Original article:

Predictive value of serum amyloid A levels for requirement of concomitant methotrexate in tocilizumab initiation: A *post-hoc* analysis of the SURPRISE study

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Abstract

Objectives. To identify predictive factors for remission by tocilizumab monotherapy in rheumatoid arthritis (RA) patients.

Methods. This is a *post-hoc* analysis of the SURPRISE study, a 2-year randomized, controlled study comparing the efficacy of tocilizumab with (ADD-ON) and without methotrexate (SWITCH). The primary endpoint was DAS28-ESR remission (< 2.6) at week 24. The change in modified total Sharp score from baseline to week 52 (ΔmTSS/year) was also assessed as an endpoint. The effect of clinical parameters at baseline on remission was estimated by logistic regression analysis.

Results. In SWITCH (n = 96), CRP, SAA, RF and DAS28 at baseline showed predictive value for DAS28 remission in unadjusted analysis. Adjusted analysis confirmed SAA and DAS28 as predictive factors, with SAA having the highest value (ROC-AUC = 0.731). Furthermore, structural remission (ΔmTSS/year ≤ 0.5) rate was significantly higher in patients with SAA of < 50.0 μg/mL than other patients. In contrast, in ADD-ON (n = 98), only DAS28 showed predictive value for DAS28 remission. In patients with SAA < 50.0 μg/mL, both DAS28 remission and structural remission rate were comparable between SWITCH and ADD-ON.

Conclusions. RA patients with low SAA levels at baseline may benefit similarly from tocilizumab with and without methotrexate.

Introduction

Methotrexate is undoubtedly an anchor drug in the current treatment of rheumatoid arthritis (RA) with its high anti-inflammatory and joint-protective effects, recommended as first-line therapy (1). However, there is a group of RA patients who are not appropriate to use methotrexate due to pregnancy, breastfeeding, hypersensitivity, blood dyscrasia, chronic liver disease, renal dysfunction, or serious lung disease (2). Data from registries indicate that 20-30% of RA patients taking biological disease-modifying antirheumatic drugs (DAMRDs) use them as monotherapy (3, 4). Therefore, the need is definite for therapeutic strategy which does not contain methotrexate but is as effective for RA as methotrexate-containing regimen.

Interleukin (IL)-6 pathway inhibitors, including tocilizumab and sarilumab, are suggested to have some advantages in RA patients who cannot use methotrexate as comedication compared with other biological DMARDs (1). Tocilizumab monotherapy has so far been shown by large database to have comparable efficacy to tocilizumab plus methotrexate (5-8), whereas most of other biological DMARDs, particularly anti-tumor necrosis factor (TNF)-α antibodies, have failed to show the non-inferiority of monotherapy to the agent plus methotrexate (9, 10). Moreover, tocilizumab monotherapy has been demonstrated by a head-to-head randomized trial and by a network meta-analysis to be superior to TNF inhibitor monotherapy (11, 12). However, it remains to be elucidated what predicts remission achievement by IL-6 pathway inhibitor monotherapy and what predicts the requirement of concomitant methotrexate in IL-6 pathway inhibitor initiation.

We herein aimed to identify predictive factors for clinical and structural remission by tocilizumab without methotrexate in patients with RA by a *post-hoc* analysis of the data set of the SURPRISE study, a 2-year, open-label, randomized clinical study in which the efficacy and safety profile of adding tocilizumab to methotrexate (ADD-ON) or switching from methotrexate to tocilizumab (SWITCH) were evaluated in patients with active RA despite methotrexate treatment (8).

Patients and Methods

Study design and participants

This is a *post-hoc* analysis of the SURPRISE study, a 2-year, open-label, randomized controlled clinical trial conducted at 30 institutes in Japan comparing the efficacy of tocilizumab with (ADD-ON) and without methotrexate (SWITCH) (Trial registration number: NCT01120366). The SURPRISE study included 226 biologic-agents-naïve patients with RA according to the 1987 American College of Rheumatology classification criteria whose disease activity score for 28-joints based on erythrocyte sedimentation rate (DAS28-ESR) exceeded 3.2 despite methotrexate treatment. Tocilizumab was administered at a dose of 8 mg/kg intravenously every 4 weeks. In the first year, efficacy and safety were compared between the randomly assigned ADD-ON and SWITCH strategies (8), followed by the second year that tocilizumab-free rates were evaluated after discontinuing tocilizumab with or without methotrexate (13). The current study analyzed the data of the first year focusing on predictive factors for remission achievement by tocilizumab monotherapy (SWITCH). This study was approved primarily by ETHICS COMMITTEE of Keio University School of Medicine (Approval number: 20090149) and then by the ethics committee at each additional site, including 29 institutes, and conducted in accordance with the Declaration of Helsinki. All participants gave their written informed consent before inclusion into the study.

Collected patient data and assessments

Data collected at baseline (the time of tocilizumab initiation) included demographics and clinical parameters, including age, gender, height, body weight, body mass index, disease duration, the dose of glucocorticoids (all prednisolone), that of methotrexate, serum levels of C-reactive protein (CRP), IL-6, serum amyloid A (SAA), matrix metalloproteinase-3, rheumatoid factor (RF), and immunoglobulin G (IgG), tender joint count (TJC), swollen joint count (SJC), ESR, patient global

assessment, evaluator global assessment, visual analogue scale for pain, clinical disease activity index (CDAI), and simplified disease activity (SADI). DAS28-ESR was assessed at baseline and at week 24. Radiographs of the hands and feet were obtained at baseline and at week 52. Each radiograph was assessed with the van der Heijde-modified total Sharp scoring system (mTSS) by two independent readers who were blinded to the patients' clinical status and treatment.

Outcome measures

The primary endpoint was the DAS28-ESR remission (< 2.6) at week 24. The effect of clinical parameters at baseline on the achievement of DAS28 remission was estimated by logistic regression analysis. Identified predictors for DAS28 remission were further assessed whether they also predicted the change in mTSS from baseline to week 52 (ΔmTSS/year), another endpoint.

Statistical analysis

Unadjusted and adjusted analyses were conducted using logistic regression. Adjusted analysis was performed after adjusting for patient demographics including age, gender, height, body weight, body mass index, disease duration, the dose of prednisolone, and that of methotrexate. Predictive value of each parameter was compared by area under receiver operating characteristic curve (ROC-AUC). Continuous variables were compared with Student's *t*-test. Categorical variables were compared with the chi-square test. P values of less than 0.05 were regarded as statistically significant. All statistical analyses were performed using JMP® Pro software (ver. 14.0.0; SAS Institute Inc., Cary, NC, USA).

Results

Patient baseline characteristics

Amongst a total of 226 patients enrolled in the SURPRISE study, 194 patients with available DAS28-ESR at week 24, were included in the clinical outcome analysis. In addition, 192 patients, whose ΔmTSS/year (0-52 week) was accessible, were included in the structural outcome analysis. Baseline characteristics of the enrolled patients were summarized in Table 1.

Predictive factors for clinical remission achievement in SWITCH

To identify predictive factors for clinical remission achievement by tocilizumab monotherapy, we first performed logistic regression analysis to estimate the effect of clinical parameters at baseline, including serum levels of CRP, IL-6, SAA, matrix metalloproteinase-3, RF, and IgG, TJC28, SJC28, ESR, patient global assessment, TJC68, SJC66, evaluator global assessment, visual analogue scale for pain, DAS28-ESR, CDAI, and SDAI, on the achievement of DAS28-ESR remission (< 2.6) at week 24 in the SWITCH group (Table 2). Among these clinical parameters, CRP, SAA, RF, TJC28, ESR, TJC68, DAS28-ESR, and SADI at baseline showed predictive value for DAS28 remission at week 24 in unadjusted analysis. After adjusting for patient demographics including age, gender, height, body weight, body mass index, disease duration, the dose of prednisolone, and the dose of methotrexate before tocilizumab initiation, adjusted analysis confirmed SAA, TJC28, ESR, TJC68, and DAS28-ESR at baseline as predictive factors, with SAA having the highest value (OR [95%CI] by decrease of 1.0 μg/mL = 1.002 [1.0003-1.004], OR [95%CI] by decrease of 5.0 μg/mL = 1.011 [1.002-1.020], p = 0.01, ROC-AUC = 0.731). Conversely, CRP was not confirmed by adjusted analysis as significant predictive factors for DAS28 remission. These results were in line with the data obtained by comparing baseline

characteristics between patients who achieved DAS28 remission at week 24 and those who did not (Table S1).

Optimal cut-off value of basal SAA for prediction of clinical remission

We next analyzed the effect of basal SAA levels with different cut-off values on the achievement of DAS28 remission at week 24 in the SWITCH group. Four cut-off values of SAA, including 25, 50, 100, and 250 μg/mL, were set and their predictive values for DAS28 remission were compared by logistic regression analysis (Table 3). Of these cut-off values, SAA of < 50.0 μg/mL vs ≥ 50.0 μg/mL showed extremely high predictive value for DAS28 remission in both unadjusted and adjusted analyses (OR [95%CI] = 6.012 [1.997-18.096], p = 0.0008, ROC-AUC = 0.761 in adjusted analysis).

Predictive factors for clinical remission achievement in ADD-ON

To test whether SAA levels at baseline predict clinical remission only in patients treated with tocilizumab monotherapy or also in those treated with tocilizumab and methotrexate, we also estimated the effect of clinical parameters at baseline on the achievement of DAS28 remission at week 24 in the ADD-ON group by logistic regression analysis (Table 4). In contrast to the previous analysis in the SWITCH group, only TJC28, TJC68, and DAS28-ESR at baseline showed predictive value for DAS28 remission at week 24 in both unadjusted and adjusted analyses. CDAI and SDAI were extracted as predictive factors in adjusted analysis. SAA was not extracted in both unadjusted and adjusted analyses. These results would indicate SAA at baseline as a specific predictive factor for clinical remission in patients treated with tocilizumab monotherapy.

Effect of basal SAA on structural outcome

We next analyzed the effect of basal SAA levels on the structural outcome by comparing ΔmTSS/year in patients with basal SAA of < 50 μg/mL and those with basal SAA of ≥ 50 μg/mL (Figure 1). In the SWITCH group, mean value of ΔmTSS/year was significantly lower (p = 0.01), the rate of clinically relevant radiographic progression (CRRP, ΔmTSS/year > 3) was significantly lower (p = 0.03), and the rate of structural remission (ΔmTSS/year ≤ 0.5) was significantly higher (p = 0.048) in patients with basal SAA of < 50 μg/mL compared with those with basal SAA of ≥ 50 μg/mL. Conversely, in the ADD-ON group, these structural parameters were all comparable in patients with basal SAA of < 50 μg/mL and those with basal SAA of ≥ 50 μg/mL. Based on these results, SAA at baseline would also predict structural remission specifically in patients treated with tocilizumab monotherapy.

Prediction of concomitant methotrexate requirement

Finally, we tested whether SAA levels at baseline can predict the requirement of concomitant methotrexate in tocilizumab initiation. Following the grouping of patients by SAA at baseline (< 50 μg/mL or ≥ 50 μg/mL), the rate of DAS28 remission at week 24, that of CRRP, and that of structural remission were compared in the SWITCH and ADD-ON group (Figure 2). In patients with basal SAA of < 50 μg/mL, the rate of DAS28 remission (74.6% vs 76.7%, p = 0.79), that of CRRP (7.9% vs 5.0%, p = 0.72), and that of structural remission (71.4% vs 68.3%, p = 0.71) were all comparable between the SWITCH and the ADD-ON group. In contrast, in patients with basal SAA of ≥ 50 μg/mL, the rate of DAS28 remission was significantly lower (33.3% vs 78.4%, p = 0.001) in the SWITCH group compared with the ADD-ON group. Although not statistically significant, the rate of CRRP was higher (25.7% vs 8.8%, p = 0.11) and that of structural remission was lower (51.4% vs 61.8%, p = 0.39) in the SWITCH group compared with the ADD-ON group. In the SWITCH group, positive predictive value of basal SAA with cut-off value of 50 μg/mL for

achievement of both DAS28 remission and structural remission was 52.5%, whereas the negative predictive value was 81.8% (data not shown). These results indicate that patients with low levels of SAA at baseline, particularly those with basal SAA of < 50 μg/mL, may benefit similarly from tocilizumab therapy with and without methotrexate in terms of achieving clinical and structural remission.

Discussion

This study first demonstrated that SAA at baseline had an effect on remission achievement by tocilizumab monotherapy and predicted the requirement of concomitant methotrexate in tocilizumab initiation in patients with RA. Patients with low levels of SAA at baseline, particularly those with basal SAA of < 50 μg/mL, showed comparable response to tocilizumab therapy with and without methotrexate. Conversely, patients with basal SAA of ≥ 50 μg/mL benefited more by tocilizumab plus methotrexate.

Several studies have so far aimed to predict the response to tocilizumab therapy in patients with RA. Although several predictive factors were identified (14-19), including serum levels of CRP, IL-6, soluble IL-6 receptor, soluble gp130, IL-1β, and osteopontin and platelet counts, most of the studies did not focus on the response to tocilizumab monotherapy, except one study by Kojima, et al. (20). They analyzed the data from their registry and showed a positive association between concomitant use of methotrexate and remission achievement by tocilizumab therapy in patients with high baseline disease activity (DAS28-ESR > 5.1), which is compatible with our results showing DAS28-ESR at baseline as a predictive factor for remission achievement in SWITCH. Furthermore, in our study, DAS28-ESR at baseline also predicted remission in ADD-ON, suggesting that DAS28-ESR is less specific than SAA levels in terms of predicting the requirement of concomitant methotrexate. In contrast to those previous studies, the novel aspects of our study include prospective design and assessment of structural remission as an additional endpoint, both of which support the higher quality of our study. In addition, we newly focused on SAA which had not been analyzed in the previous studies.

SAA and CRP are both acute phase reactants primarily synthesized by hepatocytes upon stimulation by inflammatory cytokines including IL-6 (21). Serum levels of SAA were shown to be only moderately correlated with those of CRP (correlation coefficient = 0.58) and suggested to be

a better biomarker of RA disease activity (22). Another study by Shen, et al. (23) demonstrated a better correlation between SAA and DAS28-ESR compared with that between CRP and DAS28-ESR. Moreover, radiographic progression in RA patients was independently associated with basal SAA levels but not with basal CRP levels (24). There are several possible reasons for the superiority of SAA to CRP as a biomarker to assess the activity of RA. The response of SAA to inflammation has exceptionally wide range with up to 1000-fold rise (21), suggesting SAA as an extremely sensitive biomarker. SAA is known to be less influenced by age, gender, and glucocorticoids (25-27), consistent with our data showing that SAA, but not CRP, remained as a predictive factor for DAS28 remission after adjusting for patient demographics including age, gender, and the dose of prednisolone. In addition, SAA has a direct pathophysiological role in RA by activating synovial fibroblasts and inducing their production of matrix metalloproteinases (24, 28). Synovial fibroblasts *vice versa* produce SAA following stimulation by TNF-α (29). These findings suggest that high levels of SAA reflect the activation of synoviocytes and that patients with high levels of SAA need more aggressive and synoviocyte-targeted therapy, including methotrexate and biological DMARDs, to control synoviocyte activation and protect the joints.

In the SURPRISE study (8), DAS28 remission rates were significantly higher in the ADD-ON group than in the SWITCH group at week 24 (primary endpoint), but they became comparable at week 52. In line with those findings, SAA at baseline showed predictive value for DAS28 remission at week 24, but not for DAS28 remission at week 52 (Table S2). Adding methotrexate may rapidly enhance the effect of tocilizumab particularly in patients with high levels of SAA. Interestingly, serum levels of IgG at baseline showed predictive value for DAS28 remission at week 52 in the SWITCH group, but not in the ADD-ON group (Table S2 and S3). These findings might be associated with the activation of B cells, presumably the reactivation of B cells following discontinuation of methotrexate, and the subsequent failure of biological DMARDs.

This study has some limitations. One of them is the lack of comparison of different doses of tocilizumab. All enrolled patients were given 8 mg/kg of tocilizumab intravenously every 4 weeks. Recently, shortening the dosing interval (162 mg biweekly to 162 mg weekly) was shown to improve efficacy with acceptable tolerability in RA patients receiving subcutaneous tocilizumab monotherapy with inadequate response (30). Another IL-6 receptor antagonist sarilumab also provides better clinical and structural outcomes at a dose of 200 mg every other week compared with its use at a dose of 150 mg every other week (31). Further studies are warranted to analyze whether intensive inhibition of IL-6 pathways without methotrexate is effective for patients with RA and high levels of SAA. Other limitations include the lack of double-blinding, limited number of subjects, and the lack of anti-citrullinated peptide antibody (ACPA) testing. Although structural outcomes were assessed by independent blinded readers, knowing the treatment and the clinical parameters might affect clinical outcome evaluation. The status of ACPA may influence the response to biological DMARDs, particularly that to abatacept therapy (32). Conversely, the response to tocilizumab therapy was shown to be unrelated with ACPA seropositivity (14, 33), suggesting that ACPA testing might not affect the results of our study.

In conclusion, SAA levels at baseline would predict the requirement of concomitant methotrexate in tocilizumab initiation in patients with RA. Patients with low levels of SAA at baseline may benefit similarly from tocilizumab therapy with and without methotrexate in terms of achieving clinical and structural remission. These results are likely in part to meet the needs of RA patients who are not able or suitable to use methotrexate.

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Collaborators

Other investigators of the SURPRISE study group: Takao Fujii (Kyoto University), Atsushi Kawakami (Nagasaki University Graduate School of Biomedical Sciences), Hideshi Yamazaki (Marunouchi Hospital), Yasuaki Okuda (Dohgo Spa Hospital), Kazuhide Tanimura (Hokkaido Medical Center for Rheumatic Diseases), Atsushi Kaneko (Nagoya Medical Center), Toshio Tanaka (Osaka University), Akira Murasawa (Niigata Rheumatic Center), Kazuhiko Ezawa (Kurashiki Sweet Hospital), Yukitaka Ueki (Sasebo Chuo Hospital), Yoshiki Shiohira (Yuuaikai Tomishiro Central Hospital), Hiroaki Dobashi (Kagawa University), Naoki Kondo (Niigata University Graduate School of Medical and Dental Sciences), Toshihiko Hidaka (Zenjinkai Shimin-no-Mori Hospital), Hajime Sano (Hyogo College of Medicine), Mitsuhiro Iwahashi (Higashi Hiroshima Memorial Hospital), Motohiro Oribe (Oribe Clinic of Rheumatism and Medicine), Shohei Nagaoka (Yokohama Minami Kyosai Hospital) and Kensei Tsuzaka (Tokyo Dental College Ichikawa General Hospital).

Contributors

MK, YK, NM, HY, KY, IY and TT designed the study and analyzed and interpreted the data. MK, YK, YT, MI, HK-H, KA, MM, TA and YM were involved in collecting data and managing their clinical research sites. YK, HY, SH and ET scored mTSS blinded to patients' clinical information. All authors were involved in writing the manuscript and approved the final version.

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Conflict of interests

MK has received research grants or lecture fees from GlaxoSmithKline and Actelion. YK has received grants from Abbvie and Eisai and speaking fees from AbbVie, Astellas, Ayumi, Bristol-Myers Squibb, Chugai, Eisai, Eli Lilly, Jansen, Kissei, Pfizer, Sanofi, Takeda, Mitsubishi Tanabe and UCB. YT has received grants from Mitsubishi Tanabe, Bristol-Myers Squibb, Eisai, Chugai, Takeda, Abbvie, Astellas, Daiichi-Sankyo, Ono, MSD and Taisho Toyama and speaking fees from Daiichi-Sankyo, Astellas, Eli Lilly, Chugai, Sanofi, Abbvie, YL Bio, Bristol-Myers Squibb, GlaxoSmithkline, UCB, Mitsubishi Tanabe, Novartis, Eisai, Takeda, Janssen and Asahi-Kasei. KA has received research grants from Asahi Kasei Pharma and speaking fees from AbbVie, Chugai, Eli Lilly, Mitsubishi Tanabe and Pfizer. MM has received lecture fee from Chugai, Abbie, Bristol-Myers Squibb, Eisai, Takeda, Janssen, Eli Lilly, Pfizer and UCB. YM has received grants from AsahiKasei Pharma, Chugai, Ono, Daiichi Sankyo, Teijin, Eisai, NipponKayaku and Mitsubishi Tanabe, instructor fees from Kissei, Janssen and Eisai and speaking fees from Ono, Mitsubishi Tanabe, Astellas, UCB, Chugai, AbbVie, Daiichi-Sankyo, Ayumi, Janssen, Takeda, Sanofi, Teijin, Eli Lilly and Eisai. SH has received grants from Eli Lilly and UCB, consultant fees from Bristol-Myers Squibb, Jansen and UCB, lecture fees from AbbVie, Eisai and Mitsubishi Tanabe and speaking fees from AbbVie, Astellas, Ayumi, Bristol-Myers Squibb, Chugai, Eisai, Eli Lilly, Jansen, Kissei, Pfizer, Sanofi, Takeda, Mitsubishi Tanabe and UCB. ET has received speaking fees from Abbvie, Asahi Kasei pharma, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisail, Janssen, Nippon Kayaku, Pfizer, Takeda, Taisho Toyama and UCB. HY has received research grants from AbbVie, Eisai, Bristol-Meyers Squibb, Novartis, Behringer, Astellas, Kaken,

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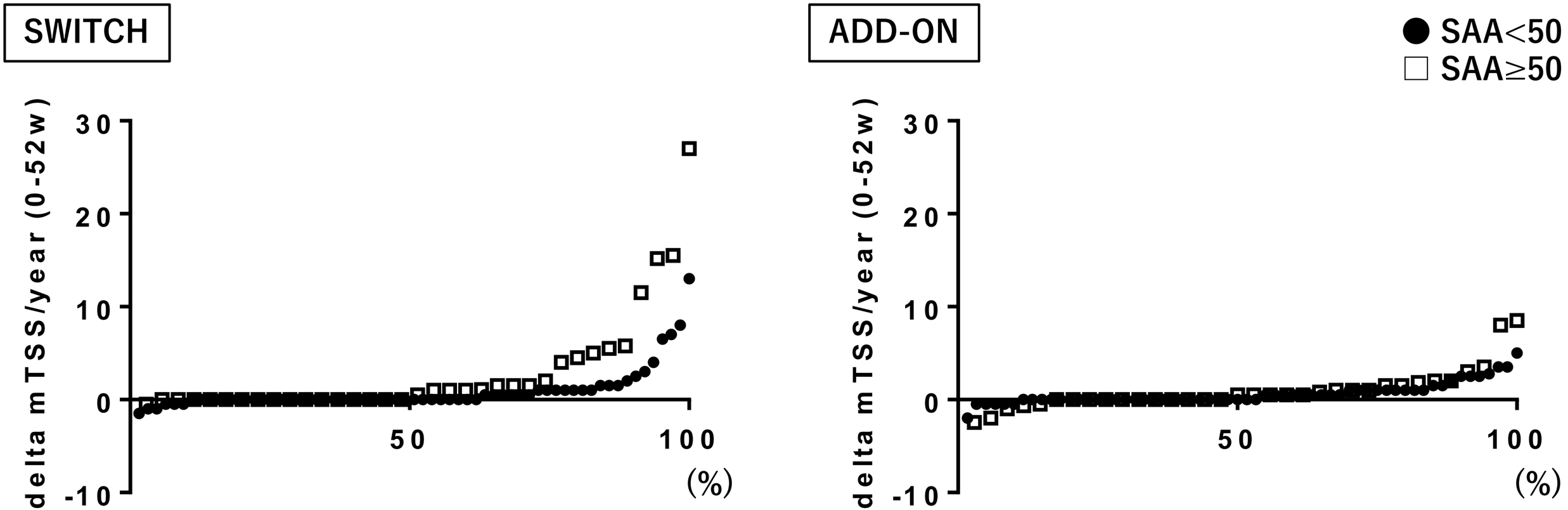
Figure legends

Figure 1. Effect of basal serum amyloid A (SAA) on structural outcome. Mean value of the change in modified total Sharp score from baseline to week 52 (ΔmTSS/year), the rate of clinically relevant radiographic progression (CRRP, ΔmTSS/year > 3), and the rate of structural remission (SR, ΔmTSS/year ≤ 0.5) were compared between patients with basal SAA of < 50 μg/mL and those with basal SAA of ≥ 50 μg/mL.

Figure 2. Prediction of concomitant methotrexate requirement. Clinical and structural outcomes were compared between SWTICH and ADD-ON following the grouping of patients by SAA at baseline (< 50 μg/mL or ≥ 50 μg/mL), evaluated by the rate of DAS28-ESR remission (< 2.6) at week 24 (**A**), that of CRRP (**B**), and that of structural remission (SR) (**C**).



	SWITCH			ADD-ON		
	SAA<50 (n = 63)	SAA>=50 (n = 35)	p value	SAA<50 (n = 60)	SAA>=50 (n = 34)	p value
mean	0.88 (±2.31)	2.99 (±5.84)	0.01	0.60 (±1.16)	0.93 (±2.21)	0.35
CRRP, n	5 (7.9%)	9 (25.7%)	0.03	3 (5.0%)	3 (8.8%)	0.66
SR, n	45 (71.4%)	18 (51.4%)	0.048	41 (68.3%)	21 (61.8%)	0.42

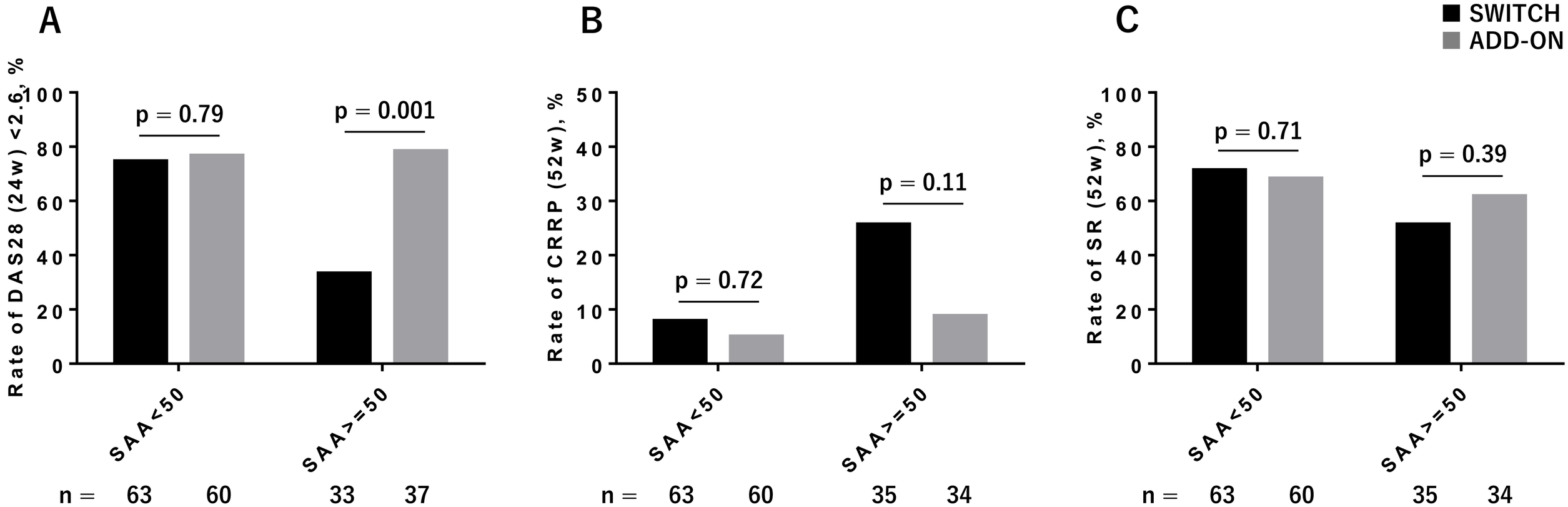

A
B
C
SWITCH
ADD-ON
Rate of DAS28 (24w) <2.6, %
Rate of CRRP (52w), %
Rate of SR (52w), %
p = 0.79
p = 0.001
p = 0.72
p = 0.11
p = 0.71
p = 0.39
SAA<50
SAA>=50
n = 63 60 33 37
n = 63 60 35 34
n = 63 60 35 34

Table 1. Baseline characteristics of enrolled patients.

	Clinical outcome analysis		Structural outcome analysis	
	SWITCH (n = 96)	ADD-ON (n = 98)	SWITCH (n = 98)	ADD-ON (n = 94)
Age, year	56 (±13)	56 (±12)	56 (±13)	55 (±11)
Female, n	86 (90%)	88 (90%)	85 (87%)	84 (89%)
Height, cm	156.9 (±7.6)	157.5 (±6.5)	157.2 (±7.8)	157.5 (±6.3)
Body weight, kg	53.7 (±9.0)	55.9 (±11.1)	54.1 (±9.6)	55.9 (±11.0)
BMI	21.9 (±3.4)	22.5 (±4.0)	21.9 (±3.4)	22.5 (±4.0)
Disease duration, year	3.7 (±3.0)	3.8 (±3.3)	3.7 (±2.9)	3.8 (±3.3)
PSL, mg/day	0.0 [0.0,3.0]	0.0 [0.0,3.0]	0.0 [0.0,3.8]	0.0 [0.0,3.0]
MTX*, mg/week	8.4 (±2.0)	8.7 (±2.5)	8.6 (±2.2)	8.9 (±2.4)
CRP, mg/dL	0.62 [0.09,2.27]	0.54 [0.13,1.76]	0.65 [0.11,2.70]	0.47 [0.11,1.68]
IL-6, pg/mL	14.4 [4.2,35.6]	13.2 [3.9,36.1]	14.4 [4.1,35.3]	13.2 [3.6,32.8]
SAA, μg/mL	25.3 [10.4,190.5]	24.7 [6.4,102.0]	27.8 [11.0,225.0]	22.2 [5.6,93.3]
MMP-3, ng/mL	102.0 [63.2,245.8]	129.0 [64.5,236.0]	105.5 [65.0,247.3]	121.5 [62.4,229.8]
RF, IU/mL	56.2 [24.9,138.5]	61.7[15.0,125.5]	51.2 [26.0,142.0]	61.7 [17.5,116.0]
IgG, mg/dL	1553 (±436)	1443 (±440)	1543 (±438)	1410 (±378)
TJC28	6.9 (±5.6)	6.6 (±5.0)	7.6 (±6.1)	6.6 (±4.9)
SJC28	7.2 (±4.7)	6.0 (±4.0)	7.4 (±4.8)	5.9 (±3.7)
ESR, mm/h	46 (±31)	40 (±27)	46 (±30)	39 (±28)
PGA, mm	52 (±24)	45 (±23)	53 (±24)	44 (±23)

TJC68	9.8 (±8.7)	9.1 (±7.3)	10.7 (±9.2)	9.3 (±7.7)
SJC66	10.2 (±7.6)	7.2 (±5.0)	10.4 (±7.6)	7.4 (±4.9)
EGA, mm	48 (±20)	45 (±21)	49 (±20)	44 (±20)
VAS Pain, mm	51 (±24)	48 (±22)	52 (±25)	47 (±23)
DAS28-ESR	5.28 (±1.19)	5.05 (±1.07)	5.37 (±1.19)	4.98 (±1.02)
CDAI	24.1 (±11.6)	21.7 (±9.9)	25.1 (±12.0)	21.3 (±9.2)
SDAI	26.0 (±12.9)	23.0 (±10.3)	27.1 (±13.3)	22.4 (±9.4)

Clinical outcome analysis included patients whose DAS28-ESR at week 24 was available. Structural outcome analysis included patients whose Δ modified total Sharp score/year (0-52 week) was available. Variables are presented as mean (± standard deviation) or median [interquartile range]. *: Represents the dose of MTX before tocilizumab initiation in SWITCH. BMI, body mass index; CDAI, clinical disease activity index; CRP, C-reactive protein; DAS28, disease activity score for 28 joints; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; IgG. Immunoglobulin G; IL, interleukin; MMP, matrix metalloproteinase; MTX, methotrexate; PGA, patient global assessment; PSL, prednisolone; RF, rheumatoid factor; SAA, serum amyloid A; SDAI, simplified disease activity index; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

Table 2. The effect of clinical parameters on the achievement of clinical remission (DAS28-ESR < 2.6) at week 24 in the SWITCH group.

	Unadjusted analysis			Adjusted analysis*		
	OR** [95%CI]	p value	ROC-AUC	OR** [95%CI]	p value	ROC-AUC
CRP, mg/dL	**1.205 [1.020-1.425]**	**0.02**	0.636	1.199 [0.988-1.455]	0.056	0.701
IL-6, pg/mL	0.998 [0.994-1.001]	0.08	0.478	0.997 [0.992-1.002]	0.047	0.680
SAA, μg/mL	**1.002 [1.0004-1.004]**	**0.007**	0.682	**1.002 [1.0003-1.004]**	**0.01**	0.731
MMP-3, ng/mL	1.001 [0.999-1.003]	0.23	0.545	1.001 [0.999-1.003]	0.35	0.672
RF, IU/mL	**1.003 [1.0002-1.005]**	**0.01**	0.601	1.003 [0.99992-1.005]	0.045	0.730
IgG, mg/dL	1.0006 [0.9997-1.002]	0.19	0.560	1.0008 [0.9997-1.002]	0.15	0.703
TJC28	**1.105 [1.020-1.198]**	**0.01**	0.609	**1.099 [1.008-1.198]**	**0.03**	0.703
SJC28	1.036 [0.950-1.130]	0.42	0.525	1.006 [0.913-1.107]	0.91	0.650
ESR, mm/h	**1.018 [1.003-1.032]**	**0.01**	0.654	**1.017 [1.0003-1.034]**	**0.04**	0.717
PGA, mm	1.010 [0.993-1.028]	0.25	0.564	1.012 [0.991-1.033]	0.27	0.663
TJC68	**1.057 [1.002-1.115]**	**0.03**	0.547	1.054 [0.997-1.113]	0.051	0.683
SJC66	1.028 [0.974-1.085]	0.31	0.493	1.016 [0.959-1.076]	0.59	0.647
EGA, mm	1.002 [0.981-1.023]	0.89	0.502	0.993 [0.970-1.017]	0.56	0.654
VAS Pain, mm	1.004 [0.987-1.021]	0.65	0.519	1.001 [0.982-1.021]	0.91	0.650
DAS28-ESR	**1.611 [1.106-2.348]**	**0.001**	0.648	**1.596 [1.027-2.480]**	**0.03**	0.712
CDAI	1.034 [0.997-1.073]	0.07	0.585	1.026 [0.986-1.067]	0.21	0.677
SDAI	**1.036 [1.002-1.071]**	**0.03**	0.609	1.028 [0.991-1.067]	0.13	0.684

*: Adjusted for age, gender, height, body weight, body mass index, disease duration, prednisolone dose, and methotrexate dose. **: Represents predictive value for clinical remission at week 24 by decrease of 1.0 unit of each parameter.

Table 3. The effect of basal serum amyloid A (SAA) levels with different cut-off values on the achievement of clinical remission (DAS28-ESR < 2.6) at week 24 in the SWITCH group.

	Unadjusted analysis			Adjusted analysis*		
	OR [95%CI]	p value	ROC-AUC	OR [95%CI]	p value	ROC-AUC
SAA < 25 μg/mL	**2.926 [1.248-6.861]**	**0.01**	0.631	**2.748 [1.060-7.123]**	**0.03**	0.713
SAA < 50 μg/mL	**5.875 [2.342-14.736]**	**<0.0001**	0.695	**6.012 [1.997-18.096]**	**0.0008**	0.761
SAA < 100 μg/mL	**4.320 [1.700-10.977]**	**0.002**	0.651	**4.609 [1.513-14.040]**	**0.005**	0.744
SAA < 250 μg/mL	**2.831 [1.066-7.520]**	**0.03**	0.593	2.809 [0.879-8.974]	0.08	0.708

*: Adjusted for age, gender, height, body weight, body mass index, disease duration, prednisolone dose, and methotrexate dose.

Table 4. The effect of clinical parameters on the achievement of clinical remission (DAS28-ESR < 2.6) at week 24 in the ADD-ON group.

	Unadjusted analysis			Adjusted analysis*		
	OR** [95%CI]	p value	ROC-AUC	OR** [95%CI]	p value	ROC-AUC
CRP, mg/dL	1.138 [0.854-1.517]	0.38	0.529	1.117 [0.811-1.538]	0.50	0.676
IL-6, pg/mL	0.9994 [0.997-1.002]	0.52	0.520	0.9999 [0.997-1.002]	0.90	0.685
SAA, μg/mL	1.001 [0.998-1.004]	0.42	0.501	1.001 [0.998-1.004]	0.57	0.685
MMP-3, ng/mL	0.998 [0.995-1.002]	0.37	0.543	0.998 [0.994-1.002]	0.27	0.698
RF, IU/mL	1.0006 [0.999-1.003]	0.58	0.505	1.0003 [0.998-1.003]	0.79	0.694
IgG, mg/dL	1.0001 [0.999-1.001]	0.84	0.477	1.0002 [0.999-1.001]	0.80	0.708
TJC28	**1.104 [1.008-1.208]**	**0.03**	0.703	**1.129 [1.022-1.247]**	**0.02**	0.745
SJC28	1.057 [0.943-1.184]	0.35	0.541	1.077 [0.949-1.221]	0.25	0.703
ESR, mm/h	1.014 [0.998-1.031]	0.09	0.641	1.014 [0.996-1.033]	0.13	0.714
PGA, mm	1.017 [0.995-1.039]	0.12	0.609	1.020 [0.994-1.046]	0.12	0.716
TJC68	**1.076 [1.011-1.146]**	**0.02**	0.680	**1.105 [1.028-1.188]**	**0.007**	0.774
SJC66	1.052 [0.961-1.152]	0.28	0.524	1.072 [0.970-1.185]	0.18	0.714
EGA, mm	0.996 [0.973-1.019]	0.73	0.520	0.995 [0.966-1.024]	0.72	0.681
VAS Pain, mm	1.015 [0.993-1.038]	0.17	0.580	1.018 [0.992-1.045]	0.17	0.710
DAS28-ESR	**1.896 [1.181-3.045]**	**0.006**	0.707	**2.030 [1.194-3.453]**	**0.006**	0.771
CDAI	1.042 [0.996-1.091]	0.08	0.654	**1.057 [1.002-1.115]**	**0.04**	0.737
SDAI	1.042 [0.997-1.088]	0.07	0.664	**1.054 [1.002-1.110]**	**0.04**	0.728

*: Adjusted for age, gender, height, body weight, body mass index, disease duration, prednisolone dose, and methotrexate dose. **: Represents predictive value for clinical remission at week 24 by decrease of 1.0 unit of each parameter.