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Original article

# Factors associated with osteoporosis medication use in Japanese patients with rheumatoid arthritis: Results from the Institute of Rheumatology Rheumatoid Arthritis cohort study

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ABSTRACT

*Objectives:* This study aimed to evaluate factors associated with osteoporosis medication use in Japanese patients with rheumatoid arthritis (RA).
*Methods:* Patients with RA who enrolled in our cohort completed self-administered questionnaires which included questions regarding their osteoporosis medications. Logistic regression was used to determine the association of variables with the use of these medications.
*Results:* Among 5660 Japanese patients with RA who responded to the questionnaires (mean age, 61.8 years; 86.0% female), 1983 patients (35.0%) and 1211 patients (21.4%) reported taking osteoporosis medications and antiresorptive agents, respectively. In multivariate models, age, female sex, lower body mass index (BMI), self-reported fracture history, Japanese Health Assessment Questionnaire-Disability Index (JHAQ-DI), daily dosage of prednisone (PSL), weekly dosage of methotrexate (MTX), and concomitant use of hypertension and hyperlipidemia medications were significantly associated with the use of osteoporosis medications ($P < 0.05$). Among women with RA, the use of hypertension medications was significantly correlated with the use of both osteoporosis medications and antiresorptive agents ($P < 0.05$).
*Conclusions:* Age, female sex, a lower BMI, duration of RA, self-reported fracture history, JHAQ-DI, daily dosage of PSL, weekly dosage of MTX, and the use of medications for hypertension and hyperlipidemia appear to be associated with the use of osteoporosis medications in Japanese patients with RA.


## 1. Introduction

Osteoporosis is commonly observed in patients with rheumatoid arthritis (RA) and many reports have been published on bone mineral density (BMD) or risk factors for fracture in patients with RA [1–3]. Inflammation due to RA causes bone resorption, the onset of which may be early during the course of disease. Glucocorticoids, which may aggravate osteoporosis, are still commonly administered to patients with RA to control disease activity, particularly as an adjunct to disease-modifying antirheumatic drugs (DMARDs) [4–7]. The American College of Rheumatology and the European League Against Rheumatism have published recommendations concerning the prevention of osteoporosis in patients with RA who are administered glucocorticoids [8,9]. The risk for vertebral and hip fractures in patients with RA is increased compared with healthy individuals without RA [2,10–13].

Previously, we have reported various clinical characteristics of osteoporosis in Japanese patients with RA by way of utilizing data from our Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort study [14–24]. For patients with RA, the prevention of fractures is important to the maintenance of their quality of life

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(QoL), thus their osteoporosis requires appropriate treatment. To date, several reports associate RA and osteoporosis; however, limited data exist in the literature about the factors associated with the use of osteoporosis medications in patients with RA. Although a few reports exist about patients of various ethnicities with RA [6,25], no reports have focused on Japanese patients with RA. The current study aimed to evaluate the factors associated with osteoporosis medication use in Japanese patients with RA using the IORRA cohort.

## 2. Methods

### 2.1. Patients

The IORRA cohort was established in October 2000 as a single, institute-based, large, observational cohort of Japanese patients with RA at the Institute of Rheumatology, Tokyo Women's Medical University. Details regarding the purpose and methodology of this study have been reported previously [14–24]. Over 139 publications have described various characteristics of Japanese patients with RA from this large cohort. This study was approved by the ethics committee of Tokyo Women's Medical University (No. 2952) and informed consent was obtained from all patients at the time of each survey. For this study, we analyzed patients who participated in the 33rd IORRA survey in October and November of 2016. In brief, patients diagnosed with RA were registered in the IORRA cohort after informed consent was obtained and they were required to complete and submit a survey biannually.

Evaluated parameters included age, sex, body mass index (BMI), RA disease duration (years), current smoking status, current alcohol intake, self-reported fracture history, the 28-joint disease activity score (DAS28), and disability measured by the Japanese Health Assessment Questionnaire Disability Index (JHAQ-DI) [26]. The following clinical parameters were also assessed: erythrocyte sedimentation rate, serum C-reactive protein, and rheumatoid factor. In addition, patients self-reported dose of methotrexate (MTX) and prednisolone (PSL), and the use of MTX, biologic disease-modifying antirheumatic drugs (bDMARDs), glucocorticoids, osteoporosis medications, as well as hypertension, hyperlipidemia, and diabetes mellitus (DM) medications.

### 2.2. Statistical analysis

A chi-square test and Fisher exact test were used to compare categorical variables. Student t-test was used to compare continuous variables. To determine the associations between patients' factors and osteoporosis medication use, Spearman rank correlation for coefficient continuous variables, and Fisher exact test for categorical variables were used (Table 1), and multivariate logistic regression analysis was employed (Table 2). In multivariate logistic regression models, age, female sex, BMI, duration of RA, current smoking and alcohol intake, self-reported fracture history, DAS28, JHAQ-DI, dose of MTX and PSL, use of bDMARDs, hypertension, hyperlipidemia, and DM medication use were considered as possible factors associated with osteoporosis medication use. A P-value of $<0.05$ was considered statistically significant. All statistical analyses were performed using the EZR (Saitama Medical Center, Jichi Medical University, Japan), which is a graphical-user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

A total of 5660 Japanese patients with RA from the IORRA cohort were enrolled in the 2016 autumn survey. Demographic and clinical variables, including the use of medication at the time of enrollment into the IORRA cohort are shown for patients in Table 3. Patients included 4868 females (86.0%) of mean age 61.8 years. Among them, 3431 (60.6%) were 55 years of age or older and thus assumed to be postmenopausal. Among all 5660 patients, 1983 (35.0%) reported osteoporosis medication use and 1211 (21.4%) reported the use of antiresorptive agents. Women were more likely to use any osteoporosis medication than men. Details of osteoporosis medications are as follows: 998 active vitamin D analogs (425 alphacalcidol, 11 calcitriol, 562 eldecalcitol), 79 selective estrogen receptor modulators (SERMs): (55 raloxifene, 24 bazedoxifene), 79 teriparatide, 1133 bisphosphonates (414 alendronate, 3 etidronate, 9 ibandronate, 211 minodronate, 496 risedronate), 94 denosumab, and 133 others. Prescriptions for 2 or more drugs are reflected in these counts.

Spearman correlations between osteoporosis medications and continuous variables are reported in addition to and categorical variables (Table 1). In the unadjusted analysis, age, duration of RA, JHAQ-DI, and PSL dose were relatively highly associated with the use of osteoporosis medications and also relatively highly associated with antiresorptive agents among continuous variables. Female sex, self-reported fracture history, and use of glucocorticoids, as well as hypertension and hyperlipidemia medication use were highly associated with the use of osteoporosis medications and the use of antiresorptive agents.

Table 2 shows the results of the multivariate models. Factors significantly associated with the use of both osteoporosis medications and antiresorptive agents were age ($P < 0.01$), female sex ($P < 0.01$), lower BMI ($P < 0.01$), self-reported fracture history ($P < 0.01$) and duration of RA ($P < 0.01$), daily dosage of PSL ($P < 0.01$), and weekly dosage of MTX ($P < 0.01$). JHAQ-DI ($P < 0.01$) and use of hypertension medications ($P < 0.05$) and hyperlipidemia medications ($P < 0.05$) were significantly associated only with the use of osteoporosis medications.

Among female patients, age ($P < 0.01$), lower BMI ($P < 0.01$), duration of RA ($P < 0.01$), self-reported fracture history ($P < 0.01$), daily dosage of PSL ($P < 0.01$), weekly dosage of MTX ($P < 0.01$), and the use of hypertension medications ($P < 0.01$) were significantly associated with the use of both osteoporosis medications and antiresorptive agents. JHAQ-DI ($P < 0.01$) were significantly associated only with the use of osteoporosis medications.

## 4. Discussion

Clinical factors associated with the use of osteoporosis medications and antiresorptive agents were evaluated in this study. Our study showed that age, female sex, lower BMI, duration of RA, self-reported fracture history, JHAQ-DI, and daily dosage of PSL were significantly associated with the use of osteoporosis medication. Age, female sex, lower BMI, self-reported fracture history, and daily dosage of PSL were significantly associated with the use of antiresorptive agents (Table 2).

In this study, 35.0% and 21.4% of patients reported using osteoporosis medications and antiresorptive agents, respectively. Although osteoporosis is usually observed in patients with RA, these utilization rates appeared to be low. This discrepancy was partly because our physicians were not encouraged to measure patients' BMD and they were not likely to notice their osteoporosis existence. New fracture occurrence significantly decreases the QoL of patients [27,28], especially among patients with RA because most of them incur multiple joint dysfunction. Thus, the measurement of BMD and the instigation of treatment for osteoporosis should be more widespread among Japanese patients with RA.

We observed a significant association between the use of osteoporosis medications or antiresorptive agents and the JHAQ-DI of Japanese patients with RA (Table 2). Previously, we and others have

**Table 1**
Unadjusted associations of patient characteristics with an osteoporosis medication or antiresorptive agent.

| Variable | Osteoporosis medication | | | | Antiresorptive agent | | | |
|---|---|---|---|---|---|---|---|---|
| | Total (n = 5660) | P-value | Females (n = 4868) | P-value | Total (n = 5660) | P-value | Females (n = 4868) | P-value |
| Continuous variable[a] | | | | | | | | |
| Age | 0.294 | <0.0001 | 0.340 | <0.0001 | 0.266 | <0.0001 | 0.302 | <0.0001 |
| Body mass index | −0.100 | <0.0001 | −0.0582 | <0.0001 | −0.0797 | <0.0001 | −0.0485 | 0.00079 |
| Duration of RA | 0.259 | <0.0001 | 0.274 | <0.0001 | 0.199 | <0.0001 | 0.209 | <0.0001 |
| DAS28 | 0.181 | <0.0001 | 0.160 | <0.0001 | 0.150 | <0.0001 | 0.139 | <0.0001 |
| JHAQ-DI | 0.280 | <0.0001 | 0.271 | <0.0001 | 0.217 | <0.0001 | 0.210 | <0.0001 |
| ESR | 0.163 | <0.0001 | 0.143 | <0.0001 | 0.141 | <0.0001 | 0.131 | <0.0001 |
| CRP | 0.0782 | <0.0001 | 0.0976 | <0.0001 | 0.0627 | <0.0001 | 0.0794 | <0.0001 |
| MTX dose | −0.0155 | 0.306 | −0.0139 | 0.394 | −0.0211 | 0.163 | −0.0186 | 0.255 |
| PSL dose | 0.278 | <0.0001 | 0.276 | <0.0001 | 0.229 | <0.0001 | 0.225 | <0.0001 |
| Categorical variable[b] | | | | | | | | |
| Female sex | 3.62 | <0.0001 | – | – | 3.51 | <0.0001 | – | – |
| Current smoking | 0.606 | <0.0001 | 0.745 | 0.0261 | 0.562 | <0.0001 | 0.681 | 0.0161 |
| Current alcohol | 0.568 | <0.0001 | 0.662 | <0.0001 | 0.597 | <0.0001 | 0.674 | <0.0001 |
| Self-reported fracture history | 1.93 | <0.0001 | 2.12 | <0.0001 | 1.86 | <0.0001 | 1.99 | <0.0001 |
| RF positive | 1.08 | 0.2111 | 1.01 | 0.841 | 1.11 | 0.1779 | 1.05 | 0.514 |
| Medication use | | | | | | | | |
| MTX | 0.967 | 0.619 | 0.978 | 0.777 | 0.962 | 0.616 | 0.998 | 0.981 |
| bDMARDs | 1.01 | 0.842 | 0.947 | 0.448 | 0.946 | 0.488 | 0.897 | 0.179 |
| Glucocorticoid | 3.58 | <0.0001 | 3.58 | <0.0001 | 3.11 | <0.0001 | 2.99 | <0.0001 |
| Hypertension | 1.98 | <0.0001 | 2.46 | <0.0001 | 1.96 | <0.0001 | 2.33 | <0.0001 |
| Hyperlipidemia | 1.82 | <0.0001 | 1.92 | <0.0001 | 1.73 | <0.0001 | 1.80 | <0.0001 |
| Diabetes mellitus | 1.27 | 0.09122 | 1.80 | 0.000247 | 1.30 | 0.0469 | 1.76 | 0.00138 |

RA, rheumatoid arthritis; DAS, disease activity score; JHAQ-DI, Japanese Health Assessment Questionnaire-Disability Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; MTX, methotrexate; PSL, prednisolone; bDMARD, biologic disease-modifying antirheumatic drugs.
[a] Spearman rank correlation for coefficient continuous variables.
[b] Odds ratios from Fisher exact test of categorical variables.

**Table 2**
Multivariate associations of patient characteristics among Japanese patients with RA using an osteoporosis medication or an antiresorptive agent.

| Variable | Osteoporosis medication | | Antiresorptive agent | |
|---|---|---|---|---|
| | Total (n = 5660) | Females (n = 4868) | Total (n = 5660) | Females (n = 4868) |
| Age per 10 year | 1.74 (1.60–1.89) | 1.79 (1.64–1.95) | 1.82 (1.65–2.01) | 1.86 (1.68–2.07) |
| Female sex | 4.57 (3.32–6.28) | – | 3.34 (2.31–4.83) | – |
| Body mass index | 0.946 (0.915–0.970) | 0.936 (0.908–0.966) | 0.937 (0.907–0.969) | 0.935 (0.904–0.968) |
| Duration of RA | 1.22 (1.12–1.34) | 1.24 (1.13–1.37) | 1.12 (1.02–1.23) | 1.13 (1.02–1.25) |
| Current smoking | 1.04 (0.742–1.45) | 1.12 (0.777–1.63) | 0.898 (0.599–1.35) | 0.873 (0.557–1.37) |
| Current alcohol | 0.835 (0.679–1.03) | 0.844 (0.675–1.06) | 1.01 (0.798–1.29) | 0.991 (0.765–1.28) |
| Self-reported fracture history | 1.67 (1.41–1.99) | 1.67 (1.39–2.01) | 1.55 (1.28–1.89) | 1.60 (1.30–1.96) |
| DAS28 | 0.927 (0.839–1.02) | 0.931 (0.836–1.04) | 0.976 (0.873–1.09) | 0.993 (0.882–1.12) |
| JHAQ-DI | 1.35 (1.16–1.56) | 1.35 (1.16–1.57) | 1.13 (0.966–1.32) | 1.11 (0.947–1.31) |
| PSL dose | 1.31 (1.25–1.37) | 1.29 (1.23–1.35) | 1.26 (1.21–1.32) | 1.24 (1.18–1.30) |
| MTX dose | 1.03 (1.01–1.05) | 1.04 (1.02–1.06) | 1.03 (1.00–1.05) | 1.03 (1.01–1.06) |
| bDMARD use | 1.05 (0.851–1.29) | 1.08 (0.873–1.34) | 1.09 (0.860–1.38) | 1.16 (0.912–1.49) |
| Hypertension medication use | 1.31 (1.04–1.66) | 1.52 (1.18–1.97) | 1.23 (0.960–1.59) | 1.43 (1.10–1.87) |
| Hyperlipidemia medication use | 1.29 (1.00–1.65) | 1.27 (0.974–1.66) | 1.19 (0.915–1.56) | 1.18 (0.892–1.56) |
| Diabetes mellitus medication use | 0.857 (0.532–1.38) | 0.851 (0.494–1.47) | 0.862 (0.519–1.43) | 0.730 (0.414–1.29) |

Values are presented as odds ratio (95% confidence interval).
RA, rheumatoid arthritis; DAS, disease activity score; JHAQ-DI, Japanese Health Assessment Questionnaire-Disability Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; MTX, methotrexate; PSL, prednisolone; bDMARD, biologic disease-modifying antirheumatic drugs.

reported that the HAQ-DI or JHAQ-DI was significantly correlated with osteoporosis and fragility fractures [18,29]. HAQ-DI was negatively associated with the BMD score, and JHAQ-DI was associated with vertebral fractures in patients with RA [18,29]. Based on our study results, we suggest that Japanese patients with RA and a high JHAQ-DI require BMD monitoring and initiation of osteoporosis treatment as deemed medically appropriate. Age and fracture history—recognized as general risk factors for osteoporosis [30] and fracture [16–19]—were associated with the use of osteoporosis medications or antiresorptive agents (Table 2).

The daily dosage of PSL was significantly correlated with osteoporosis medication use and antiresorptive agent use (Table 2). Using univariate analysis, the use of glucocorticoids, as well as the daily dosage of PSL, was significantly associated with use of osteoporosis medication and antiresorptive agent (Table 1). According to the Glucocorticoid-induced Osteoporosis guidelines of Japan and the United States, patients administered glucocorticoids should also use osteoporosis medications [31,32]. We and others have reported that the dose of PSL is a risk factor for fractures in patients with RA [16–19].

A significant association was observed between a lower BMI and the use of osteoporosis medications or antiresorptive agents (Table 2). Although we did not collect BMD data in this study, BMI could be a surrogate marker for BMD. Previous reports have shown that a lower BMI [11] and lower BMD [33–35] are risk factors for vertebral fractures in patients with RA. In our previous studies using the IORRA cohort, BMI was significantly and inversely associated with hip fractures [16] and positively related to distal radius

**Table 3**
Characteristics of Japanese patients with rheumatoid arthritis.

| Characteristic | All patients (N = 5660) | | Male (N = 792) | | Female (N = 4868) | | P-value[a] |
|---|---|---|---|---|---|---|---|
| | Mean ± SD or % | No. | Mean ± SD or % | No. | Mean ± SD or % | No. | |
| Age, yr | 61.8 ± 13.2 | 5660 | 64.1 ± 12.6 | 792 | 61.4 ± 13.2 | 4868 | <0.0001 |
| Body mass index, kg/m$^2$ | 21.4 ± 3.22 | 5567 | 23.0 ± 3.13 | 782 | 21.1 ± 3.16 | 4785 | <0.0001 |
| Duration of RA, yr | 16.0 ± 10.4 | 5320 | 14.8 ± 10.1 | 740 | 16.2 ± 10.5 | 4580 | 0.00074 |
| Current smoking, % | 7.82 | 5445 | 18.8 | 780 | 5.99 | 4665 | <0.0001 |
| Current alcohol, % | 26.5 | 5537 | 52.6 | 781 | 22.3 | 4756 | <0.0001 |
| Self-reported fracture history, % | 37.4 | 5660 | 40.5 | 792 | 36.9 | 4868 | 0.0525 |
| DAS28 | 2.58 ± 0.996 | 5635 | 2.16 ± 1.08 | 789 | 2.65 ± 0.964 | 4846 | <0.0001 |
| JHAQ-DI (range, 0–3) | 0.543 ± 0.698 | 5655 | 0.317 ± 0.561 | 790 | 0.580 ± 0.711 | 4865 | <0.0001 |
| ESR, mm/h | 22.8 ± 18.0 | 5635 | 18.0 ± 18.1 | 790 | 23.6 ± 17.9 | 4845 | <0.0001 |
| CRP, mg/dL | 0.360 ± 0.862 | 5639 | 0.513 ± 1.20 | 791 | 0.336 ± 0.790 | 4848 | <0.0001 |
| RF positive[b], % | 72.2 | 5603 | 66.5 | 788 | 73.1 | 4815 | 0.000016 |
| MTX, mg/wk | 6.07 ± 4.90 | 4366 | 5.65 ± 5.14 | 597 | 6.14 ± 4.86 | 3769 | 0.00193 |
| PSL, mg/d | 1.01 ± 2.28 | 5657 | 1.15 ± 2.60 | 792 | 0.991 ± 2.22 | 4865 | 0.024 |
| Medication use, % | | | | | | | |
| MTX | 77.1 | 5660 | 72.7 | 792 | 77.8 | 4868 | <0.0001 |
| bDMARDs | 22.9 | 5660 | 15.7 | 792 | 24.1 | 4868 | 0.796 |
| Glucocorticoids | 26.9 | 5660 | 26.5 | 792 | 27.0 | 4868 | 0.0674 |
| Osteoporosis | 35.0 | 5660 | 14.6 | 792 | 38.4 | 4868 | <0.0001 |
| Antiresorptive agents | 21.4 | 5660 | 8.1 | 792 | 23.6 | 4868 | <0.0001 |
| Hypertension | 24.0 | 5152 | 33.5 | 722 | 22.5 | 4430 | <0.0001 |
| Hyperlipidemia | 17.1 | 4891 | 17.4 | 672 | 17.1 | 4219 | 0.826 |
| Diabetes mellitus | 5.05 | 4757 | 11.2 | 675 | 4.01 | 4082 | <0.0001 |

SD, standard deviation; RA, rheumatoid arthritis; DAS, disease activity score; JHAQ-DI, Japanese Health Assessment Questionnaire-Disability Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; MTX, methotrexate; PSL, prednisolone; bDMARD, biologic disease-modifying antirheumatic drugs.
[a] Between males and females.
[b] > 15 IU/mL.

fractures [17]. Thus, our current result indicates that BMI may be useful if BMD could not be measured.

A significant association was observed between hypertension medication and the use of osteoporosis medications or antiresorptive agents, especially in females (Table 2). Hypertension is a risk factor for osteoporosis [36,37]. Women with hypertension tend to have a lower BMD at the femoral neck than those without the disease, and hypertension has been shown to be an independent risk factor for fragility fractures [37]. Prolonged use of certain hypertension drugs has exacerbated the loss of BMD and osteoporosis [38,39]. Collectively, women with RA and hypertension have a potentially high risk for osteoporosis and exerting tight control over both RA and hypertension is recommended.

A significant association was observed between hyperlipidemia medication and the use of osteoporosis medications (Table 2). Lipid profile is reported to be associated with osteoporosis [40]. A recent meta-analysis indicated that statins may decrease the risk of fractures and increase BMD [41]. Our previous report showed that low-density lipoprotein receptor–related 5 gene polymorphism significantly associated with serum cholesterol levels and fractures in Japanese patients with RA [24]. Thus, hyperlipidemia may be associated with osteoporosis in Japanese patients with RA.

This study has some limitations. First, data on patient characteristics and medications were obtained via self-reported questionnaires; as such, some degree of under- or over-reporting is likely. Second, we did not collect BMD data. The importance of BMD data should not be understated, yet not all clinics or hospitals have dual-absorptiometry X-ray machines available. Future investigations that include BMD data are necessary. Third, we do not have our common therapeutic strategy for osteoporosis in our institute. At our outpatient clinic, more than 20 rheumatologists, including physicians and orthopedic surgeons having varied backgrounds, assess fracture risk in terms of age, female sex, lower BMI, past fracture histories, use of glucocorticoids, and low BMD, and prescribe osteoporosis medications for the patients with high risk of fractures. Fourth, IORRA is a single-institute–based cohort study. As our institution is located in midtown Tokyo, Japan, most patients likely used public transportation and walked into our institution unassisted. Patients with severe functional impairments, such as those unable to walk without assistance, were excluded from our cohort. Therefore, our results might not be generalizable to all Japanese patients with RA.

## 5. Conclusions

We evaluated factors associated with osteoporosis medications and antiresorptive agents. Age, female sex, a lower BMI, duration of RA, self-reported fracture history, JHAQ-DI, daily dosage of PSL, weekly dosage of MTX, and the use of medications for hypertension and hyperlipidemia appear to be associated with the use of osteoporosis medications in Japanese patients with RA.

## Conflicts of interest

**Masanori Nakayama** has served on speakers' bureaus for Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., and Shionogi & Co., Ltd. **Takefumi Furuya** has served on speakers' bureaus for Asahi Kasei Pharma Corporation, Bristol-Myers Squibb, Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., and UCB Japan Co., Ltd. **Eisuke Inoue** has received lecture fees from Bristol-Myers Squibb and Pfizer Japan Inc. **Eiichi Tanaka** has served on speakers' bureaus for Abbvie, Ayumi Pharmaceutical Co., Ltd., Bristol-Myers Squibb, Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Nippon Kayaku, Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., and UCB Japan Co., Ltd. **Katsunori Ikari** has served on speakers' bureaus for Abbvie, Astellas Pharma Inc., Asahi Kasei Pharma Corporation, Ayumi Pharmaceutical Co., Ltd., Bristol-Myers Squibb, Eisai Co., Ltd., Chugai Pharmaceutical Co., Ltd., Hisamitsu Pharmaceutical Co., Inc., Janssen Pharmaceutical K.K., Kaken Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Taisho Toyama Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Co.,

Ltd. **Atsuo Taniguchi** has served on speakers' bureaus for Pfizer Japan Inc. **Hisahi Yamanaka** has received a research grant from and has served on speakers' bureaus for AbbVie, Astellas Pharma Inc., Ayumi Pharmaceutical Co., Ltd., Boehringer Ingelheim GmbH., Bristol-Myers Squibb, Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Kaken Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co.,Ltd., Nippon Shinyaku Co., Ltd., Novartis Pharma K.K., Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc., Taisho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma, Ltd., Torii Pharmaceutical Co., Ltd., UCB Japan Co., Ltd. and YL Biologics Ltd. **Masayoshi Harigai** has received research grants and/or honoraria from Abbvie Japan Co., Ltd., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Co., Ono Pharmaceutical Co., Ltd., Taisho Pharmaceutical Co., Ltd., Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma, Ltd. and Pfizer Japan Inc. and serves as a consultant for Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., and Pfizer Japan Inc.

## CRediT author statement

**Masanori Nakayama:** Study design and conduct, Data collection, Drafting manuscript, Revising manuscript, responsibility for the integrity of the data analysis. **Takefumi Furuya:** Study design and conduct, Data collection, Drafting manuscript, Revising manuscript, Responsibility for the integrity of the data analysis. **Eisuke Inoue:** Data collection, Revising manuscript content. **Eiichi Tanaka:** Data collection, Revising manuscript content. **Katsunori Ikari:** Data collection, Revising manuscript content. **Atsuo Taniguchi:** Data collection, Revising manuscript content. **Hisahi Yamanaka:** Data collection, Revising manuscript content. **Masayoshi Harigai:** Data collection, Revising manuscript content.

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