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Relationship Between Inflammation and Radiographic Progression in Patients With Ankylosing Spondylitis Attaining a BASDAI of Less Than 4 During Tumor Necrosis Factor Inhibitor Treatment

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ABSTRACT. ***Objective.*** To determine the relationship between inflammation and radiographic progression over time in patients with ankylosing spondylitis (AS) attaining a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of < 4 during tumor necrosis factor inhibitor (TNFi) treatment.

Methods. Medical records data of patients with AS with BASDAI scores of < 4 during TNFi treatment were analyzed at 6-month intervals from January 2001 to December 2018. To determine the relationship between the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) and C-reactive protein (CRP) over time, we fitted linear mixed models with mSASSS as the response variable, baseline mSASSS and the cumulative sum of CRP with different lag times (6, 12, 18, 24, 30, and 36 months) as fixed effects, and patients as random effects. Associations between mSASSS and the cumulative sum of CRP, or the lag times with the highest beta coefficients, were further investigated with linear mixed models that included additional clinical variables.

Results. A total of 2956 intervals were obtained from 333 patients. Among different lag times, the cumulative sum of log CRP in the previous 18 to 36 months associated with mSASSS showed significant beta coefficients. In the final linear mixed model, the cumulative sum of log CRP in the previous 24 months was significantly associated with mSASSS at 24 months (β 0.04, 95% CI 0.01-0.07, $P = 0.004$).

Conclusion. Remnant inflammation correlates with radiographic progression, even in patients attaining a BASDAI of < 4 during TNFi treatment. CRP is a surrogate marker for radiographic progression despite clinical improvement with TNFi treatment.

Key Indexing Terms: ankylosing spondylitis, C-reactive protein, disease progression, radiography, tumor necrosis factor inhibitor

Ankylosing spondylitis (AS) is a chronic inflammatory disease that causes ankylosis of the spine and sacroiliac (SI) joints over a long period.[1] Patients with AS may experience varying degrees of back pain, stiffness, and ankylosis. In addition, the recurrence and persistence of inflammatory conditions throughout life lead to disabilities and socioeconomic burden in patients with AS.[2,3]

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Inflammation is the representative risk factor related to radiographic progression.[4,5] The Ankylosing Spondylitis Disease Activity Score (ASDAS) and C-reactive protein (CRP) have shown good correlations with radiographic damage, suggesting that using low levels of ASDAS and CRP as treatment targets would be useful for reducing radiographic damage.[5-7] However, there is a lack of evidence as to which surrogate markers should be targeted for slowing radiographic progression.[8-10]

Several previous studies showed that treatment with tumor necrosis factor inhibitors (TNFi) reduced radiographic progression.[4,7,11-13] Moreover, we previously demonstrated that the intervals in which patients were treated with TNFi were significantly associated with lower radiographic disease progression compared with the intervals in which patients were not treated with TNFi.[11] However, the changes in the modified Stoke Ankylosing Spondylitis Spinal Scores (mSASSS) per year were not notably different between the 2 groups (0.85 vs 0.96 per year, respectively). This result suggested that even though TNFi treatment improved a patient's inflammatory status and symptoms, complete avoidance of structural damage was difficult. However, considering that radiographic progression is highly correlated

with inflammation,[5-7] the inflammation may not have been completely suppressed in patients treated with TNFi. Therefore, it is necessary to determine whether the proper target of treatment (eg, disease activity index) is being used, and whether TNFi is the best treatment for inhibiting radiographic progression in patients with AS.

This study aimed to use real-world data to investigate whether inflammation is correlated with radiographic progression of AS over time, even in patients attaining a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of < 4 during TNFi treatment, and to find a surrogate marker for radiographic progression.

METHODS

Data collection. We retrospectively reviewed the electronic medical records (EMRs) of 1280 patients with AS who were treated at the Hanyang University Hospital in Seoul, Korea, for up to 18 years between January 2001 and December 2018.[11] The diagnosis of AS was made according to the modified New York (mNY) criteria at the initial follow-up.[14] Clinical characteristics such as age, sex, disease duration between the first and last follow-up, HLA-B27 positivity, history of smoking, eye involvement with uveitis, and peripheral joint involvement were collected from the EMRs. To evaluate disease activity during treatment with TNFi, we assessed the erythrocyte sedimentation rate (ESR), CRP level, ASDAS, and BASDAI for each patient.[15] The mSASSS, assessed from spinal radiographs that had been performed for reasons such as the diagnosis of AS, worsening pain, or patients' needs, were retrospectively reviewed.

Assessment of radiographic progression. Two radiologists (SL and KBJ) evaluated the mSASSS[16] and performed independent reviews of patients' radiographs, while blinded to the EMR data. Accuracy of the mSASSS were confirmed, based on excellent intraobserver reliability with consistency (intraclass coefficient [ICC] 0.98, 95% CI 0.98-0.98). Interobserver reliability with agreement between the 2 readers was also excellent (ICC 0.95, 95% CI 0.94-0.95).

Patients. In Korea's medical insurance system, if AS is diagnosed in patients based on the mNY criteria and their BASDAI is ≥ 4, they can receive health insurance benefits for TNFi treatment. Treatment can be continued only if significant response is noted in the disease activity assessment performed every 6 months. Considering that most patients on TNFi treatment are covered by insurance, of the 1280 patients, those treated with TNFi were included in the analysis. To select patients who maintained a BASDAI of < 4 for this study, those who had a BASDAI of ≥ 4 at least once during the TNFi treatment were excluded.

The duration of treatment with TNFi was defined as the period from the date of TNFi prescription until 90 days (washout period) plus 14, 3.5, 7, 60, and 30 days after the prescription dates for adalimumab, etanercept 25 mg, etanercept 50 mg, infliximab, and golimumab, respectively. Biosimilar drugs were considered as effective as branded drugs. All periods treated with TNFi were divided into 6-month intervals from the start of the treatment. CRP, ESR, ASDAS, and mSASSS were imputed by the linear interpolation method using 6-month intervals (Figure 1). Intervals of the observational and clinical data that were measured are presented in Supplementary Table S1 (available with the online version of this article).

Statistical analysis. All data were summarized as mean (SD) or as percentages. We used a linear mixed model with random intercepts to investigate the correlation between inflammatory markers and mSASSS, while allowing for a clustering effect within each patient. The initial model was constructed with the baseline mSASSS and time (t) as explanatory variables and mSASSS at time (t) as the outcome, expressed as follows: mSASSS (t) ~ baseline mSASSS + t.

First, we investigated which timepoint of inflammatory markers was related to increases in mSASSS. CRP and ESR were normalized using log transformation.[11] Log CRP, log ESR, and ASDAS (X) were selected as explanatory variables. For each of the 3 explanatory variables, the beta coefficient of lagged inflammatory markers for predicting mSASSS was estimated at 6-month intervals from 0 to 36 months. Because the baseline (starting point of TNFi treatment) values of log CRP, log ESR, and ASDAS were higher than the follow-up values, the baseline values were used as separate explanatory variables. Subsequently, we selected inflammatory markers and lag times that generated statistically significant beta coefficients. Additionally, the cumulative sum of log CRP and that of log ESR (X) were also identified to reflect the effects of subsequent inflammatory status that were frequently measured and changed occasionally in AS. The cumulative sum was the sum of values imputed every month. Considering the very high baseline values, the cumulative sum of inflammatory markers during a 6-month period was calculated as the cumulative sum of the past 5 months, and the 12-month cumulative sum was calculated as the cumulative sum of the past 11 months, with baseline inflammatory markers as the explanatory variables. The cumulative sums for 18, 24, 30, and 36 months were calculated similarly. The cumulative sum of inflammatory markers and lag times that had significant beta coefficients was also selected. The statistical model of the relationship between inflammation and mSASSS over time is expressed as follows: mSASSS (t) ~ baseline mSASSS + t + X (t-lag t) + baseline X.

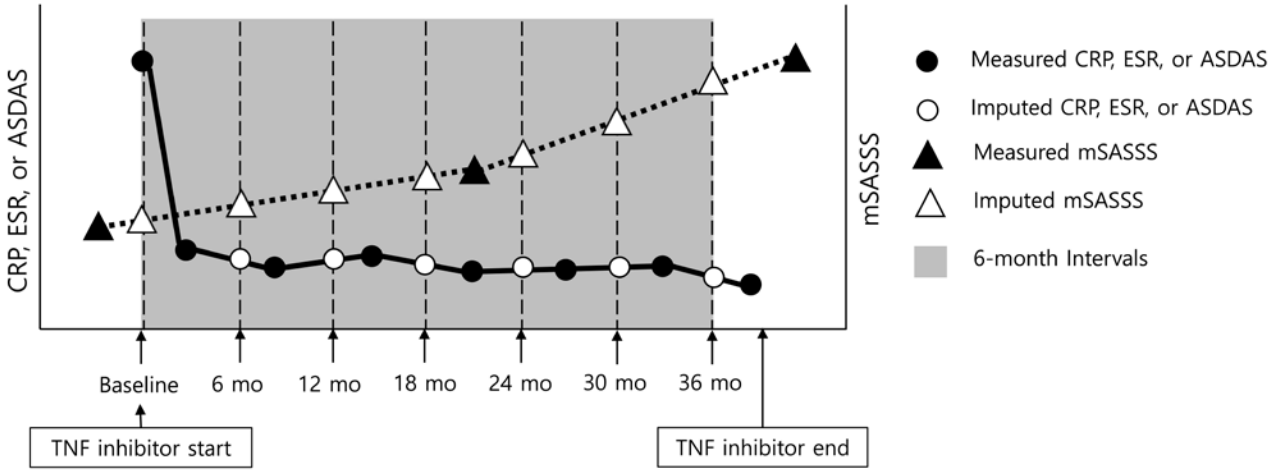

Figure 1. Definition of interval. The duration of treatment with TNFi is divided into 6-month intervals and the values of CRP, ESR, and ASDAS are imputed every 6 months by interpolation. ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; TNF: tumor necrosis factor.

Second, using the highest beta coefficients at a significant timepoint, 2 linear mixed models for inflammatory markers lagged by the significant timepoint and for the cumulative sum of significant duration as main independent variables (X) were established, based on the initial linear mixed model. Fixed effects were baseline mSASSS, time, interaction between baseline mSASSS and time, clinical characteristics (eg, sex, eye involvement, peripheral arthritis, and HLA-B27), and the inflammatory markers. Random effects were the random intercept for each patient and intervals, and nested intervals in patients with multiple intervals. Finally, we used the following model: mSASSS (t) ~ baseline mSASSS + t + X + clinical characteristics. The goodness-of-fit of the final models was evaluated with the Akaike information criterion (AIC). All statistical analyses were performed with R version 3.6.1 (R Foundation for Statistical Computing).

Statement of ethics and consent. The Institutional Review Board of Hanyang University Seoul Hospital approved this study (HYUH 2018-07-007); the study was conducted in accordance with the board's guidelines and regulations. The requirement for informed consent was waived by the Institutional Review Board of Hanyang University Seoul Hospital, considering the retrospective nature of this study.

RESULTS

Patients and intervals. Of 1280 patients with AS treated at our center, 677 had a history of treatment with TNFi (Figure 2). Among them, we excluded those who had BASDAI ≥ 4 at least once during treatment, those whose mSASSS could not be interpolated because they only had 1 radiograph examination, and patients with < 6 months of TNFi prescription. In total, 333 patients were included in this study. The baseline characteristics of the patients are shown in Table 1.

Of the 333 patients, the number of baseline (start of TNFi therapy) data were 611 because there were patients who had been prescribed TNFi for > 2 periods. In addition, 2956 intervals were obtained by dividing the treatment periods by 6-month intervals. The characteristics of the 2956 intervals are summarized in Supplementary Table S2 (available with the online version of this article), and the changes in mSASSS according to the 6-month intervals are shown in Supplementary Figure S1.

Table 1. Baseline characteristics of study patients.

	No. of Baseline Data	Value
Age at diagnosis, yrs, mean (SD)	333	30.56 (8.71)
Female, n (%)	333	25 (7.5)
Follow-up duration, yrs, mean (SD)	333	9.16 (3.19)
HLA-B27, n (%)	333	323 (97.0)
Eye involvement, n (%)	301	127 (42.2)
Peripheral joint involvement, n (%)	297	168 (56.6)
Duration treated with TNFi per patient, yrs, mean (SD)	333	5.07 (3.08)
Duration not treated with TNFi per patient, yrs, mean (SD)	333	4.09 (3.38)
ESR, mm/h, mean (SD)	611	20.44 (23.59)
CRP, mg/dL, mean (SD)	611	1.65 (1.84)
ASDAS, mean (SD)	164	2.33 (0.77)
mSASSS, mean (SD)	611	16.77 (19.17)

ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; TNFi: tumor necrosis factor inhibitors.

Initial models for mSASSS over time. An initial linear mixed model was constructed for mSASSS using time and baseline mSASSS (Supplementary Table S3, available with the online version of this article). The baseline mSASSS and the time (6-month intervals) were positively correlated with mSASSS (β 1.03, 95% CI 1.01-1.04, $P < 0.001$ and β 0.43, 95% CI 0.41-0.45, $P < 0.001$, respectively).

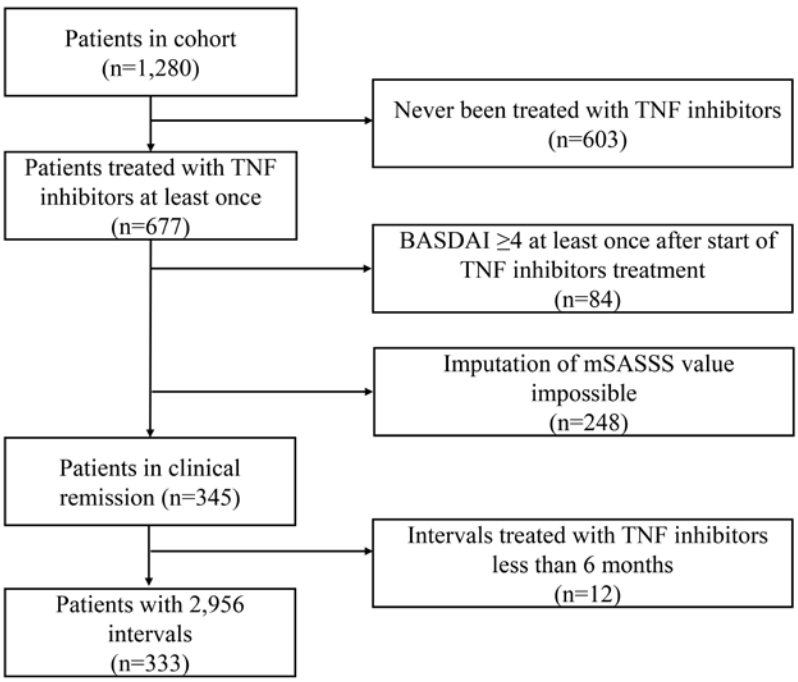

Figure 2. Patient selection flow. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; TNF: tumor necrosis factor.

Relationship between inflammation and mSASSS over time. The baseline and lagged values of CRP, ESR, and ASDAS were added to the initial models as explanatory variables. The β coefficients for the relationships between lagged inflammatory markers and mSASSS are shown in Figure 3 and Supplementary Tables S4 and S5 (available with the online version of this article). CRP showed a significant positive correlation with the mSASSS at the lagged times of 12, 18, 24, 30, and 36 months (Figure 3A), whereas ESR and ASDAS did not show significant correlations at any lagged time (Figure 3B and 3C, respectively). In the cumulative sums of inflammatory markers, the cumulative sum of CRP in the previous 18, 24, 30, and 36 months, the cumulative sum of ESR in the previous 24, 30, and 36 months, and the cumulative sum of ASDAS in the previous 6 months showed significantly positive correlations with mSASSS (Figures 3D, 3E, and 3F, respectively). Among the inflammatory markers and the timepoints that showed significant correlations with the mSASSS, we selected CRP lagged by 18 months and the cumulative sum of CRP in the previous 24 months, which had the highest significant beta coefficients, as the main independent variables to investigate the relationship between inflammation and mSASSS.

Models for the relationship between CRP lagged by 18 months and mSASSS. Table 2 shows the linear mixed models with log CRP lagged by 18 months as the main independent variables. Model 0 showed the correlations between each variable and mSASSS. In models 1 and 2, log CRP lagged by 18 months showed significant positive correlations with mSASSS (β 0.62, 95% CI 0.18-1.06, $P = 0.006$, and β 0.58, 95% CI 0.15-1.02, $P = 0.009$, respectively). When clinical characteristics were added in models 1 and 2, log CRP lagged by 18 months also showed significant positive correlations with mSASSS (β 0.63, 95% CI 0.18-1.09, $P = 0.006$, and β 0.59, 95% CI 0.14-1.05, $P = 0.01$, respectively). In addition, peripheral arthritis in models 1 and 2 with clinical characteristics showed significant negative correlations with mSASSS (β −1.18, 95% CI −2.36 to −0.003, $P = 0.049$, and β −1.20, 95% CI −2.38 to −0.02, $P = 0.046$, respectively). Among the models, model 1 with clinical characteristics showed the best fit, with an AIC value of 7172.29.

Models for the relationship between the cumulative sum of CRP in the previous 24 months and mSASSS. Table 3 shows the linear mixed models with the cumulative sum of log CRP in the previous 24 months as the main independent variable. Model 0 showed the correlations between each variable and mSASSS. In models 1 and 2, the cumulative sum of log CRP in the previous 24 months showed positive correlations with mSASSS (β 0.04, 95% CI 0.01-0.07, $P = 0.003$, and β 0.04, 95% CI 0.01-0.07, $P = 0.006$, respectively). When clinical characteristics were added in model 1, the cumulative sum of log CRP in the previous 24 months also showed a significant positive correlation with mSASSS (β 0.04, 95% CI 0.01-0.07, $P = 0.004$). In addition, peripheral arthritis had a significant negative correlation with mSASSS (β −1.23, 95% CI −2.44 to −0.03, $P = 0.04$). Among the models, model 1 with baseline characteristics showed the best fit, with an AIC value of 7061.80.

DISCUSSION

In this study, we found that inflammatory markers had a positive correlation with mSASSS changes over time in patients attaining a BASDAI of < 4 during TNFi treatment. Although TNFi treatment leads to low BASDAI, it may not sufficiently inhibit inflammation. Even though TNFi can significantly slow radiographic progression,[11] remnant inflammation might lead to the acceleration of radiographic progression. In addition, the cumulative sum of CRP in the previous 24 months may be a better predictive marker for radiographic progression than symptom-related disease activity indices such as BASDAI or ASDAS. Disease activity markers and indices such as ESR, BASDAI, and

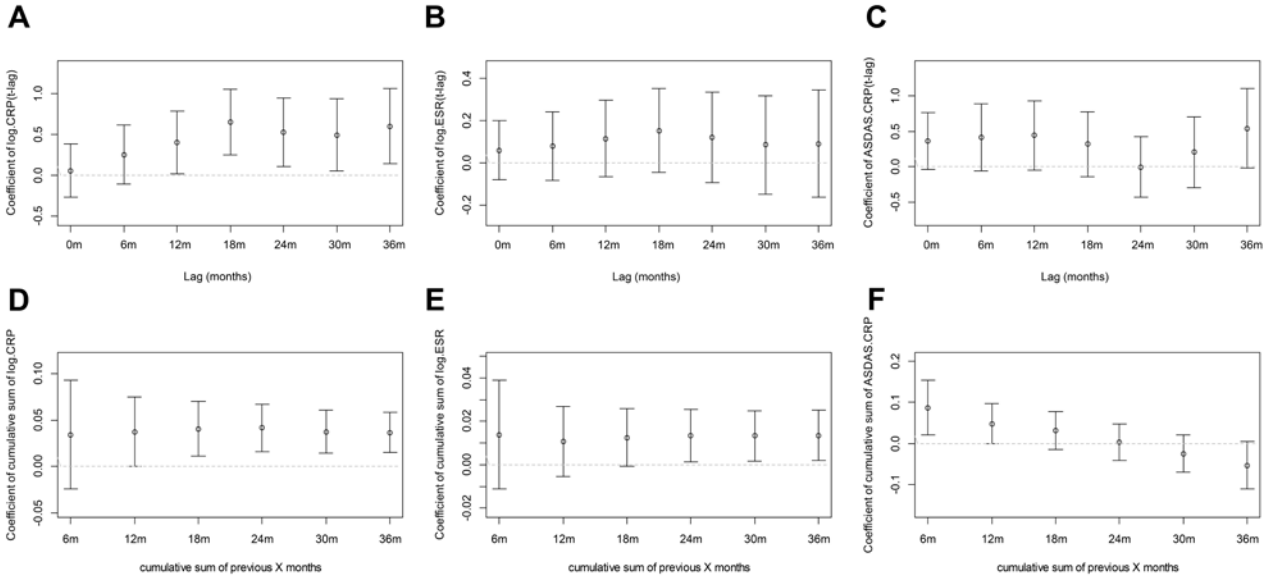

Figure 3. Relationship between inflammation and mSASSS over time. The relationship between (A-C) inflammatory markers lagged by 6, 12, 18, 24, 30, and 36 months; or (D,E) cumulative sum of inflammatory markers in the previous 6, 12, 18, 24, 30, and 36 months, and mSASSS are shown as beta coefficients. ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Table 2. Linear mixed models using log CRP lagged by 18 months as the main independent variable.

	Model 0[a]				Model 1				Model 2				Model 1 + Clinical Characteristics[b]				Model 2 + Clinical Characteristics[b]			
		95% CI				95% CI				95% CI				95% CI				95% CI		
	β	LB	UB	*P*	β	LB	UB	*P*	β	LB	UB	*P*	β	LB	UB	*P*	β	LB	UB	*P*
Baseline mSASSS	–	–	–	–	1.06	1.03	1.08	< 0.001	1.05	1.02	1.08	< 0.001	1.05	1.01	1.08	< 0.001	1.03	1.00	1.07	< 0.001
Time	–	–	–	–	0.45	0.42	0.48	< 0.001	0.42	0.38	0.46	< 0.001	0.46	0.42	0.49	< 0.001	0.43	0.38	0.47	< 0.001
Baseline mSASSS × time (interaction)	–	–	–	–	–	–	–	–	0.002	0.00	0.003	0.04	–	–	–	–	0.002	0.00	0.003	0.05
Log CRP lagged by 18 months	0.62	0.18	1.06	0.006	0.62	0.18	1.06	0.006	0.58	0.15	1.02	0.009	0.63	0.18	1.09	0.006	0.59	0.14	1.05	0.01
Female sex	−0.41	−1.37	0.55	0.40	–	–	–	–	–	–	–	–	−0.61	−2.59	1.37	0.55	−0.61	−2.58	1.37	0.55
Eye involvement	0.08	−0.49	0.66	0.78	–	–	–	–	–	–	–	–	0.32	−0.84	1.48	0.59	0.32	−0.84	1.48	0.59
Peripheral arthritis	−0.53	−1.13	0.08	0.09	–	–	–	–	–	–	–	–	−1.18	−2.36	−0.003	0.049	−1.20	−2.38	−0.02	0.046
HLA-B27 positivity	0.30	−1.13	1.74	0.68	–	–	–	–	–	–	–	–	−0.67	−3.65	2.31	0.66	−0.67	−3.65	2.32	0.66
AIC					7650.14				7660.34				7172.29				7182.77			

[a] mSASSS(t) ~ baseline mSASSS + time + variable. [b] Clinical characteristics including female sex, eye involvement, peripheral arthritis, and HLA-B27 positivity. AIC: Akaike information criterion; LB: lower bound; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; UB: upper bound.

Table 3. Linear mixed models using the cumulative sum of log CRP in the previous 24 months as the main independent variable.

	Model 0[a]				Model 1				Model 2				Model 1 + Clinical Characteristics[b]			
		95% CI				95% CI				95% CI				95% CI		
	β	LB	UB	*P*	β	LB	UB	*P*	β	LB	UB	*P*	β	LB	UB	*P*
Baseline mSASSS	–	–	–	–	1.06	1.03	1.09	< 0.001	1.05	1.02	1.08	< 0.001	1.05	1.01	1.08	< 0.001
Time	–	–	–	–	0.46	0.43	0.49	< 0.001	0.44	0.40	0.48	< 0.001	0.47	0.43	0.50	< 0.001
Baseline mSASSS × time (interaction)	–	–	–	–	–	–	–	–	0.001	0.00	0.003	0.16	–	–	–	–
Cumulative sum of previous 24 months' log CRP	0.04	0.01	0.07	0.003	0.04	0.01	0.07	0.003	0.04	0.01	0.07	0.006	0.04	0.01	0.07	0.004
Woman	−0.41	−1.37	0.55	0.40	–	–	–	–	–	–	–	–	−0.65	−2.66	1.36	0.53
Eye involvement	0.08	−0.49	0.66	0.78	–	–	–	–	–	–	–	–	0.35	−0.83	1.53	0.56
Peripheral arthritis	−0.52	−1.13	0.08	0.09	–	–	–	–	–	–	–	–	−1.23	−2.44	−0.03	0.04
HLA B27 positivity	0.30	−1.13	1.74	0.68	–	–	–	–	–	–	–	–	−0.55	−3.64	2.54	0.73
AIC					7527.44				7539.84				7061.80			

[a] mSASSS(t) ~ baseline mSASSS + time + variable. [b] Clinical characteristics including woman, eye involvement, peripheral arthritis, and HLA B27 positivity. AIC: Akaike information criterion; LB: lower bound; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; UB: upper bound.

ASDAS also showed significant correlations with radiographic progression; however, our results showed that CRP was the best predictor of radiographic progression, considering the delayed effect of inflammation.

In patients with AS, increases in inflammation were shown to be significantly correlated with radiographic changes.[6,17] Specifically, several studies have shown positive correlations between baseline or time-averaged inflammatory markers and mSASSS progression over 2 years in patients with AS.[5,12,18] In addition, Ramiro et al demonstrated that the rate of change in mSASSS over an extended period could be accelerated or slowed, according to the change in inflammation.[6] We examined the relationship between inflammation and radiographic progression in patients with AS maintaining low BASDAI with TNFi treatment. Rather than affecting radiographic progression immediately, inflammation likely affects the spinal or SI joints over an extended period. However, it is difficult to pinpoint the time at which severe inflammation causes the spinal radiographic changes seen in patients with AS.

To clarify the relationship between inflammation and radiologic changes over time, we first examined the lagged effect of inflammatory markers on radiographic progression. Inflammatory markers and disease activity data from EMRs were imputed using an interpolation method to measure inflammatory markers at intervals of 6 months. In clinical practice, inflammatory markers and disease activity are frequently measured for various reasons, such as evaluating response to treatment with TNFi, observing side effects, and evaluating disease activity to meet patient insurance requirements.[2,3] Therefore, the EMR data were more useful than the general cohort data with 2-year intervals for evaluating the inflammatory markers at shorter intervals. As a result, by using the data of 6-month intervals, we identified that mSASSS was significantly correlated with CRP lagged by 12 to 36 months, cumulative sums of CRP in the previous 18 to 36 months, and cumulative sums of ESR in the previous 24 to 36 months. Among them, CRP lagged by 18 months and the cumulative sum of CRP in the previous 24 months had the highest correlation coefficients with mSASSS. In addition, the cumulative sum of ASDAS in the previous 6 months was significantly associated with mSASSS. Considering that ASDAS has a longer average measurement interval than ESR or CRP (9 months vs 6.5 months), the decrease in the ASDAS by TNFi treatment would not have been properly reflected in the interpolation of the ASDAS values. Therefore, if the ASDAS values from more frequent measurements were used, it is likely that the cumulative sum of ASDAS in the previous 6 months would not have been significantly associated with mSASSS.

Regarding clinical characteristics, we observed that peripheral arthritis was negatively correlated with radiographic progression. This result is consistent with past findings that patients with AS with peripheral arthritis do not have severe radiographic changes compared to those without peripheral arthritis.[19,20] Given the differences in prognosis associated with radiographic changes, patients with AS may need to be classified based on the presence of peripheral arthritis.[21] Further studies are needed to better elucidate the differences in patients with AS according to the presence of peripheral arthritis, including genetic and clinical characteristics.[22]

There were several limitations to this study. First, because of the characteristics of real-world data, such as missing data, there may have been unmeasured confounders (eg, smoking). Second, because of the retrospective nature of the study, it was not possible to obtain the measured values every 6 months for all variables. Nevertheless, since a large amount of data was collected for analysis using imputed values, we were able to identify significant relationships between the variables. Third, inflammatory markers such as CRP may have fluctuated temporarily as a result of numerous factors other than AS disease activity. In addition, measurements of inflammatory markers every few months may not sufficiently reflect AS-related inflammation. Therefore, we reasoned that using the cumulative values of the inflammation markers would complement the limitations stemming from fluctuations in the disease activity of AS. Fourth, most patients treated with TNFi had high baseline inflammation, and their changes in mSASSS were shown to be different from those who had not been treated with TNFi.[11,23] Therefore, the delayed effect of inflammation on mSASSS may be different in patients not treated with TNFi.

In conclusion, we found that even in patients with AS attaining a BASDAI of < 4 during TNFi treatment, the CRP level was significantly correlated with radiographic progression. Therefore, CRP may be used as a reliable predictor in the management of such patients.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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