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Comparison of remission criteria in patients with rheumatoid arthritis treated with biologic or targeted synthetic disease-modifying anti-rheumatic drugs: results from a nationwide registry

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Abstract

Background: Biologic or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARD) are widely used for treatment of rheumatoid arthritis (RA), enabling patients to better achieve remission.

Objective: The objective of the study was to investigate and compare remission rates in RA patients treated with different b/tsDMARDs during the period 2013–2019.

Design: A longitudinal observational analysis was performed on data from a nationwide RA registry.

Methods: Remission rates in the KOBIO-RA registry were defined by a disease activity score in 28 joints (DAS28), clinical disease activity index (CDAI), simplified disease activity index (SDAI), and Boolean-based assessment. After initiating treatment with b/tsDMARDs, yearly remission rates in response to b/tsDMARDs, either all or as subgroups (tumor necrosis factor-α inhibitors, tocilizumab, abatacept, and Janus kinase inhibitors), were investigated for 5 years. Sustained remission was defined as remission maintained for two consecutive years.

Results: Patients ($N = 1805$) who completed at least one follow-up visit were analyzed (mean age = 55 years; 83.2% female). At month 12, 56.0% of patients achieved remission based on DAS28-C-reactive protein (CRP), 36.2% on DAS28-erythrocyte sedimentation rate (ESR), 10.4% on CDAI, 12.7% on SDAI, and 12.9% on Boolean criteria. Sustained remission rates were 62%, 40%, 13%, 11%, and 8% for the DAS28-CRP, DAS28-ESR, Boolean, SDAI, and CDAI remission criteria, respectively. Remission rates using the DAS28 definition varied most among the b/tsDMARD subgroups.

Conclusion: Assessment of sustained remission using the CDAI, SDAI, or Boolean criteria is more stringent, yet congruous with the DAS28-based criteria in RA patients treated with b/tsDMARDs.

Keywords: anti-rheumatic agents, biological products, Janus kinase inhibitors, remission, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease, which leads to articular cartilage and juxta-articular bone destruction[1] and is ultimately associated with physical disability and reduced quality of life.[2,3] In recent decades, the development of novel therapeutic agents, followed by treatment guidelines aiming for early and persistent remission, has revolutionized treatment of RA.[1] The latest therapeutic strategy is based on the treat-to-target recommendation: initiation of treatment with disease-modifying

anti-rheumatic drugs (DMARDs) as soon as the diagnosis of RA is made, and modification of treatment to minimize disease activity to reach a targeted, sustained remission or low disease activity (LDA).[3–5] With this therapeutic approach and the introduction of biological agents, the typical outcome of RA has been dramatically improved.[6–8]

Sustained remission, rather than LDA, is the ultimate treatment target in the management of patients with RA.[4] Conceptually, clinical remission implies an absence of articular and extra-articular inflammation. For detecting and documenting remission, it has been defined using various composite disease activity indices. Remission criteria according to DAS28 (disease activity score in 28 joints), and more stringent disease activity score–based criteria, such as the simplified disease activity index (SDAI) and clinical disease activity index (CDAI), measure disease activity in RA, both in daily clinical practice and in clinical trials.[9,10] The American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) Boolean-based definition of remission was developed for use in clinical trials.[11]

A meta-analysis of real-world evidence demonstrated that the pooled remission rate according to the DAS28 criteria in 2017 was 21.5% for 12 months of follow-up.[12] In a longitudinal observational study, the proportion of patients in DAS28-CRP remission was 39% in 2006 and 58% in 2013, and that of ACR/EULAR Boolean remission was 12% and 19%, respectively.[13] In another study of patients between 2017 and 2019, the remission rate was calculated by the DAS28-CRP and Boolean criteria, and was found to increase to 62% and 24.7%, respectively.[14] Those studies included 30% and 18% of patients who were treated with biologic or targeted synthetic DMARDs (b/tsDMARDs), respectively.[13,14] The remission rate is lower when it is defined by more stringent criteria.[14,15] To date, different definitions of remission have been used and different proportions of patients treated with b/tsDMARDs have been included.

With the introduction of targeted agents with different modes of action, the spectrum of therapeutic options has broadened. Few studies, however, have focused on the real-world efficacy of b/tsDMARDs. The aim of this study of real-world data from a drug register was to investigate and compare remission rates in response to targeted treatment with different modes of action in patients with RA during the period 2013–2019.

Materials and methods

Study population

This study used the KOrean College of Rheumatology BIOlogics and Targeted therapy (KOBIO) registry to investigate clinical remission rates in patients with RA in Korea. The KOBIO registry is a nationwide web-based observational registry used to prospectively assess the clinical manifestations and outcomes of RA patients who initiate or switch to another b/tsDMARD.[16] All patients were adults (⩾18 years) and met the 2010 ACR/EULAR classification criteria for RA.[17] RA patients had follow-up assessments by individual investigators at 12-month intervals. Ethical approval of the KOBIO Registry was provided by the institutional review boards (IRBs) of all 58 participating institutions. All patients provided written consent to participate in the registry. This study was approved by the IRB of Seoul Metropolitan Government-Seoul Boramae Medical Center (approval number: 07-2021-46). STROBE guidelines were used to ensure the reporting of this observational study.[18]

To determine remission rates, patients who were followed up for at least 1 year were included. For this study, we analyzed patients enrolled between December 2012 and January 2019. Patients with any other combined autoimmune inflammatory disease, such as systemic lupus erythematosus, Sjogren's syndrome, or dermatomyositis were excluded.

In Korea, national health insurance covers the entire population. For reimbursement, b/tsDMARDs should be prescribed for patients with RA who have an inadequate response to two or more conventional synthetic DMARDs (csDMARDs), including methotrexate (MTX). In addition, such treatment can be instituted for patients with high disease activity and those with moderate disease activity documented by radiographic progression. Anti-CD20 monoclonal antibodies were only available as a second-line biological agent after failure of other b/tsDMARDs. Thus, few patients used anti-CD20 monoclonal antibodies (0.9% in the KOBIO registry at baseline) and they were excluded from this analysis. As of January 2019, the tumor necrosis factor inhibitors (TNFis) approved for prescription in Korea were infliximab and its biosimilars, etanercept and its biosimilars, adalimumab, and golimumab. An interleukin-6 (IL-6) receptor inhibitor was tocilizumab, a T-cell costimulatory

blocker was abatacept, and Janus kinase inhibitors (JAKis) were tofacitinib and baricitinib.

Variables

The main variables documented in the KOBIO registry include age, sex, disease duration, comorbidities, and previous or current use of medications. The following laboratory findings were measured: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), and anti-cyclic citrullinated peptides antibodies (ACPAs). Physical examinations to assess disease activity were based on clinical counts of tender and swollen joints. The results of the 10-cm visual analog scale for patient global assessment (PGA) and physician global assessment (PhGA) were also recorded. Quantitative measurements of RA disease activity, such as disease activity scores of 28 joints (DAS28) based on ESR and CRP, SDAI, and CDAI, were evaluated when b/tsDMARD treatment was initiated and at each follow-up visit. In addition, there was an annual assessment of whether remission, as defined by the Boolean criteria, was achieved.

Remission was defined by DAS28-CRP < 2.6, DAS28-ESR < 2.6, CDAI $\leqslant 2.8$, SDAI $\leqslant 3.3$, and Boolean-based remission [28 swollen joint counts (SJCs), 28 tender joint counts (TJCs), PGA, and CRP (mg/dl), all $\leqslant 1$].[11] Remission rates defined by various remission criteria and modes of action of b/tsDMARDs were analyzed at 12, 24, 36, 48, and 60 months after enrollment in the KOBIO registry. Sustained remission rate, defined as the proportion of patients who maintained remission at two consecutive visits, was also analyzed.

We assessed residual SJC in patients meeting each definition of remission at the 12-month visit. Swollen joints are related to progression of joint damage assessed by plain radiography;[19] thus residual SJC, despite satisfying the remission criteria, is used for assessing face validity of remission criteria.[11,20]

Statistical analysis

Analyses were carried out using the observed data with pairwise deletion of missing values (0.1%) that were likely missing at random since Little's test was insignificant (normed $\chi^2 = 0.963$). Demographic and disease characteristics are described as mean ± standard deviation (SD) or proportion (%). Mean changes in each disease activity score–based index were analyzed by the Wilcoxon rank-sum test. Remission rates are presented as percentages. To compare the remission rate of each b/tsDMARD by its mechanism of action, the chi-square test was used, and p values < 0.05 were considered significant. The median time required to achieve DAS28-CRP sustained remission for two consecutive years was analyzed by Kaplan–Meier survival estimates. SPSS 24 (IBM, Chicago, IL, USA) software was used for data analysis.

Results

Baseline characteristics

From December 2012 to January 2019, 2261 patients with RA were enrolled in the KOBIO registry. Among them, 2241 patients started TNFi, abatacept, tocilizumab, or JAKi and 1805 patients (80.5%) completed the 12-month assessment (Figure 1). The mean (± SD) duration of follow-up was 36 ± 18 months. The mean age at the time of inclusion was 55 ± 13 years and 83.2% were female. Median disease duration at enrollment was 5.5 [interquartile range (IQR) = 2–12] years, and 83.8% and 85.1% of patients were positive for RF and ACPA, respectively. CsDMARDs were used in combination with b/tsDMARDs in 93.6% of patients; 81.6% of patients received MTX. Glucocorticoids were prescribed for 85.5% of patients (Table 1). For 6 years, TNFi was the most prescribed b/tsDMARD (52.7%), followed by tocilizumab (26.4%) and abatacept (13.2%).

Disease activity at baseline was mostly moderate to severe (93–97%, according to the indices), with a mean (± SD) DAS28-ESR of 5.6 ± 1.1, DAS28-CRP of 4.9 ± 1.1, CDAI of 27.0 ± 11.0, and SDAI of 29.3 ± 11.8.

Prevalence of remission

All disease activity indices decreased significantly after initiating b/tsDMARD treatment; DAS28-CRP decreased by 2.1 ± 1.5 (mean ± SD), DAS28-ESR by 2.3 ± 1.6, CDAI by 15.8 ± 13.2, and SDAI by 17.2 ± 14.2.

At month 12, 1013 patients achieved remission in response to DAS28-CRP (56%), with 60.5%, 65.9%, 65.2%, and 65% of those at months 24, 36, 48, and 60, respectively [Figure 2(a)]. Including patients with LDA, 71.4%, 76.8%,

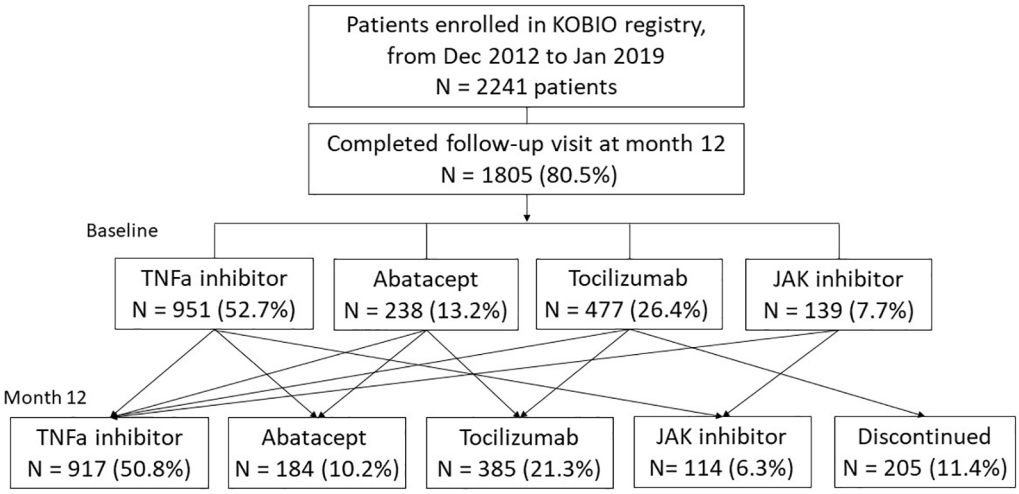

Figure 1. Overview of the study.
JAK, Janus kinase; TNF, tumor necrosis factor.

80.3%, 80.6%, and 78.5% achieved the DAS28-CRP treatment goal at months 12, 24, 36, 48, and 60, respectively.

The remission rate was lower when it was based on other composite measures of disease activity [Figure 2(b)–(e)]. Compared with the other indices, remission rates based on CDAI were lowest: 10.4%, 10.8%, 12.8%, 11.7%, and 12.7% at months 12, 24, 36, 48, and 60, respectively [Figure 2(c)]. The proportion of patients with both LDA and remission determined by CDAI was 62.6%, 72.1%, 78.4%, 89.2%, and 76.3% at months 12, 24, 36, 48, and 60, respectively.

Among patients who visited for more than two consecutive years, 62% were in sustained remission as defined by DAS28-CRP. The sustained remission rate was lower when it was defined by DAS28-ESR, CDAI, SDAI, or the Boolean criteria: 39.8%, 8.3%, 10.8%, and 13.0%, respectively [Figure 2(f)]. The median time required to achieve sustained remission for at least 2 years based on DAS28-CRP was 39.6 (IQR = 28.3–46.2) months.

When remission rates were compared by the mechanism of action of the b/tsDMARDs, those based on DAS28-CRP were lower in TNFi users than in other b/tsDMARD users at month 12; however, they were not different thereafter [Figure 3(a)]. Tocilizumab showed the highest remission rate determined by DAS28-ESR on each follow-up visit [Figure 3(b)]. For 12–36 months, the remission rates based on CDAI and SDAI were not different between b/tsDMARDs [Figure 3(c) and (d)]. The Boolean-based remission rate was higher for abatacept than other b/tsDMARDs at month 12 [Figure 3(e)]. The remission rates defined by CDAI, SDAI, and the Boolean criteria were lower in patients treated with tocilizumab and JAKi at month 48 [Figure 3(c)–(e)].

Patients in DAS28 remission showed more residual SJC than those in SDAI or CDAI remission [Figure 4(a)]; 6.6% of DAS28-ESR remitters and 7.4% of DAS28-CRP remitters had more than one swollen joint, followed by 1.3% and 1.1% of SDAI and CDAI remitters, respectively. Among patients in DAS28-ESR remission, 10.2% of those treated with tocilizumab had at least two swollen joints, followed by 5.7% with TNFi and 2.6% with JAKi [Figure 4(b)].

Discussion

In this longitudinal observational study, we used KOBIO-RA registry data to compare remission rates based on five remission criteria. Over 5 years, DAS28-CRP criteria generated remission rates that were 1.4- to 1.6-fold higher than DAS28-ESR and 5.1- to 5.6-fold higher than CDAI. Remission rates determined by SDAI, CDAI, and the Boolean definition were consistently similar to each other. At month 12, more than half of patients treated with b/tsDMARDs achieved remission based on DAS28-CRP; however, a considerable proportion of patients did not satisfy the ACR/EULAR criteria for remission. For 6 years, 61.6%

Table 1. Baseline characteristics of the study population at enrollment.

Variables	(*N* = 1805)
Age, years (IQR)	55 ± 13
Female, *n* (%)	1501 (83.2)
BMI, kg/m^2 (IQR)	22.7 ± 3.5
Disease duration, years (IQR)	5.5 (1.8–11.6)
Smoking status, *n* (%)	
Never smoker	126 (84.5)
Ex-smoker	121 (6.7)
Current smoker	158 (8.8)
RF positive, *n* (%)	1452/1733 (83.8)
ACPA positive, *n* (%)	1278/1501 (85.1)
Comorbidity, *n* (%)	
Hypertension	533 (29.5)
Type 2 DM	214 (11.9)
ILD	87 (4.8)
Chronic hepatitis B	53 (2.9)
Chronic hepatitis C	11 (0.6)
Previous use of b/tsDMARDs, *n* (%)	440 (24.4)
Baseline disease activity	
Swollen joint count (0–28)	7 ± 5
Tender joint count (0–28)	9 ± 7
Patient's Global Assessment (0–10 cm)	7 ± 2
Physician's Global Assessment (0–10 cm)	6 ± 2
ESR, mm/h (IQR)	49 ± 28
DAS28-ESR	5.6 ± 1.1
DAS28-CRP	4.9 ± 1.1
CDAI	27.0 ± 11.0
SDAI	29.3 ± 11.8
Conventional DMARD combination	1689 (93.6)
Methotrexate	1473 (81.6)
Leflunomide	218 (12.1)
Sulfasalazine	120 (6.7)
Hydroxychloroquine	193 (10.7)

ACPA, anti-citrullinated protein antibody; BMI, body mass index; b/tsDMARDs, biologic or targeted synthetic disease-modifying anti-rheumatic drug; CDAI, clinical disease activity index; CRP, C-reactive protein; DM, diabetes mellitus; DMARD, disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; ILD, interstitial lung disease; IQR, interquartile range; RF, rheumatoid factor; SDAI, simplified disease activity index.

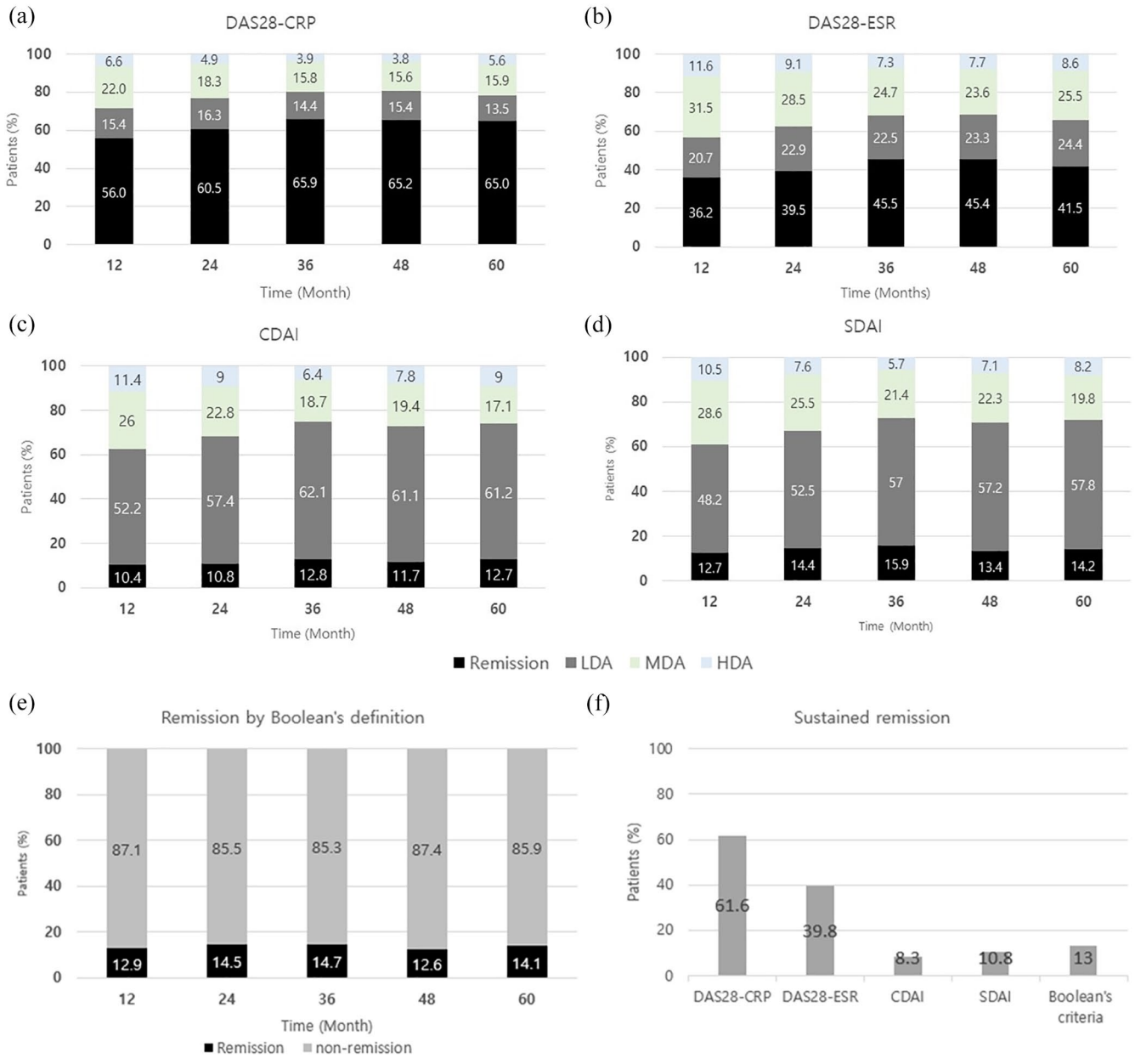

Figure 2. Annual response to initiation of b/tsDMARD treatment. The percentage of patients with different disease activities according to (a) DAS28-CRP, categorized as follows: DAS28-CRP ⩽ 2.6 (remission), 2.6 < DAS28-CRP ⩽ 3.2 (low disease activity, LDA), 3.2 < DAS28-CRP ⩽ 5.1 (moderate disease activity, MDA), and DAS28-CRP > 5.1 (high disease activity, HDA); (b) DAS28-ESR, categorized as follows: DAS28-ESR ⩽ 2.6 (remission), 2.6 < DAS28-ESR ⩽ 3.2 (LDA), 3.2 < DAS28-ESR ⩽ 5.1 (MDA), and DAS28-ESR > 5.1 (HDA); (c) CDAI, categorized as follows: CDAI ⩽ 2.8 (remission), 2.8 < SDAI ⩽ 10 (LDA), 10 < CDAI ⩽ 22 (MDA), and SDAI > 22 (HDA); (d) SDAI, categorized as follows: SDAI ⩽ 3.3 (remission), 3.3 < SDAI ⩽ 11 (LDA), 11 < SDAI ⩽ 26 (MDA), and SDAI > 26 (HDA); and (e) Boolean-based assessment. (f) Prevalence of sustained remission according to each set of criteria.
CDAI, clinical disease activity index; CRP, C-reactive protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; SDAI, simplified disease activity index.

of patients achieved sustained DAS28-CRP remission for at least two consecutive years, followed by DAS28-ESR, 40%; CDAI, 8.3%; SDAI, 10.8%; and the Boolean definition, 13%.

As remission is the ultimate target of modern RA treatment, the definition of remission is critically important. In contrast to the clinical trial setting, the definition of disease remission in clinical practice is

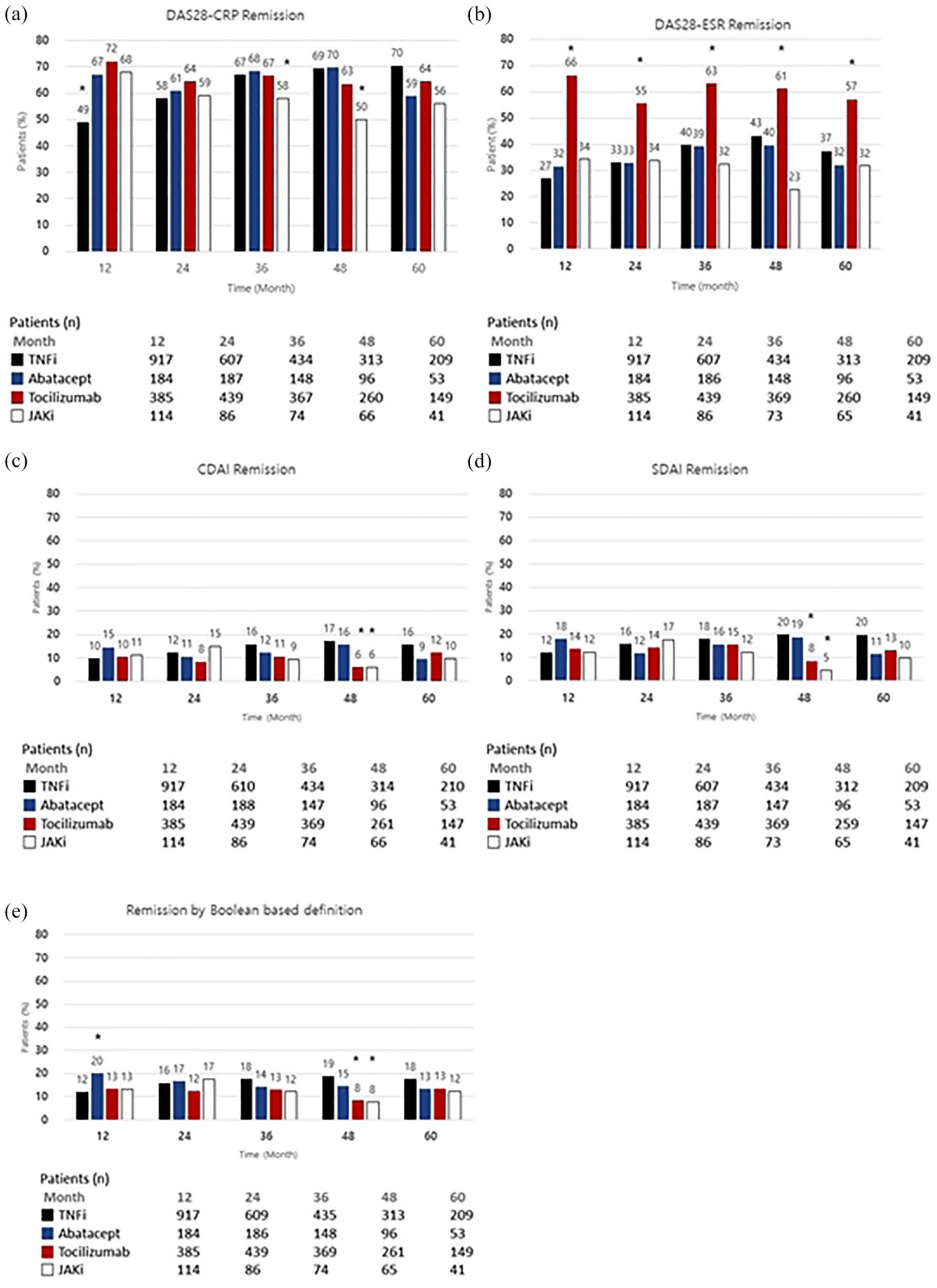

Figure 3. Distinct effects of different therapies on remission according to various criteria: (a) DAS28-CRP, (b) DAS28-ESR, (c) CDAI, (d) SDAI, and (e) Boolean's criteria.
Disease activity score in 28 joints using C-reactive protein level (DAS28-CRP) $<$ 2.6, a DAS28 using the erythrocyte sedimentation rate (DAS28-ESR) $<$ 2.6, a clinical disease activity index (CDAI) score $\leqslant$ 2.8, a simplified disease activity index (SDAI) score $\leqslant$ 3.3, and Boolean-based remission. JAKi, Janus kinase inhibitors; TNFi, tumor necrosis factor inhibitors.

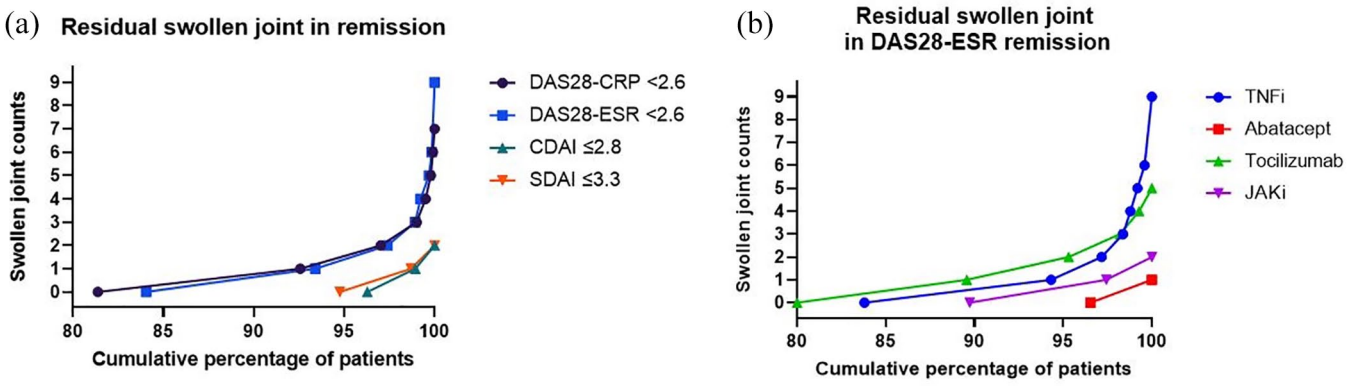

Figure 4. Residual swollen joints in patients in remission. The X-axis shows the cumulative percent of patients. The Y-axis shows swollen joint counts (SJC28). (a) SJC28 of patients in remission according to DAS28-CRP, DAS28-ESR, CDAI, and SDAI; (b) SJC28 of patients in DAS28-ESR remission (DAS28-ESR < 2.6) according to the mechanism of action of biologic and targeted synthetic disease-modifying anti-rheumatic drugs.

not clear.[11] Arguably, DAS28 calculated with CRP or ESR has been widely employed to trace disease activity in real-world clinical practice.[12] Due to significant residual disease activity, the DAS28-based definition is excluded from the ACR/EULAR provisional definitions of remission.[11] A lower DAS28 remission threshold ('deep remission') has been suggested to taper bDMARDs.[21] Even with a lower cut-off, however, DAS28-based remission is frequently associated with considerable residual clinical disease activity.[11,22] In this study, we observed that DAS28 remission allows a considerable proportion of patients to be classified as in remission despite the presence of a significant SJC. Moreover, with a remission cut-off of < 2.6, DAS28-CRP may underestimate disease activity more than DAS28-ESR. There is some discussion that the threshold for DAS28-CRP remission should be lowered.[23]

Compared with other b/tsDMARDs, IL-6 receptor inhibitor elicits more frequent DAS28-ESR-based remission than do DAS28-CRP, CDAI, SDAI, or Boolean. This can be explained by the secretion of the acute-phase reactant being largely dependent on IL-6 and TNFα, while IL-6 inhibitor, TNFi, and JAKi interrupt this pathway.[24,25] Indeed, among patients in DAS28-ESR remission, users of tocilizumab, TNFi, and JAKi had considerable residual SJCs. Although ESR and CRP are the only completely objective disease activity indices, they often do not correlate with disease activity as measured by joint counts, global assessment, or histological inflammation in the synovial tissue.[26,27] DAS28-ESR and DAS28-CRP formulae share identical variables and multiplicands; however, the contributions of ESR and CRP are different: ESR contributes about 15% to DAS28-ESR, while CRP contributes approximately 5% to DAS28-CRP, similar to SDAI.[28] Thus, the DAS28-based definition of remission may not be a reliable instrument for assessing remission in RA patients treated with b/tsDMARDs.

The level of remission in Korean patients with RA has been reported in two cross-sectional, registry-based studies. The remission rate of a multicenter cohort of patients between 2009 and 2016, most of whom (93%) used csDMARDs, was highest when it was based on the DAS28-CRP score (47.1%), followed by DAS28-ESR (28.6%), SDAI (18.0%), CDAI (17.6%), and the Boolean definition (12.2%).[29] The other study, which included 16% bDMARD users, investigated remission rates between 2012 and 2014, and found the remission rate to be even lower: DAS28-CRP, 27.5%; DAS28-ESR, 14.5%; SDAI, 11.0%; and CDAI, 5.4%.[30] While significant treatment advances have been made over several decades, remission according to the most stringent definition was not achieved in the majority of Korean RA patients. If patients with LDA were included, 60–70% achieved the treatment target defined by CDAI or SDAI. Because patients with LDA continued to have residual disease, more aggressive treatment, however, seems to be necessary to achieve remission defined by the CDAI, SDAI, or Boolean criteria.

This study has some limitations. First, as radiographic data are not quantitatively assessed in the

KOBIO registry, we could not analyze the relationship between remission as defined by each criterion and subsequent radiographic progression. Second, we did not compare remission rates in patients treated with csDMARDs. Third, the time period was different for each b/tsDMARD reported in the registry. TNFi was the most frequently used bDMARD, as it was approved as a first-line b/tsDMARDs after an insufficient response to csDMARD combination therapy in Korea before 2013. The first JAKi, tofacitinib, was released in Korea in 2015 as a second-line agent after failure of bDMARD treatment and it was approved as a first-line agent starting in July 2017. For that reason, the period for which responses to JAKi were reported was relatively short (median = 1.2 years; IQR = 1.0–2.1 years). Finally, differences in patient responses according to line of therapy (i.e. first-line therapy following csDMARD failure, and second-line or more therapy after failure of b/tsDMARDs) are possible. Although the rates of remission defined by CDAI and SDAI were not different between first- and second-line therapy or more with each b/tsDMARD (data not shown), the mechanism of action of previous agents may need to be taken into consideration when comparing remission rates.

The advantage of our study was analysis of nationwide registry data, which included a large number of patients treated with b/tsDMARDs and followed for a long period of time. In the targeted treatment era, this study provides real-world remission data for b/tsDMARDs that have been widely used. By comparing remission rates according to all available composite disease activity indices and the mechanisms of action of b/tsDMARDs, we confirmed that remission can be overestimated to an extent that depends on which index and definition is used. Thus, comparisons of remission rates between b/tsDMARDs should be carefully interpreted and analyzed.

Conclusion

DAS28-based remission criteria are more sensitive to changes in acute-phase reactants, which leads to the distinctive variation in remission rates among the b/tsDMARD therapies. Remission rates based on CDAI, SDAI, or the Boolean criteria are more stringent, yet are congruous with the DAS28-based criteria in RA patients treated with b/tsDMARDs.

Ethics approval and consent to participate

Ethical approval of the KOBIO Registry was provided by the Institutional Review Boards (IRB) of all 58 participating institutions. All patients provided written consent to participate in the registry. This study was approved by the IRB of Seoul Metropolitan Government-Seoul Boramae Medical Center (approval number: 07-2021-46).

Author contribution(s)

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Yusun Lee: Conceptualization; Funding acquisition; Project administration; Writing – original draft.

Hyoun-Ah Kim: Conceptualization; Investigation; Supervision; Writing – review & editing.

Jinhyun Kim: Conceptualization; Data curation; Investigation; Supervision; Writing – review & editing.

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Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article.

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