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# Similarity of Response to Biologics Between Elderly-onset Rheumatoid Arthritis (EORA) and Non-EORA Elderly Patients: From the FIRST Registry

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*ABSTRACT.* ***Objective.*** Increasing numbers of patients are developing rheumatoid arthritis (RA) at an older age, and optimal treatment of patients with elderly-onset RA (EORA) is attracting greater attention. This study aimed to analyze the efficacy and safety of biologic/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) in EORA and non-EORA elderly patients.

***Methods.*** A cohort of patients with RA treated with b/tsDMARDs were retrospectively analyzed. Only patients aged ≥ 60 years were included. Among them, patients who developed RA aged ≥ 60 years were categorized as EORA, whereas those aged < 60 years were categorized as non-EORA elderly. Disease activity was compared between the EORA and non-EORA elderly groups.

***Results.*** In total, 1040 patients were categorized as EORA and 710 as non-EORA elderly. There were no significant differences in characteristics at baseline between the 2 groups. The proportion of patients with low and high disease activity was comparable at Weeks 2, 22, and 54 between the EORA and the non-EORA elderly group. There were no significant differences in the reasons for the discontinuation of b/tsDMARDs between the 2 groups. Elderly RA onset did not affect changes in Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire–Disability Index, nor did it affect the reasons for b/tsDMARD discontinuation between the 2 groups. The trajectory analysis on CDAI responses to b/tsDMARDs for 54 weeks identified 3 response patterns. The proportion of patients categorized into each group and CDAI response trajectories to b/tsDMARDs were very similar between EORA and non-EORA elderly patients.

***Conclusion.*** CDAI response patterns to b/tsDMARDs and HR of adverse events were similar between EORA and non-EORA elderly patients.

*Key Indexing Terms*: aged, biological product, rheumatoid arthritis

Rheumatoid arthritis (RA) is an inflammatory disease that involves synovial tissue and causes joint destruction. While it has been considered to predominantly affect middle-aged women, a previous study showed that the age of RA onset is increasing with time.[1] Consistent with the aging population and increasing longevity of patients with RA, treatment of elderly patients with RA is becoming increasingly important in clinical practice.

Patients with elderly-onset RA (EORA) comprise those who develop RA after the age of 60 years,[2] and these patients tend to have different disease characteristics than patients with younger-onset RA (YORA). Previous reports have demonstrated that patients with EORA are more likely to be male, have a more abrupt disease onset, have more severe physical symptoms (frequently accompanied by a polymyalgic onset), not be rheumatoid factor (RF)-positive, have a higher interleukin (IL)-6

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titer, and have a lower tumor necrosis factor-α (TNF-α) titer compared with patients with YORA.[2–10]

However, biological factors such as serological findings, organ function, and fragility differ between elderly vs younger patients. For example, average erythrocyte sedimentation rate (ESR) titers and Health Assessment Questionnaire–Disability Index (HAQ-DI) may be higher among elderly patients than younger patients, making RA activity appear more severe in elderly patients compared with younger patients. Therefore, comparing EORA patients with the same age group of patients with RA who have had a longer disease duration is as important as comparing patients with EORA and YORA.

EORA and YORA also differ in the risk of adverse events (AEs). Despite acute and severe symptoms, patients with EORA are not always treated with sufficient doses of disease-modifying antirheumatic drugs (DMARDs). In general, elderly patients with RA are more likely to be treated with glucocorticoids (GCs) and with lower doses of methotrexate (MTX) compared with younger patients.[11] As MTX is contraindicated in patients with declined renal functions and low albuminemia, infrequent use of MTX in elderly patients may reflect declined organ function.

Although biologic/targeted synthetic (b/ts) DMARDs are promising treatment options for elderly RA patients with comorbidities, patients with EORA are also less frequently treated with b/tsDMARDs[12,13] compared with younger patients, which might be due to concerns about the risk of AEs. Previous studies have shown that advanced age is a significant risk factor for infectious diseases[14] and serious AEs[15] among patients with RA treated with b/tsDMARDs, particularly TNF inhibitors (TNFi),[16,17] although others have reported no differences.[13,18] This recognition of serious AEs often makes physicians hesitant to treat elderly patients with b/tsDMARDs.[11,12,13] Most of these studies compare patients with EORA to those with YORA. As general risk for AEs increases with age, the safety of these treatments may also need to be assessed within the same age group.

From this viewpoint, our study retrospectively compares patients with EORA to non-EORA elderly patients, with respect to the efficacy and safety of b/tsDMARDs.

## METHODS

*Study setting*. The FIRST registry is a multiinstitutional cohort of patients with RA treated with b/tsDMARDs. Patients were recruited at the University of Occupational and Environmental Health and its affiliated hospitals.

All patients were treated following the 2019 European Alliance of Associations for Rheumatology and the 2014 Japan College of Rheumatology recommendations for the management of RA treatment.[19,20] In practice, MTX, leflunomide, or sulfasalazine are first used, and if the treatment target is not achieved with at least 1 of these conventional synthetic (cs-) DMARDs, then treatment with b/tsDMARDs is considered. If patients cannot receive csDMARDs due to reasons such as renal dysfunction, treatment with a bDMARD is considered to be the first treatment choice.

The registry has accumulated data since the first b/tsDMARD agent was approved in Japan in 2003. As of June 2019, 3535 patients had been enrolled in this registry. Agents include 5 TNFi (infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol [CZP]), an anti–IL-6 receptor antibody (tocilizumab [TCZ]), a cytotoxic T lymphocyte antigen-4 immunoglobulin (abatacept), and a Janus kinase inhibitor (tofacitinib [TOF]).

*Patient selection and data collection.* At the start of b/tsDMARD treatment, baseline data were collected, including demographics (birth date, sex), disease characteristics (disease duration, titers of anticyclic citrullinated peptide antibodies [anti-CCP], and RF), measures of disease activity (swollen joint count, tender joint count, patient global assessment, and titers of ESR and C-reactive protein [CRP]), functional status (class, stage, HAQ-DI), and treatment (current GC and MTX doses, previous use of csDMARDs and b/tsDMARDs). Follow-up data regarding disease activity were collected at 2, 22, and 54 weeks, and then yearly after initiation of therapy. If treatment was discontinued, the date and reasons for discontinuation were recorded.

Patient ages at the start of treatment were calculated in months based on their birth date. The age of RA onset was calculated by subtracting disease duration from patient age.

*Inclusion and exclusion criteria*. Patients who were ≥ 60 years old at the start of the treatment were included. Those whose age of onset was ≥ 60 years were categorized as patients with EORA, and those whose age of onset was < 60 years were categorized as non-EORA elderly patients.

For assessment of treatment outcomes, the Clinical Disease Activity Index (CDAI) was used rather than Disease Activity Score in 28 joints–ESR for assessment of disease activity because CRP and ESR titers were expected to be more strongly affected by TCZ usage than other b/tsDMARDs. Therefore, patients whose CDAI scores at Week 0 were not available were excluded.

*Statistical analyses*.

- Simple comparisons between 2 groups — For continuous variables, Mann-Whitney *U* testing was conducted to compare the EORA and non-EORA elderly groups. The normality of distribution of the data was assessed using the Shapiro-Wilk test. If the normality of distribution of a variable was rejected, the variable was converted into a categorical variable for further analysis. For categorical variables, differences between groups were assessed using the chi-square test.
- Panel data analyses — For longitudinal panel data analyses, regression analyses were conducted using the xt suite of functions in Stata 16 (StataCorp.). Random effects regression was used to estimate the effects of variables on disease activity.
- Latent class analysis — We have previously reported that different patterns of treatment response may exist among b/tsDMARD-naïve patients with RA treated with TNFi.[21] Therefore, we hypothesized that a similar pattern might be observed among our present group of patients. To identify different patterns of drug response, latent class analysis was conducted using the gsem suite of functions in Stata 16 and categorizing patients into 3 classes. To calculate the probability that a case will fall in a particular latent class, the maximum likelihood method is used. The maximum likelihood estimates are those that have a higher chance of accounting for the observed results. We estimated 3 classes because drug response usually shows 3 patterns: null response, partial response, and good response.

*Hazard analyses*. To compare hazards of treatment dropout due to lack of response, infections, and other AEs, a Cox proportional hazards regression model was used. A $P$ value < 0.05 was considered statistically significant for each analysis.

*Ethical approval and consent to participate*. The institutional review board of the University of Occupational and Environmental Health approved the study (approval code: 04-23). Informed consent was obtained from all participants in the FIRST registry.

## RESULTS

*Patient selection*. Of the 3535 participants in the FIRST registry, 2081 (58.9%) were ≥ 60 years old at the start of treatment. Among these patients, CDAI data at Week 0 were missing for

331 (15.9%) patients. As a result, 1750 patients were included in the study, of whom 1040 (59.4%) were categorized as having EORA and 710 (40.6%) as non-EORA elderly (Figure 1).

*Background characteristics of EORA and non-EORA elderly patients*. The characteristics of patients in each group are shown in Table 1. Age and disease activity at the start of b/tsDMARD treatment were higher in the EORA group than in the non-EORA elderly group, as were the proportions of male, RF-negative, and anti-CCP–negative patients. Also in the EORA group, the proportion of GC-free patients was higher, but the average GC dose was higher than in the non-EORA elderly group. No differences in the proportion of b/tsDMARD-naïve patients or choice of agents, including MTX and b/tsDMARDs, were observed between the 2 groups. Among those who had history of any b/tsDMARD failure, non-EORA elderly showed higher proportion of > 3 failures, although the difference was not significant.

*Responses to b/tsDMARDs in the EORA and non-EORA elderly patients*. Change in CDAI score over time and treatment retention rates in each group are shown in Figure 2A. At the start of treatment, the EORA group included a numerically higher proportion of patients with high disease activity (HDA; CDAI > 22.0) than the non-EORA elderly group. The proportion of patients with low disease activity (LDA; CDAI ≤ 10.0) as well as that with HDA was comparable at Weeks 2, 22, and 54 between the EORA group and the non-EORA elderly group. During the 54-week study, 436 patients (41.9%) and 276 patients (38.9%) discontinued the trial in the EORA group and the non-EORA elderly group. There were no significant differences in reasons for the discontinuation of the treatment, including less efficacy, infectious events, serious AEs, between EORA and non-EORA elderly patients (Figure 2B; Supplementary Table 1, available with the online version of this article).

*Baseline factors associated with changes in CDAI and HAQ-DI during the 54-week study period in elderly patients with RA*. To control variables at baseline that affected treatment outcomes, multiple regression was conducted using CDAI and HAQ-DI panel data (Figure 3). After controlling for variables that may affect treatment outcomes (age ≥ 70, sex, RF positivity, GC use, MTX dose, and past use of b/tsDMARDs), EORA was not associated with change in CDAI scores over time. In contrast, concomitant use of GCs was associated with higher CDAI scores, while use of MTX 1–10 mg/week was associated with lower scores compared with MTX nonusers. With respect to HAQ-DI, EORA, male sex, and MTX use were associated with lower scores, whereas older age (≥ 70 yrs) and concomitant GC use were associated with higher scores. Thus, elderly onset affected changes in HAQ-DI, but not CDAI changes for 54-week treatments.

For sensitivity analysis, the same regression was conducted using DAS28-CRP and DAS28-ESR as outcomes (Supplementary Figure 1, available with the online version of this article). Another analysis was conducted using only b/tsDMARD-naïve elderly patients (Supplementary Figure 2).

*Hazard analysis of clinical factors of discontinuation of b/tsDMARDs*. To assess whether dropout hazards of multiple clinical factors affecting the discontinuation of b/tsDMARDs differed between the EORA and non-EORA elderly groups, a Cox proportional hazards regression model was fitted for 206 patients (EORA: 124; non-EORA: 82) who discontinued treatment of b/tsDMARDs due to lack of efficacy within 54 weeks (Figure 4). No significant difference in dropout rates due to lack of efficacy in b/tsDMARDs was observed between the EORA and non-EORA elderly groups.

In addition to efficacy, drug safety is a major concern when treating elderly patients with RA. Therefore, hazard ratios of

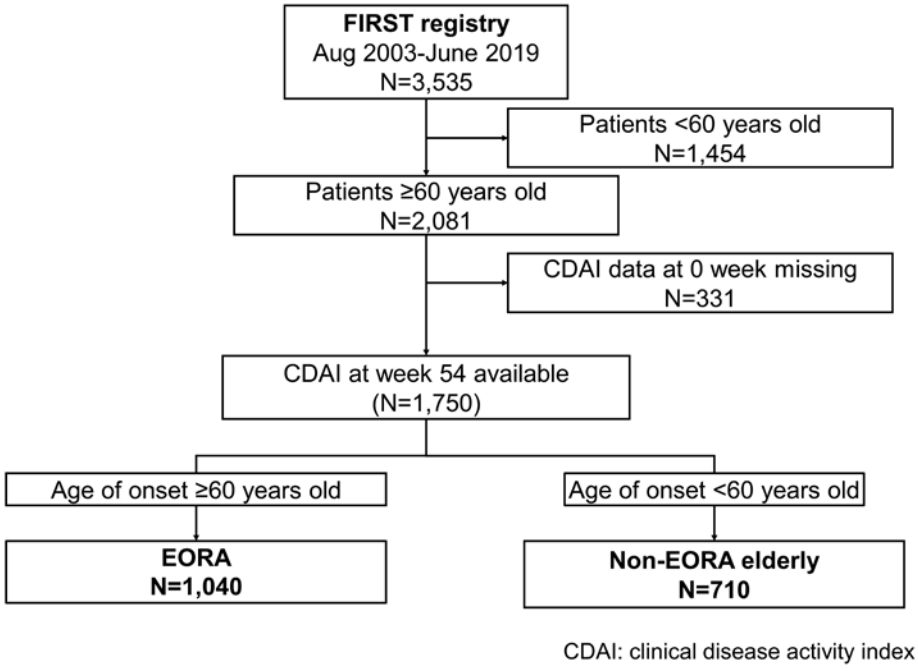


*Figure 1*. Process of patient selection. CDAI: Clinical Disease Activity Index; EORA: elderly-onset rheumatoid arthritis.

*Table 1*. Patient background characteristics.

| | | EORA, n = 1040 | | | | Non-EORA Elderly, n = 710 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | % | Mean ± SD | Median | n | % | Mean ± SD | Median | *P** | *P*** |
| Sex | Female | 779 | 74.9 | N/A | | 606 | 85.4 | N/A | | N/A | < 0.01 |
| | Male | 261 | 25.1 | | | 104 | 14.6 | | | | |
| Age, yrs | 60–69 | 344 | 33.1 | 72.8 ± 6.4 | 72.5 | 478 | 67.3 | 67.2 ± 5.9 | 66.0 | < 0.01 | < 0.01 |
| | 70–79 | 520 | 50.0 | | | 204 | 28.7 | | | | |
| | 80+ | 176 | 16.9 | | | 28 | 3.9 | | | | |
| Disease duration, months | < 12 | 204 | 19.6 | 50.5 ± 54.9 | 25.0 | 7 | 1.0 | 222.5 ± 140.6 | 204.0 | < 0.01 | < 0.01 |
| | 12–24 | 178 | 17.1 | | | 16 | 2.3 | | | | |
| | 24–60 | 354 | 34.0 | | | 65 | 9.2 | | | | |
| | 60–120 | 187 | 18.0 | | | 109 | 15.4 | | | | |
| | > 120 | 117 | 11.3 | | | 513 | 72.3 | | | | |
| CDAI score | < 2.8 | 9 | 0.9 | 26.92 ± 12.62 | 25.4 | 8 | 1.1 | 26.03 ± 13.14 | 23.45 | 0.05 | 0.04 |
| | 2.8–10 | 60 | 5.8 | | | 44 | 6.2 | | | | |
| | 10–22 | 337 | 32.4 | | | 274 | 38.6 | | | | |
| | > 22 | 634 | 61.0 | | | 384 | 54.1 | | | | |
| GC dose[a], mg/d | 0 | 776 | 74.6 | 1.9 ± 5.5 | 0.0 | 509 | 71.7 | 1.7 ± 5.3 | 0.0 | 0.47 | 0.02 |
| | 0.5–3 | 89 | 8.6 | | | 90 | 12.7 | | | | |
| | 4–5 | 87 | 8.4 | | | 65 | 9.2 | | | | |
| | > 5 | 88 | 8.5 | | | 45 | 6.3 | | | | |
| | No data | 0 | 0.0 | | | 1 | 0.1 | | | | |
| MTX dose, mg/week | 0 | 316 | 30.4 | 8.0 ± 6.2 | 8.0 | 224 | 31.5 | 7.7 ± 6.1 | 8.0 | 0.22 | 0.57 |
| | 1–6 | 86 | 8.3 | | | 72 | 10.1 | | | | |
| | 7–9 | 144 | 13.8 | | | 101 | 14.2 | | | | |
| | 10–14 | 273 | 26.3 | | | 174 | 24.5 | | | | |
| | ≥ 15 | 221 | 21.3 | | | 139 | 19.6 | | | | |
| RF, IU/mL | Negative | 278 | 26.7 | 194.30 ± 523.15 | 67.3 | 97 | 13.7 | 237.21 ± 442.73 | 99.4 | < 0.01 | < 0.01 |
| | Positive[b] | 753 | 72.4 | | | 608 | 85.6 | | | | |
| | No data | 9 | 0.9 | | | 5 | 0.7 | | | | |
| Anti-CCP, U/mL | Negative | 270 | 26.0 | 350.0 ± 840.3 | 86.2 | 83 | 11.7 | 319.4 ± 561.0 | 100.0 | 0.01 | < 0.01 |
| | Positive | 689 | 66.3 | | | 532 | 74.9 | | | | |
| | No data | 81 | 7.8 | | | 95 | 13.4 | | | | |
| Drug type | IFX | 100 | 9.6 | N/A | | 48 | 6.8 | N/A | | N/A | 0.13 |
| | ETN | 164 | 15.8 | | | 110 | 15.5 | | | | |
| | ADA | 141 | 13.6 | | | 83 | 11.7 | | | | |
| | GOL | 51 | 4.9 | | | 38 | 5.4 | | | | |
| | CZP | 76 | 7.3 | | | 56 | 7.9 | | | | |
| | TCZ | 208 | 20.0 | | | 154 | 21.7 | | | | |
| | ABA | 267 | 25.7 | | | 183 | 25.8 | | | | |
| | TOF | 33 | 3.2 | | | 38 | 5.4 | | | | |
| b/tsDMARD-naïve | Yes | 623 | 59.9 | N/A | | 400 | 56.3 | N/A | | N/A | 0.14 |
| No. of b/tsDMARD failures[d] | 1 | 256 | 24.6 | N/A | | 174 | 24.5 | N/A | | N/A | 0.06 |
| | 2 | 106 | 10.2 | | | 72 | 10.1 | | | | |
| | 3 | 36 | 3.5 | | | 39 | 5.5 | | | | |
| | ≥ 4 | 19 | 1.8 | | | 25 | 3.5 | | | | |

[a] Prednisolone equivalent. [b] RF >15 IU/mL. [c] Anti-CCP antibody > 4.5 U/mL. [d] b/tsDMARD-naïve patients were excluded. * Mann-Whitney *U* test was conducted for continuous variables to compare EORA and non-EORA elderly patients. ** Chi-square testing was used for categorical variables to compare EORA and non-EORA elderly patients. ABA: abatacept; ADA: adalimumab; b/tsDMARD: biologic/targeted synthetic disease-modifying antirheumatic drug; anti-CCP: anticyclic citrullinated protein; CDAI: Clinical Disease Activity Index; CZP: certolizumab pegol; EORA: elderly-onset rheumatoid arthritis; ETN: etanercept; GC: glucocorticoid; GOL: golimumab; IFX: infliximab; N/A: not applicable; RF: rheumatoid factor; TCZ: tocilizumab; TOF: tofacitinib.

infection and serious AEs were compared using a Cox proportional hazards regression model. Sixteen patients stopped treatment due to infection, and 88 stopped due to other serious AEs. After controlling for age, sex, GC and MTX doses, and agent types, no differences in hazard ratios were observed between groups (Figure 5, middle and right columns). Thus, elderly onset did not affect dropouts due to lack of efficacy of b/tsDMARDs, infectious diseases, and severe AEs for 54-week treatments in elderly patients with RA.

*CDAI response trajectories in elderly patients treated with b/tsDMARDs*. Based on the hypothesis that different people experience different patterns of CDAI response to b/tsDMARDs,

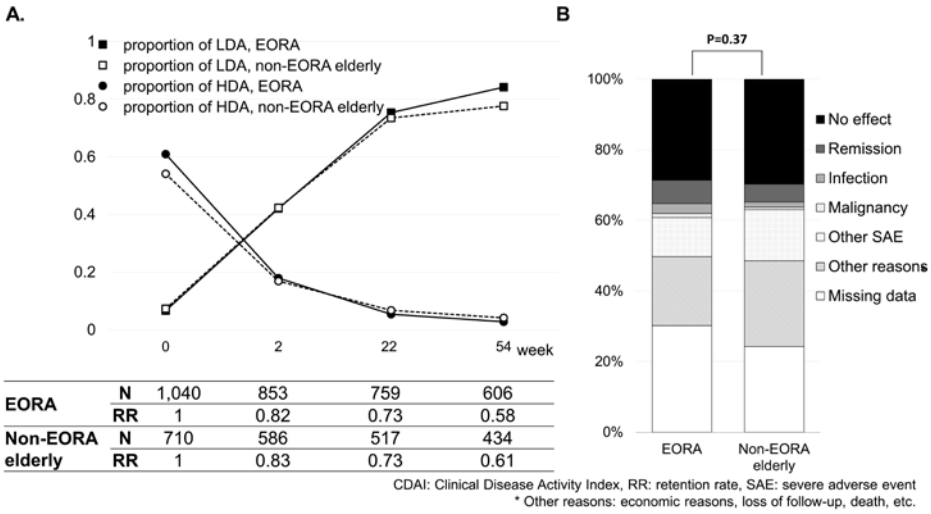


*Figure 2*. Responses to b/tsDMARDs and patient retention rate in the EORA and non-EORA elderly patients. The time course of CDAI score changes and treatment retention rate in the EORA and non-EORA elderly patients are shown at baseline and Weeks 2, 22, and 54 after treatment with b/tsDMARDs. (A) Proportion of patients with HDA (CDAI > 22.0) and LDA (CDAI ≤ 10.0) at each timepoint are plotted. (B) Reasons for the discontinuation of treatment in each group are shown. * Other reasons include but are not limited to economic reasons, loss of follow-up, and death. CDAI: Clinical Disease Activity Index; EORA: elderly-onset rheumatoid arthritis; HDA: high disease activity; LDA: low disease activity; RR: retention rate; SAE: severe adverse event.

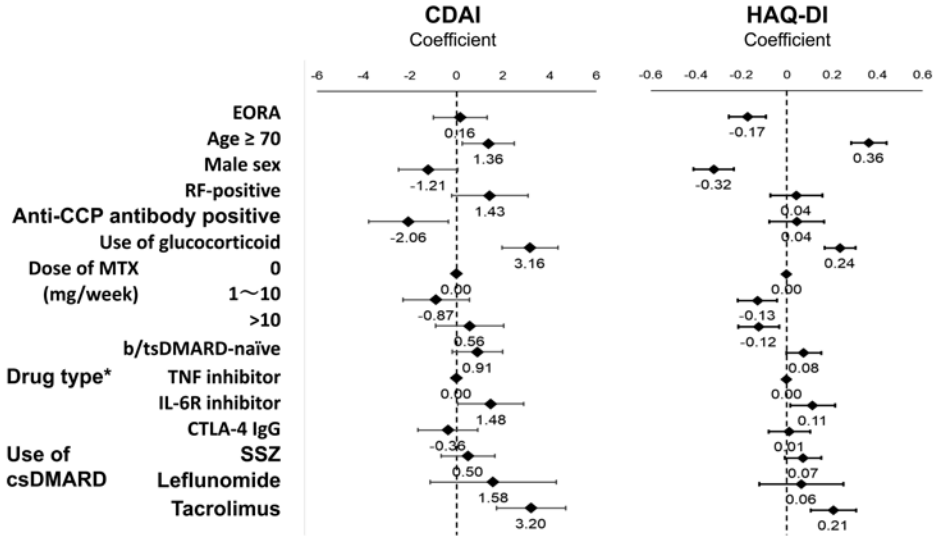


*Figure 3*. Clinical characteristics at baseline associated with changes in CDAI and HAQ-DI during the 54-week study period in elderly patients with RA. The associations between clinical variables and changes in CDAI and HAQ-DI during the 54-week study period were analyzed using multiple panel regression analysis with random effect. The lines for each variable indicate the 95% CI. * Use of tofacitinib was omitted due to the small number. Anti-CCP: anticyclic citrullinated protein; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CTLA-4: cytotoxic T lymphocyte antigen 4; EORA: elderly-onset rheumatoid arthritis; HAQ-DI: Health Assessment Questionnaire–Disability Index; IL-6R: interleukin-6 receptor; MTX: methotrexate; RA: rheumatoid arthritis; RF: rheumatoid factor; SSZ: sulfasalazine; TNF: tumor necrosis factor.

trajectory analysis was conducted to categorize patients by 3 patterns of response to 54-week treatments with b/tsDMARDs. As shown in Figure 5, the patterns of fluctuation in CDAI responses to b/tsDMARDs in the EORA and non-EORA elderly groups were divided into the 3 groups. Group 1 included rapid responders, who had lower baseline CDAI scores, responded rapidly to treatment, and maintained low disease activity for up to 54 weeks (EORA: n = 859, 83.0%; non-EORA: n = 572, 81.6%). Group 2 included slow responders, who had higher baseline CDAI scores and continued to improve over 54 weeks (EORA:

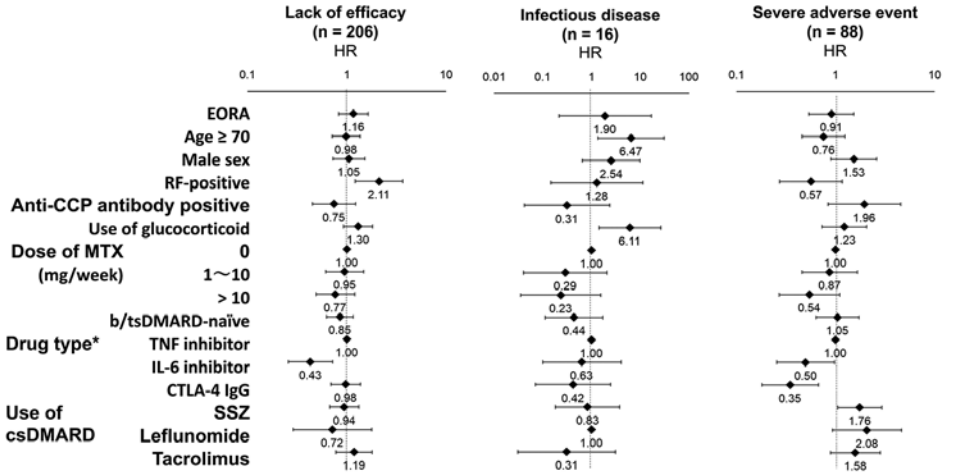


*Figure 4*. HRs of clinical factors for discontinuation of b/tsDMARDs in elderly patients with RA. Cox regression analyses were conducted, controlling for age (≥ 70 vs < 70 yrs), sex, RF positivity, glucocorticoid use, MTX dose, and past use of b/tsDMARDs. The lines for each variable indicate the 95% CI. * Use of tofacitinib was omitted due to small number. Anti-CCP: anticyclic citrullinated protein; b/tsDMARD: biologic/targeted synthetic disease-modifying antirheumatic drug; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CTLA-4: cytotoxic T lymphocyte antigen 4; EORA: elderly-onset rheumatoid arthritis; HAQ-DI: Health Assessment Questionnaire–Disability Index; IL-6R: interleukin-6 receptor; MTX: methotrexate; RA: rheumatoid arthritis; RF: rheumatoid factor; SSZ: sulfasalazine; TNF: tumor necrosis factor; Y/MORA: younger/middle-aged onset rheumatoid arthritis.

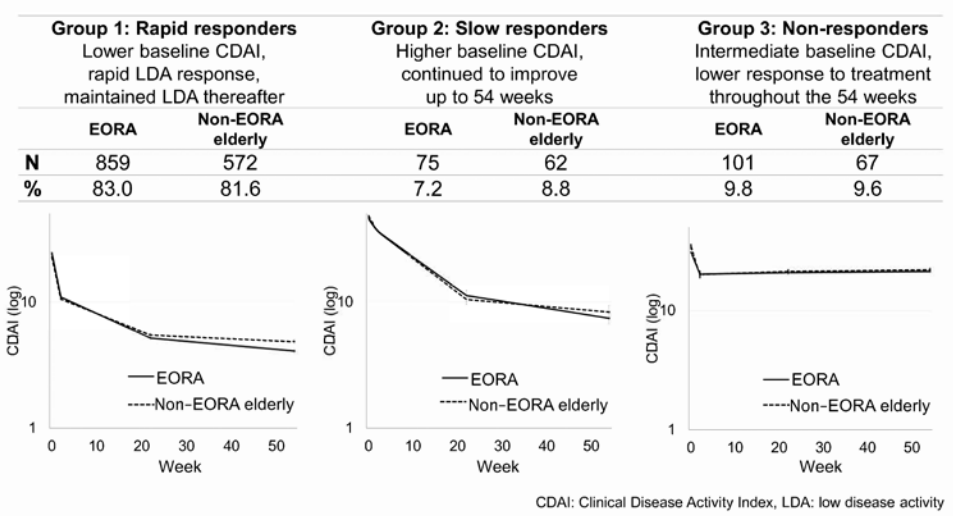


*Figure 5*. CDAI response trajectories in elderly patients treated with b/tsDMARDs. Means of each model with 95% CIs are shown for the EORA and non-EORA elderly groups. Explanations of the pattern with numbers and percentages of patients included in each group are listed in the upper table. b/tsDMARD: biologic/targeted synthetic disease-modifying antirheumatic drug; CDAI: Clinical Disease Activity Index; EORA: elderly-onset rheumatoid arthritis; LDA: low disease activity; Y/MORA: younger/middle-aged onset rheumatoid arthritis.

n = 75, 7.2%; non-EORA: n = 62, 8.8%). Group 3 included nonresponders, who showed intermediate disease activity and responded to treatment within 2 weeks but showed no further improvement thereafter (EORA: n = 101, 9.8%; non-EORA: n = 67, 9.6%). Thus, the proportions of patients categorized into each group and CDAI response trajectories to b/tsDMARDs were very similar between EORA and non-EORA elderly patients.

For sensitivity analysis, the same analysis was conducted using only b/tsDMARD-naïve elderly patients (Supplementary Figure 3, available with the online version of this article).

## DISCUSSION

To our knowledge, this is the first study to compare EORA and non-EORA elderly patients with respect to efficacy and safety of b/tsDMARD treatment. The improvement and treatment response trajectories in CDAI were comparable between the EORA and non-EORA elderly groups and elderly onset did not affect reasons for the discontinuation of 54-week treatments with b/tsDMARDs.

Previous studies have shown that patients with EORA are more refractory to conventional treatments compared to patients with

YORA.[22,23] However, as older age confounds with many factors such as organ functions and degenerative arthritis, comparing EORA and YORA cannot completely reveal how EORA is different from non-EORA. This study revealed that CDAI response pattern was similar between EORA and non-EORA elderly among the same age group (Figure 4), suggesting that EORA might not be quite different from non-EORA elderly with respect to b/tsDMARDs responsiveness.

The latent class analyses also revealed that about 1/10 patients in both the EORA and non-EORA elderly groups showed little response to a b/tsDMARD (Figure 4, Group 3). This is compatible with our previous study, which demonstrated that a difference might exist between insensitivity and poor response to TNFi among b/tsDMARD-naïve patients.[21] The results of the present study further suggest that the same might be true for patients treated with other b/tsDMARDs and for patients who are not naïve to b/tsDMARDs. To improve efficacy and to prevent unnecessary AEs, further research is needed to determine how to identify these nonresponders prior to treatment.

Our study is unique in that it included all types of b/tsDMARDs. In clinical practice, choice of treatment depends on many nonclinical factors, such as patients' cognitive level, access to care, and economic issues, which may cause selection bias. The present study has minimized this selection bias by including multiple b/tsDMARD treatment options. The number of patients treated with CZP or TOF was small, so we deemed comparisons between b/tsDMARDs as inappropriate. Increased numbers of recruited patients may make it possible to obtain more detailed evidence about the efficacy and safety of each agent.

The importance of early intervention for elderly patients with RA is underscored by the observation that multiple or widespread chronic pain may lead to declined activity and onset of disability among elderly people.[24] Thus far, low doses of GC appear to be preferred in such situations.[11] However, GCs increase the risk of osteoporosis and pathological fracture, so they may also contribute to comorbidities among the elderly. In addition, the present research as well as previous studies[14,16,25] showed that GC use could increase the risk of poor treatment outcomes (Figure 3) and serious infectious diseases (Figure 4). Therefore, when elderly patients are refractory to conventional therapy, introduction of a b/tsDMARD would be a treatment option that can be used to minimize GC doses.

Risk of serious infectious diseases can be a major concern when treating elderly patients with b/tsDMARDs. Although the risk of infection increases with age, the reported overall risk is declining over time,[25] presumably due to accumulation of clinical experience. Therefore, additional evidence about the risks of serious infections among these populations might be the key to safe treatment. Data synthesis such as metaanalysis may elucidate the amplitude of the net risk currently observed.

The present study is limited by its inherently retrospective nature. As the data were collected prior to study initiation, we had limited access to detailed patient background data. Another limitation is that this registry included several instances of patients who received multiple agents. An additional limitation is that comorbidity data, such as chronic kidney disease and interstitial pneumonia, were not included; this may have confounded the treatment selection and outcomes of patients. Finally, the number of dropouts included in hazard analyses was small. Therefore, Cox regression analyses could not determine whether the absence of statistically significant differences truly indicated a lack of a difference or simply that the sample size was too small to show a difference. Nevertheless, this small number suggests the safety of treatment. Further, due to the study design, there is a significant difference in disease duration at baseline in the EORA group compared to the non-EORA group that may affect b/tsDMARD treatment response.[26] Even with these limitations, our results provide an important perspective that is different from those obtained by comparison between EORA and YORA.

In conclusion, comparison of EORA and non-EORA elderly patients revealed that trajectories of CDAI response to b/tsDMARDs were similar between EORA and non-EORA elderly groups. There were no significant differences in reasons for the discontinuation of b/tsDMARDs, and elderly onset did not affect changes in CDAI and HAQ-DI nor the reasons for discontinuation between the 2 groups.

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## ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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