNF-α inhibitors or tofacitinib (61% for abatacept, 68% for tocilizumab, 43% for TNF-α inhibitors, and 45% for tofacitinib, $p=0.001$, Fig. 1F). The percentage of patients who switched from other bDMARDs that achieved a good or moderate EULAR response rate at 1 year was lower than that of biologic-naïve patients (75.3% *vs*. 85.1%, respectively; $p=0.044$).

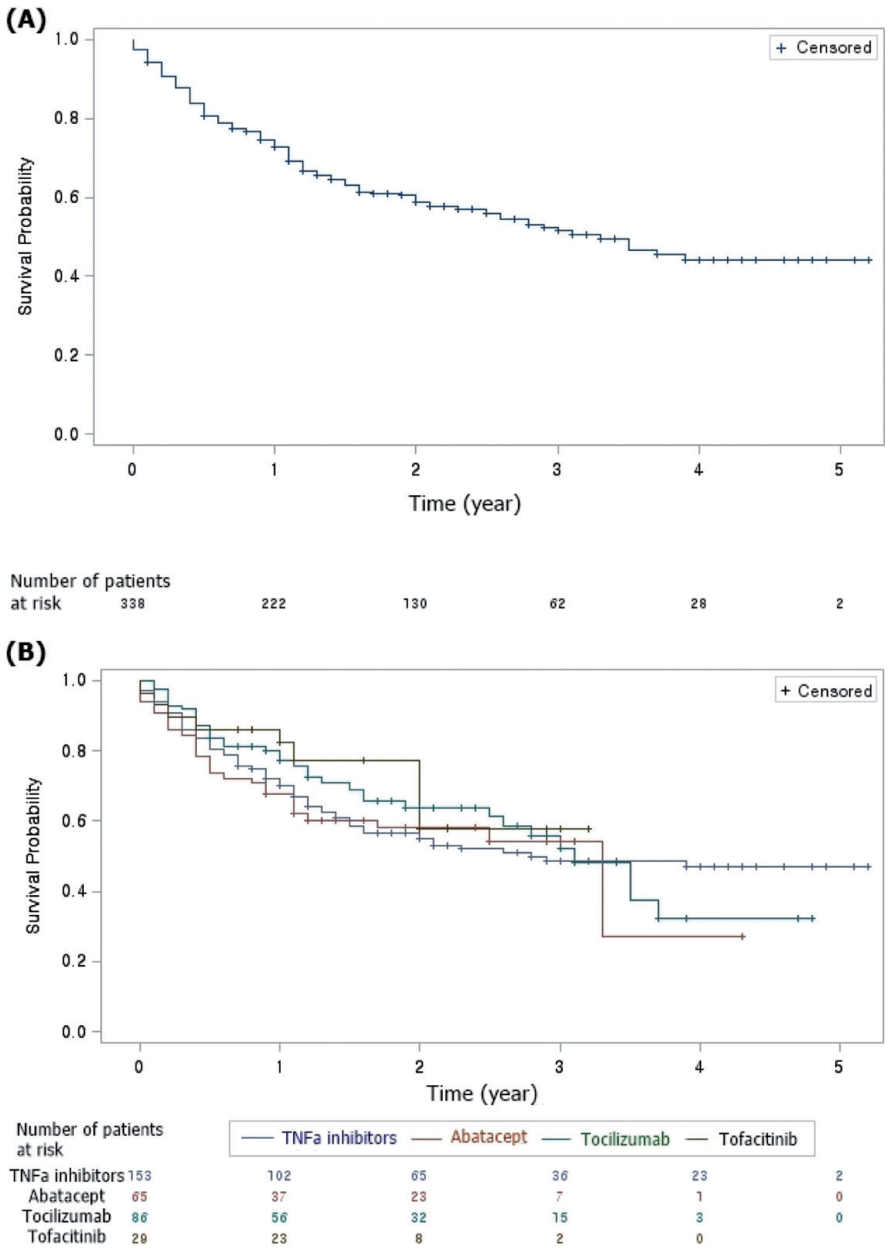

Fig. 2. Drug retention rates of b/tsDMARDs in elderly patients (≥65 years): all b/tsDMARDs **(A)** and individual b/tsDMARDs **(B)**. The number of patients still receiving each drug at various time points is shown.

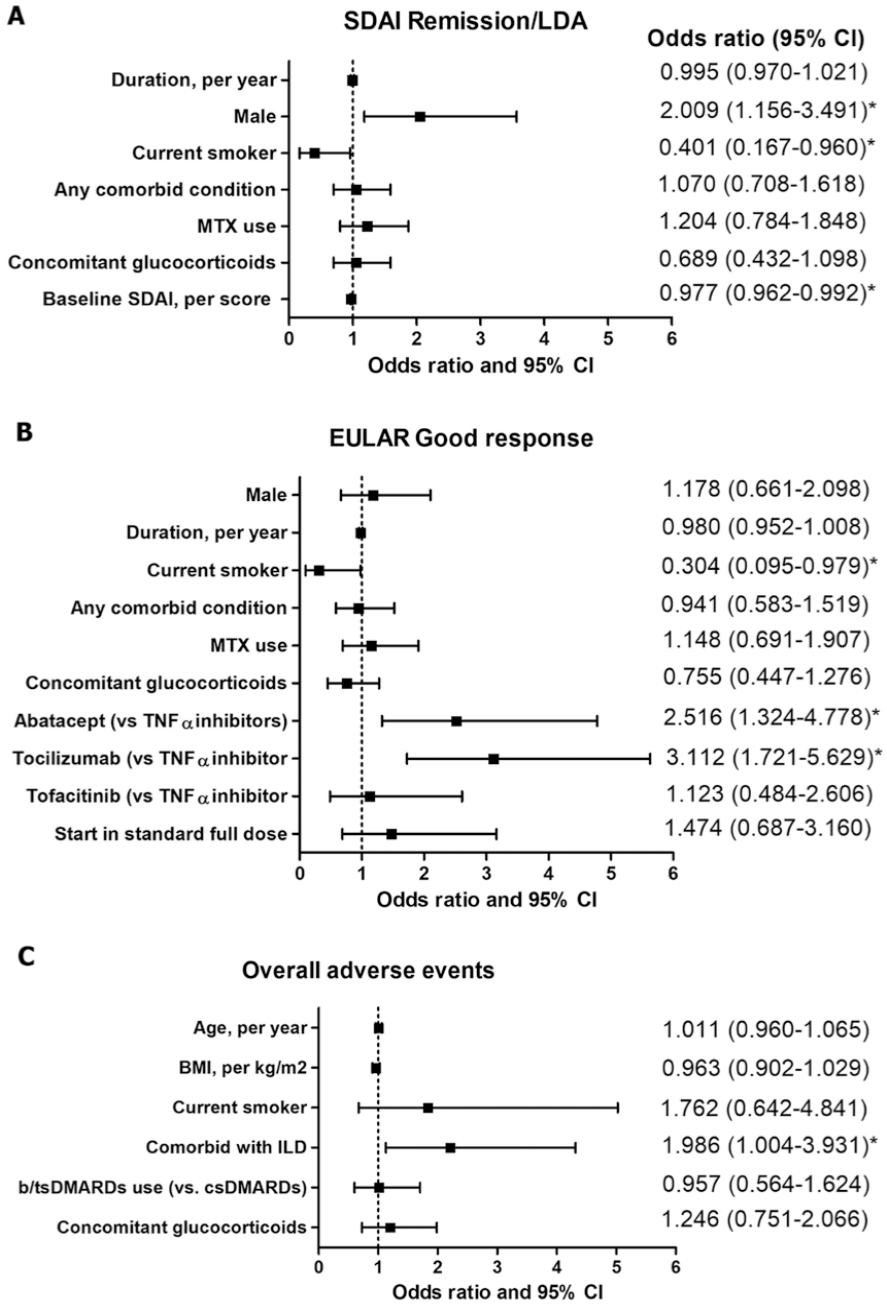

Fig. 3. Predictors of treatment response at the first-year follow-up and AE. Achievement of low disease activity (LDA) or remission **(A)**. Obtaining a good EULAR treatment response after using b/tsDMARDs **(B)**. AE recorded in elderly patients during the follow-up period **(C)**.

Drug retention of b/tsDMARDs

The overall b/tsDMARD retention rates at 1, 2, and 3 years in the KOBIO Registry were 72.6%, 58.7%, and 51.6%, respectively (Fig. 2A). The unadjusted estimate of median retention was 2.5 years. The unadjusted retention rate in the first year was similar between agents: TNF-α inhibitors, 70%; abatacept, 65%; tocilizumab, 77%; and tofacitinib, 83% (log-rank test p=0.718) (Fig. 2B). A total of 148 (43%) patients discontinued b/tsDMARD therapy during the follow-up period. The most common reason for discontinuing b/tsDMARDs in elderly patients was "other reasons" (32.9%), followed by lack of effectiveness (32.2%), AE (30.8%), and remission (4%) (Table II). Patient requests accounted for half of the "other reasons", financial reasons for 20%, and follow-up loss for 20%. Of the AE cited for b/tsDMARD discontinuation, infection was most common (12 patients; two nontuberculous mycobacteria (NTM) infection, two herpes zoster reactivation, and eight "other infections"), followed by malignancy (six solid tumours, two lymphomas, and one skin cancer), and infusion reactions (six patients).

Adverse events

Overall, 120 (27%) patients experienced at least one AE during the observation period (22 months [IQR, 12–36]). The most common AE was infection, with pneumonia being the most common type. Two cases of hepatitis B reactivation were reported; one patient used adalimumab and the other used rituximab. NTM infection was diagnosed in five patients using b/tsDMARDs and in one patient using csDMARDs, whereas no case of TB was reported. Twenty patients (4.4%) reported herpes zoster reactivation during the observation period (Table III).

Malignancies were reported in 20 patients using b/tsDMARDs (seven lung cancers, three lymphomas, two pharyngeal cancers, two melanomas, one basal cell carcinoma, one esophageal cancer, one uterine cancer, one soft tissue neoplasm, one peritoneal cancer, and one cancer with an unknown primary site) and in five patients using csDMARDs (two colon cancers, one endometrial cancer, one pancreatic cancer, and one lung cancer).

In addition, seven serious cardiac disorders (cardiac arrest, myocardial infarction, and acute coronary syndrome) were reported in the b/tsDMARD group and two in the csDMARD group. Two cases with pulmonary venous thromboembolism were reported, one in a tofacitinib user and one in a csDMARD user.

Twenty-two deaths were reported in patients using b/tsDMARDs: nine due to infection, five due to malignancy, two due to cardiac disorders, two due to ILD, two due to acute respiratory distress syndrome (ARDS), and two due to an "unknown cause". Two deaths were reported in patients using csDMARDs, one due to ARDS and one "cause unknown".

Predictors of treatment response

After adjusting for disease duration, overall comorbidities, medications,

Table III. Adverse events

n (%)	csDMARDs (n=104)	b/tsDMARDs (n=347)	*p*-value
Overall adverse events	25 (24.0)	95 (27.4)	0.499
Infection	22 (21.2)	79 (22.8)	0.729
Pneumonia	4 (3.9)	29 (8.4)	0.137
URI	7 (6.7)	16 (4.6)	0.389
NTM	1 (1.0)	5 (1.4)	>0.999
Other infections	8 (7.7)	18 (5.2)	0.336
Herpes zoster	3 (2.9)	17 (4.9)	0.587
New or worsening ILD	2 (1.9)	18 (5.1)	0.185
Cardiovascular event	1 (1.0)	7 (2.0)	0.689
Infusion reaction	-	10 (2.9)	
Malignancy			
Solid neoplasm	5 (4.8)	17 (4.8)	0.994
Lymphoma	0	3 (0.9)	>0.999
Death	2 (1.9)	22 (6.2)	0.084

b/tsDMARDs: biologic or targeted synthetic disease-modifying anti-rheumatic drugs; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; ILD: interstitial lung disease; NTM: non-tuberculosis mycobacterial infection; URI: upper respiratory infection.

and baseline SDAI scores, we found that male gender and non-exposure to tobacco at baseline were independent factors associated with achieving remission or LDA after 1 year of b/tsDMARD therapy (Fig. 3A).

Among patients using b/tsDMARDs, the OR for achieving a good EULAR response at the first-year follow-up was 2.516 (95% CI, 1.324–4.778) for abatacept and 3.112 (1.721–5.629) for tocilizumab [using TNF-α inhibitors as the reference drug]. In addition, the OR for a good EULAR response at baseline was 0.304 (0.905–0.979) for current smokers [in reference to non-smokers] (Fig. 3B).

During the observational period, we found no significant association between the type of DMARD used and development of AE. However, having ILD was an independent predictor for an AE. Among patients using b/tsDMARDs, longer disease duration (OR, 1.038; 95% CI, 1.003–1.073), being a current smoker (OR, 3.248; 95% CI, 1.079–9.780), and ILD (OR, 8.866; 95% CI, 1.804–8.285) at baseline were associated with AE leading to b/tsDMARDs discontinuation (Fig. 3C).

Discussion

The data show that b/tsDMARDs are as effective and well tolerated by elderly patients with RA as csDMARDs. In the present study using longitudinal data from a nationwide cohort, half of the elderly patients with RA who started b/tsDMARDs achieved a good EULAR response, and 63% achieved LDA or remission, after 1 year.

All b/tsDMARDs markedly reduced disease activity. In particular, the ORs for a good treatment response after 1 year were 3.9 for tocilizumab and 3.4 for abatacept, with TNF-α inhibitors being the reference treatment. It is unclear whether treatment response is affected by age. Some studies report age as an important predictor of disease activity improvement after using TNF-α inhibitors (28) and tocilizumab (29), whereas others report similar treatment responses in young and elderly patients after using TNF-α inhibitors (30, 31) and abatacept (32, 33). We found that the proportion of elderly patients prescribed tocilizumab who showed a good EULAR response was comparable with that of younger patients (<65 years) reported in a previous study (29). With respect to the drug persistency of each treatment line, all bDMARDs showed comparable retention rates. Also, the retention rates found in this study were similar to those in previous studies involving elderly patients or patients of all ages (34, 35).

Smoking was a negative predictor for achieving LDA or remission, obtaining a good treatment response after b/tsDMARDs therapy, or having AE leading to discontinuation of b/tsDMARDs. This finding is in line with previous reports showing the negative effects of smoking on treatment responses to TNF-α inhibitors (36, 37). Smoking alters innate and adaptive immune responses, which could result in a systemic proinflammatory state (38). Moreover, current smokers use DMARDs at higher doses, which may indicate that cigarette smoking diminishes the potency of DMARDs (39, 40).

Males were more likely to achieve the treatment goal after 1 year, regardless of the agent used. The baseline DAS28, CDAI, and SDAI scores were not different between males and females; however, the disease activity scores were significantly lower for male patients after 1 year. Moreover, DMARDs were given in a similar manner between genders. In this cohort, tender joint counts and patient global assessment scores were markedly lower for male patients than for female patients. This is consistent with previous studies showing that male patients with RA respond more favourably to treatment (41).

In terms of AE, b/tsDMARDs and csDMARDs demonstrated similar rates of infection and cardiovascular events. No new case of TB was reported in this cohort, presumably because patients followed the latent TB screening/treatment guidelines, although a longer observation period would be needed to confirm this.

As ILD was an independent predictor for AE in elderly patients, we advocate close monitoring in these patients when starting b/tsDMARDs. Furthermore, the risk of developing ILD is higher in RA patients who are older at the time of disease onset, and in individuals with severe RA (42, 43). New-onset or worsening ILD is a possible consequence of TNF-α inhibitors (44). In addition, the proportion of deaths attributable to RA-associated ILD is higher for those on TNF-α inhibitors (45). Among bDMARDs, abatacept is effective for RA-associated ILD and is less likely to trigger or worsen ILD (46, 47). In the present study, abatacept was the drug prescribed most often to patients with ILD. Also, the proportion of new or worsening ILD occurrences was not different between treatment agents. This result is in line with that reported by Curtis *et al*., who showed no difference in the

risk of ILD between RA patients receiving TNF-α inhibitors, tocilizumab, rituximab, and abatacept (48).

At the time of the last follow-up, 30% of patients were prescribed b/tsDMARDs below the standard dose, and 82% of these were in remission or LDA. Life-long b/tsDMARDs therapy at a standard dose may do more harm than good in elderly patients, and the costs of these medications are high. Thus, de-escalation of b/tsDMARD therapy is an attractive option when patients have reached long-standing remission (10, 21). However, further studies are needed.

Frailty is a common clinical syndrome in older adults; this includes unintentional weight loss (or sarcopenia), slow walking speed, self-reported exhaustion, low grip strength, and low levels of physical activity (49). Elderly RA patients with higher DAS28 scores and lower hemoglobin levels are at a greater risk of frailty and related geriatric syndrome (*i.e.* cognitive impairment, depressive symptoms, falls, malnutrition, and urinary incontinence) (50). In this study, physical function (measured using the RAPID3) improved significantly after b/tsDMARD treatment. Thus, to prevent progression to frailty and irreversible geriatric syndrome, intensive treatment using a treatment-to-target strategy should be considered for non-frail or pre-frail elderly patients.

The strength of this study is that it compared treatment outcomes and drug persistency, as well as reasons for discontinuation, for three bDMARDs plus tofacitinib in elderly RA patients in a real-world setting. In addition, we demonstrated that some patients received less than the standard dose of b/tsDMARDs yet maintained disease activity.

The study has some limitations. First, the KOBIO-RA csDMARD cohort included some stable patients. However, the KOBIO-RA b/tsDMARD cohort mostly included patients that switched to b/tsDMARDs from csDMARDs or other b/tsDMARDs. In line with that, the backgrounds of the patients in the two groups were different; this may affect clinical outcomes even after adjusting for potential confounders such as baseline SDAI scores. Second, the only tsDMARD in this study, tofacitinib, was released most recently and is licensed in Korea as a first-line b/tsDMARD agent after failure to achieve treatment targets with csDMARDs; thus there are only a small number of prescriptions, which may have affected the results. Third, the treatment choice and decision to discontinue were made at the discretion of each rheumatologist, with no standardised protocol. However, the majority of patients were heading toward a common goal of LDA or remission; in addition, the proportion of patients achieving LDA or remission was similar between each group or agent. Fourth, the baseline characteristics of patients (ILD, disease duration, or disease activity) using each b/tsDMARDs were different. These differences may have resulted in channeling bias. In addition, the mode of action of each b/tsDMARDs may have biased the treatment response in the first year. A marked reduction in the ESR and CRP levels was observed during the course of anti-IL-6 treatment, which may or may not correspond to changes in other clinical signs and symptoms (51, 52). Fifth, this study analysed registry data, which are affected by inherent limitations such as non-randomisation, observational trial design, and loss of patients to follow-up. However, despite these limitations, these real-world data from a nationwide registry enable the study of a specific population, such as elderly patients and patients with comorbidities, that is often excluded from randomised control trials.

The results of this study suggest that b/tsDMARD treatment is effective and safe in elderly patients with RA in a real-world setting. Abatacept and tocilizumab were associated with better clinical responses than TNF-α inhibitors or tofacitinib in the adjusted model of elderly RA patients. Furthermore, we found that female gender and cigarette smoking were negative predictors of achieving 1-year treatment goals, and having ILD was strongly associated with AE.

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