

Change of ARASHI scores for large joints in rheumatoid arthritis patients treated with abatacept for three years: A clinical observational study

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ABSTRACT

Objectives: This study aims to investigate large joint damage progression using the assessment of rheumatoid arthritis (RA) by scoring of large joint destruction and healing in radiographic imaging (ARASHI) score in patients with RA treated with abatacept for three years.

Patients and methods: A total of 71 consecutive patients with RA (7 males, 64 females; median age 68 years; range, 41 to 81 years) and joint lesions (141 shoulders, 139 elbows, 141 hips, 134 knees, and 142 ankles) treated with abatacept for three years were examined. Radiographic changes were assessed using the ARASHI score, and factors associated with radiographic progressive damage of large joints were analyzed using multivariate logistic regression.

Results: The three-year radiographic progressive damage rates for the upper and lower limb large joints were 18.3% and 22.5%, respectively. Rates for the shoulder and knee decreased significantly ($p=0.025$ and 0.039 , respectively), whereas rate for the ankle increased significantly ($p=0.043$). Multivariate logistic regression analysis identified the baseline ARASHI status score as an independent predictor of progressive damage of upper limb large joints within three years ($p=0.004$; odds ratio, 1.17). The cutoff value of the ARASHI status score for the upper limb large joints was 4, as determined from the receiver operating characteristics curve. No significant predictors of progressive damage were identified in the lower limb large joints within three years.

Conclusion: The greatest suppression of the radiographic progressive damage of large joints was achieved for the shoulders and knees. Meanwhile, ankle damage progressed. Therefore, ankle joint damage should be monitored even in patients treated with abatacept. In the upper limbs, prescribing abatacept to patients with RA depending on their state of upper limb large joint damage may suppress damage progression.

Keywords: Abatacept, ARASHI score, large joint, rheumatoid arthritis.

Rheumatoid arthritis (RA) is associated with joint inflammation and destruction, which lead to pain, swelling, stiffness, and loss of function of joints throughout the body. Patients with RA experience a gradual deterioration of their quality of life, including disabilities that can affect their activities of daily living and work.¹⁻³ Conventional synthetic disease-modifying antirheumatic drugs

(DMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs are used in an attempt to achieve clinical and structural remission in patients with RA. Poor prognostic factors include rheumatoid factor (RF) positivity, anti-cyclic citrullinated peptide antibody (anti-CCP Ab) positivity, high disease activity, and early joint damage.⁴ Moreover, the predictors of radiographic

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progression include high disease activity and high serum C-reactive protein (CRP) level.⁵

Small joint damage is associated with large joint damage in patients with early RA.⁶ Damage to large joints, particularly of the shoulder, wrist, knee, and ankle, leads to functional disability.⁷ Therefore, suppressing damage to the large and small joints is paramount to maintain functional remission. Radiographic changes are generally assessed on radiographs of the hands and feet. Therefore, large joints are not usually evaluated during structural remission assessments. The Larsen grading system is widely used for the radiographic assessment of large joints. DMARDs improve and suppress small joint damage in patients with RA.⁸⁻¹³ Meanwhile, healing changes on radiographic images of large joints have been reported in the same patients.¹⁴⁻¹⁶ The phenomenon of healing is characterized by the reappearance of a cortical plate, fillings of erosions, or subchondral bone sclerosis with osteophyte formation.¹⁷ Assessment of rheumatoid arthritis by scoring of large joint destruction and healing in radiographic imaging (ARASHI) score include the status and change scores that are significantly correlated to Larsen grade ($\gamma=0.89$, $p<0.0001$ and $\gamma=0.83$, $p<0.0001$, respectively). However, 20.4% of joints without changes according to the Larsen grading system show improved ARASHI change scores.¹⁸ Therefore, the ARASHI score is useful to assess large joint damage and healing, such as in secondary osteoarthritis (OA).

Thus, assessing the effect of each bDMARD on large joints may be important, although few reports on the use of bDMARDs for large joints exist.^{15,16,19-21} Moreover, to our knowledge, the effects of mid-term abatacept treatment on large joints have not been published. Therefore, in this study, we aimed to investigate large joint damage progression using the ARASHI score in patients with RA treated with abatacept for three years.

PATIENTS AND METHODS

This retrospective clinical study investigated the clinical course and background variables of patients with RA who fulfilled the American College of Rheumatology (ACR) classification criteria (1987) and/or the ACR/European League against Rheumatism (EULAR) criteria.^{22,23} A total

of 110 consecutive patients who started abatacept treatment at Kamagaya General Hospital between November 2011 and October 2014 were enrolled. Data of 39 patients who terminated the treatment before the three-year period or incomplete data (13 experienced inadequate effect, seven developed adverse events, eight were transferred, two developed onset of other diseases, and nine lacked baseline data) were excluded. In addition, individuals who had undergone joint operations were excluded. Finally, data of 71 patients (7 males, 64 females; median age 68 years; range, 41 to 81 years) were analyzed. Rheumatologists at our institution introduced abatacept to the patients. Overall, 50 patients received intravenous abatacept and 21 received subcutaneous abatacept. Clinical characteristics including methotrexate (MTX) use and dose, corticosteroid use and dose, CRP, erythrocyte sedimentation rate (ESR), disease activity score 28 (DAS28)-CRP, and Health Assessment Questionnaire Disability Index (HAQ-DI) of the patients were examined at baseline and at first, second, and third years. DAS28-CRP is a composite measure of disease activity.⁴ HAQ-DI is a patient-reported measure of physical disability,²⁴ with questions related to 20 activities of daily living, such as dressing, grooming, arising, eating, walking, maintaining hygiene, reaching objects, maintaining grip, opening things, and other daily activities. Table 1 summarizes the demographic characteristics including age, sex, disease duration, body weight, RF positivity, anti-CCP positivity, first bDMARDs, administration method, MTX use, MTX dose, corticosteroid use, corticosteroid dose, CRP, ESR, DAS28-CRP, and HAQ-DI at baseline; and MTX use, MTX dose, corticosteroid use, corticosteroid dose, and CRP, ESR, DAS28-CRP, and HAQ-DI at first, second, and third years. The patients in this study had low MTX use and dose. In Japan, the approved MTX dose was ≤ 8 mg/week until February 2011, and it was increased to ≤ 16 mg/week thereafter. The patients in this study showed long disease durations and many were old enough to present chronic kidney disease; thus, the use of MTX was limited. The study protocol was approved by the Kamagaya General Hospital Ethics Committee (approval number: TGE00888-064). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Table 1. Demographic characteristics at baseline and at first, second, and third years

	Baseline			1 st year			2 nd year			3 rd year		
	n	%	Median	Q1-Q3	n	%	Median	Q1-Q3	n	%	Median	Q1-Q3
Age (year)	64	90.1	68	58.5-72								
Sex												
Female												
Disease duration (year)			6	2-11.5								
Body weight (kg)			51.2	44.5-59								
RF positive	53	74.6										
Anti-CCP Ab positive	57	80.3										
Abatacept: first bDMARDs	47	66.2										
Intravenous	50											
Subcutaneous formulation	21											
MTX use	48	67.6			46	64.8			45	63.4		
MTX dose (mg/week)			7	6-8			6	4-8			6	4-6
Prednisolone use	32	45.1			28	39.4			25	35.2		
Prednisolone dose (mg/day)			5	3-5			4	3-5			4	2-5
CRP (mg/dL)			0.8	0.4-1.85			0.11	0.1-0.3			0.11	0.1-0.335
ESR (mm/hr)			37	22-53.5			21	12-30			18	13-31
DAS28-CRP			3.80	3.12-4.675			1.94	1.435-2.555			1.87	1.38-2.72
HAQ-DI			0.50	0.25-1.125			0.25	0-0.8125			0.25	0-0.75

Q1: First quartile; Q3: Third quartile; RF: Rheumatoid factor; Anti-CCP Ab: Anti-cyclic citrullinated peptide antibody; bDMARDs: Biological disease-modifying antirheumatic drugs; MTX: Methotrexate; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; DAS28: Disease activity score 28; HAQ-DI: Health Assessment Questionnaire Disability Index.

Intravenous abatacept was administered as a 30-minute infusion on day zero (first infusion) and at two, four, and every four weeks thereafter. Patients weighing <60, 60-100, or >100 kg received 500, 750, or 1000 mg of abatacept, respectively. Subcutaneous abatacept was administered at 125 mg once a week.

The ARASHI scores for 697 joints (141 shoulders, 139 elbows, 141 hips, 134 knees, and 142 ankles), excluding those that had undergone surgical operations, were calculated. Radiographs were acquired at baseline (ARASHI status score) and first, second, and third years (ARASHI change scores). Two physicians separately measured the ARASHI scores on radiographs while being blinded to the patient information. Paramedical staff recorded the ARASHI scores. Disagreements were resolved by consensus among the observers. Radiographic progression rate of damage to large joints of the upper and lower limbs (shoulders, elbows, hips, knees, and ankles) were analyzed. Radiographic large joint progression damage was defined in patients with deterioration of the total ARASHI change score. In addition, factors associated with the progression of upper and lower limb large joint damage were analyzed.

Radiographs of weight-bearing knees and ankles were obtained with patients in the standing position. The ARASHI status score and the ARASHI change score were calculated for all upper and lower limb joints. Joint-space narrowing (normal, 0 point; narrowing <1/2, 1 point; narrowing $\geq 1/2$, 2 points; disappearance, 3 points); bone erosion (none, 0 point; 1, 1 point; 2, 2 points; ≥ 3 , 3 points); joint surface destruction at every opposite joint surface (normal, 0 point; surface irregularity <1/2 of surface area, 1 point; surface irregularity $\geq 1/2$ of surface area, 2 points; destruction or disappearance, 3 points); and joint conformity (normal, 0 point; mild deterioration, 2 points; severe deterioration, 4 points) were assessed on the basis of the ARASHI status score. Bone quality (improve, -1 point; no change, 0 point; decrease, 1 point); joint space narrowing (improve, -1 point; no change, 0 point; progression <1/2, 1 point; progression $\geq 1/2$, 2 points); bone erosion (no change, 0 point; new appearance or enlargement for 1 lesion, 1 point; new appearance or enlargement for ≥ 2 lesions, 2 points; disappearance, scale-down or marginal

sclerosis for 1 lesion, -1 point; disappearance, scale-down, or marginal sclerosis for ≥ 2 lesions, -2 points); joint surface destruction (normal, 0 point; surface irregularity, 1 point; slight destruction of original surface, 2 points; severe destruction, 3 points; partial disappearance of irregularity, -1 point; marked disappearance of irregularity, -2 points; subchondral bone reappearance, -3 points); and joint conformity (no change, 0 point; deterioration, 1 point; improve as OA change; -1 point) were assessed on the basis of the ARASHI change scores.¹⁸

Statistical analysis

Cochran-Armitage test was used to analyze large joint deterioration rates for years zero-one, one-two, and two-three. Variables of patients with or without large joint damage progression over a three-year period were compared to identify factors associated with the progression of upper and lower limb joint damage. Wilcoxon rank-sum and chi-squared tests were used to compare the following data between patients with or without large joint damage progression of upper and lower limbs: age, sex, disease duration, body weight, RF positivity, anti-CCP Ab positivity, MTX use at baseline, DAS28-CRP use at baseline, and at first, second, and third years, and the ARASHI status score for large joints of the upper and lower limbs. Multivariate logistic regression analysis was performed using the variables with $p < 0.1$ in the univariate analysis. Moreover, the cutoff values for factors associated with the progression of large joint damage were estimated by multivariate logistic regression analysis using the receiver operating characteristics (ROC) method with the corresponding sensitivity and specificity and area under the curve (AUC). AUC ranges from 0.5 (no accuracy for discriminating) to 1.0 (perfect accuracy for discriminating). Significance was established at $p < 0.05$. All analyses were performed using the R Statistical Package, version 3.3.2 (Product by Murdoch D).²⁵

RESULTS

Radiographic progressive damage rate for large joints using the ARASHI score was 18.3% for the upper limbs and 22.5% for the lower limbs in patients treated with abatacept for three years. Figure 1 shows the ARASHI status

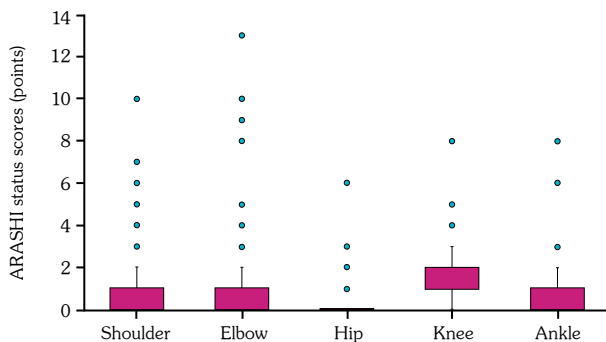


Figure 1. ARASHI status scores represented by box and whisker plots for shoulder, elbow, hip, knee, and ankle joints.

ARASHI: Assessment of rheumatoid arthritis by scoring of large joint destruction and healing in radiographic imaging; Upper and lower horizontal line, interquartile range; middle horizontal line, median; error bar, upper and lower limit.

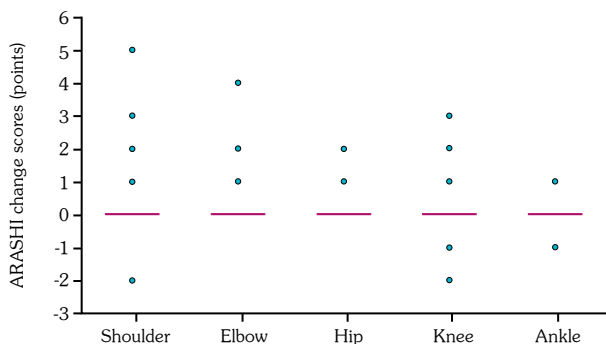


Figure 2. ARASHI change score after three years represented by box and whisker plots for shoulder, elbow, hip, knee, and ankle joints.

ARASHI: Assessment of rheumatoid arthritis by scoring of large joint destruction and healing in radiographic imaging; Upper and lower horizontal line, interquartile range; middle horizontal line, median; error bar, upper and lower limit.

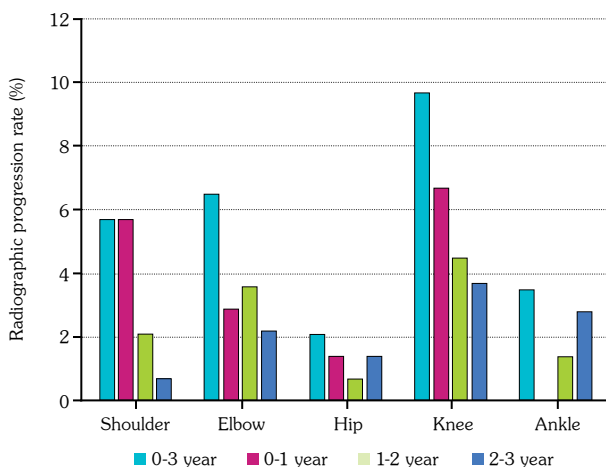


Figure 3. Radiographic damage progression rates for shoulder, elbow, hip, knee, and ankle joints.

scores represented by box and whisker plots of the shoulder, elbow, hip, knee, and ankle joints. Figure 2 shows the ARASHI change score represented by box and whisker plots of the shoulder, elbow, hip, knee, and ankle joints after three years of abatacept treatment. Figure 3 shows the radiographic progression rates. In large joints of the upper limb, the three-year radiographic progression rate for the shoulder ($p=0.025$) and knee ($p=0.039$) decreased significantly but that for the ankle increased significantly ($p=0.043$).

Univariate analysis for comparing variables between patients with and without upper limb large joint damage progression identified the following factors as significant: two-year DAS28-CRP, three-year DAS28-CRP, and ARASHI status score (Table 2). Moreover, multivariate logistic regression analysis revealed the ARASHI status score of the upper limb large joints ($p=0.004$; odds ratio, 1.17) to be significantly associated with damage progression rate (Table 3). The cutoff value for the ARASHI status score for the upper limb large joints, as calculated by the ROC method, was 4.0 (sensitivity, 69.2%; specificity, 91.4%; AUC, 0.845). However, there was no factor associated with damage progression of the lower limb large joints.

DISCUSSION

In this study, we investigated large joint damage and healing on the basis of the ARASHI score. Assessment of the ARASHI score is a radiographic method used to evaluate large joint damage, and it may be more useful than the Larsen grading system for identifying changes in joint damage.¹⁸ In a study of 270 large joints, the ARASHI score detected radiographic progressive changes more superiorly than the Larsen grading.¹⁹ In the present study, the rate of radiographic progressive damage of large joints using the ARASHI score was 18.3% for upper limb large joints and 22.5% for lower limb large joints of patients treated with abatacept for three years. Using the Larsen grading system, Seki et al.²⁰ reported a radiographic progression rate of 19% for weight-bearing joints (of hips, knees, and ankles) of patients treated with tumor necrosis factor (TNF) inhibitor for one year.

Table 2. Univariate analysis of factors associated with damage progression of large joints for three years

	Damage progression in large joints of upper limb						Damage progression in large joints of lower limbs							
	Positive (n=13)			Negative (n=58)			Positive (n=16)			Negative (n=55)				
	n	%	Median	Q1-Q3	n	%	Median	Q1-Q3	p	n	%	Median	Q1-Q3	p
Age (year)			60	53-74			68.5	59.5-71	0.417			68	63.25-74.25	0.401
Sex														
Female	11	84.6			53	91.4			0.822	14	87.5			1.000
Disease duration (year)			9	6-21			4.5	2-11	0.104			4	2-12	0.679
Body weight (kg)			51.9	49.5-57.6			51.1	44.0-59.0	0.457			54.5	43.5-62.0	0.549
RF positivity	9	69.2			44	75.9			0.886	13	81.3			0.716
Anti-CCP positivity	12	92.3			45	77.6			0.412	11	68.8			0.337
Concomitant MTX use	11	84.6			37	63.8			0.464	10	62.5			0.221
DAS28-CRP														
At baseline			3.46	3.13-4.32			3.88	3.12-4.72				3.54	2.81-4.12	0.234
At 1 st year			2.57	1.66-2.98			1.85	1.40-2.49				1.77	1.39-2.30	0.496
At 2 nd year			2.50	2.17-2.81			1.71	1.33-2.62				2.06	1.59-2.65	0.640
At 3 rd year			2.38	1.95-2.80			1.77	1.29-2.47				2.04	1.74-2.88	0.173
ARASHI status score in large joints of upper limb			7	3-15			0	0-1.75	<0.001			1	0-1.75	0.913
ARASHI status score in large joints of lower limb			4	2-6			3	2-4.75	0.700			4	2-5.25	0.339

Q1: First quartile; Q3: Third quartile; RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide; MTX: Methotrexate; DAS28: Disease activity score 28; CRP: C-reactive protein; ARASHI: Assessment of rheumatoid arthritis by scoring of large joint destruction and healing in radiographic imaging.

Table 3. Multivariate logistic regression analysis of factors associated with damage progression of upper limb large joint damage for three years

Variables	Odds ratio	95% CI	<i>p</i>
DAS28-CRP at 2 year	2.16	0.82-5.70	0.121
DAS28-CRP at 3 year	1.65	0.62-4.37	0.313
ARASHI status score in large joints of upper limb	1.17	1.05-1.30	0.004

CI: Confidence interval; DAS28: Disease activity score 28; CRP: C-reactive protein; ARASHI: Assessment of rheumatoid arthritis by scoring of large joint destruction and healing in radiographic imaging.

Meanwhile, using the ARASHI scores, Kanbe et al.¹⁶ reported a radiographic progression rate of 20% for large joints of patients treated with golimumab for one year. Moreover, using the Larsen grading system, Nakajima et al.²¹ reported a radiographic progressive damage rate of 20.9% for large joints of patients treated with bDMARDs for 18.6 months and Matsushita et al.¹⁵ reported radiographic progressive damage rates of 11.5%, 14.7%, and 15.9% at first, second, and three years, respectively, for hips and knees of patients treated with TNF inhibitor for three years. In the present study using the ARASHI score, the radiographic progressive damage rates for the hip and knee were 4.0%, 2.5%, and 2.5% at first, second, and third years, respectively, in patients with RA treated with abatacept for three years. We speculate that these differences in radiographic progressive damage rates are due to the use of different scoring methods and variations in the baseline disease activity. While the patients in the study by Matsushita et al.¹⁵ showed high baseline disease activity, patients in our study showed moderate disease activity. Moreover, in our study, the mean disease activity was maintained at remission after one year and was not associated with large joint damage. Osteoarthritic changes primarily include joint space narrowing and osteophyte formation. We noted improvements in ARASHI change score for osteoarthritic changes such as subchondral bone sclerosis and osteophyte formation. These changes tended to appear in lower limb large joints, suggesting that if the disease activity is suppressed, the ARASHI change score for lower limb large joints, particularly of the knees, can improve. In fact, eight knees showed osteoarthritic changes, although our patients were relatively old.

In a study by Nakajima et al.,²¹ patients treated with bDMARDs showed moderate baseline disease activity, as in our study, and they reported progressive damage rates of 6.8%, 4.1%, 0.0%, 7.0%, and 8.7% for the shoulder, elbow, hip, knee, and ankle joints, respectively, at 18.6 months; these rates are similar to our rates at one year but different from those at three years. Continuous treatment with abatacept may suppress RA in the upper limb large joints. However, Drossaers-Bakker et al.²⁶ reported a higher percentage of patients with erosive large joints (Larsen score ≥ 2) of the upper limbs than of the lower limbs after 12 years of follow-up, although the treatment details remain unclear. We speculate that our results are a feature of abatacept for large joints and warrant long-term observation.

In this study, the ARASHI status score was associated with the progressive damage of the upper limb large joints of patients treated with abatacept for three years. However, we did not identify other factors associated with progressive damage of lower limb large joints after three years of abatacept treatment. In other reports, Larsen grade at baseline, DAS28-ESR at one year, and the EULAR response have been reported as the factors associated with the progressive damage of large joints.^{15,16,20,21} In assessments performed using fluorodeoxyglucose positron emission tomography combined with computed tomography, the maximum standardized uptake value at the baseline was associated with progressive damage of large joints in patients treated with bDMARDs for three years.¹⁹ Moreover, high-intensity weight-bearing exercises appeared to accelerate large joint damage progression in patients with pre-existing joint damage.²⁷ In our study, large joint damage at the baseline was an important factor associated with progressive joint damage. This result supports the notion that in patients with ARASHI status scores of ≤ 4 , abatacept may suppress the progressive damage of upper limb large joint. According to Asai, concomitant MTX use reduced the requirement of large joint replacement in patients treated with TNF inhibitors.²⁸ However, progressive damage of the hip and knee joints did not depend on combined treatment with MTX and TNF inhibitors.¹⁵ In our study, MTX was not a factor associated with progressive damage of upper or lower

limb large joints. We had reported that in patients with RA, abatacept treatment achieved structural remission in small joints independent of MTX treatment.²⁹ Therefore, our results demonstrate that abatacept with or without MTX may suppress radiographic progressive damage of large and small joints.

There are some limitations in our study. First, this was a single center study. Second, we did not include a control group. Multicenter studies including a control group and long-term follow-up are warranted to confirm the factors associated with progressive damage of large joints. Finally, our study lacked data of the excluded patients; however, we believe that the impact of these data on the results would be minor because only a few patients discontinued abatacept due to inadequate effects.

In conclusion, on the basis of the ARASHI score, we demonstrated large joint damage changes in patients with RA treated with abatacept for three years. In particular, the greatest suppression of the radiographic progressive damage of large joints was achieved for the shoulders and knees. Meanwhile, ankle damage progressed relentlessly. Pre-existing joint damage was associated with upper limb large joint damage progression. Prescribing abatacept to patients with RA depending on the status of their upper limb large joint damage may suppress the damage progression. However, ankle joint damage should be monitored even in patients on abatacept treatment.

Declaration of conflicting interests

T. M. received honorariums for lectures from AbbVie, Astellas, Bristol-Myers, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Janssen, Mochida, Pfizer, Takeda, and Tanabe-Mitsubishi. K. Y. received honorariums for lectures from AbbVie, Astellas, Ayumi, Bristol-Meyers, Eisai, Hisamitsu, Mochida, and Takeda. K. I. received honorariums for lectures from AbbVie, Astellas, Bristol-Myers, Chugai, Eisai, Eli Lilly, Janssen, Takeda, Tanabe-Mitsubishi, and UCB. The other authors declare that they have no conflicts of interest. The sponsors were not involved in the study design; collection, analysis, and interpretation of data; writing of the paper; and/or decision to submit the results for publication.

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