Mod Rheumatol, 2015; 25(6): 842–848

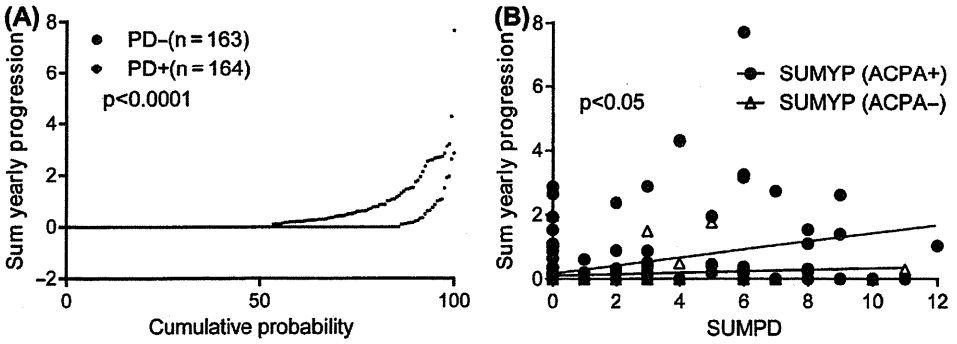

Figure 1. Patient-based analysis. (A) Cumulative probability plot of sum of yearly progression (SUMYP) in patients having PD-negative (black dots) and -positive joints (red dots). (B) Correlation between SUMPD and sum of yearly progression. *P* value within the graph indicates difference between slopes from ACPA-positive (closed circles and red line) and -negative (open triangles and black line) patients.

patients who underwent treatments (68.5% with MTX and 8.7% with biologics) [26].

Patient-based analysis

We evaluated the data in a patient-based manner. Among 331 patients, 327 patients, having PD data for all 4 MCP joints, were eligible for the analysis (4 patients were excluded because they did not have data on all 4 joints). As shown in Figure 1A, patients having more than one PD-positive joint exhibited significantly higher sum yearly progression score than all negative joints ($p < 0.0001$). Joint destruction in the 4 joints was significantly frequent in PD-positive patients (77/164) than that in the PD-negative patients (23/163, $p < 0.0001$). SUMPD slightly associated with sum of yearly joint progression (Figure 1B). Consistent with previous reports, ACPA- and RF-positive RA patients showed higher rate of joint destruction (data not shown) [27]. We also asked whether high- (>3-fold normal range) or low-titer ACPA could have any impact on joint destruction. However, we did not detect significant difference of yearly progression of joints destruction between the two groups within our dataset (data not shown).

Logistic regression analysis was performed with the presence of progressive joint destruction as a dependent variable. In univariate analysis, SUMPD, observation period, and SUMBS were significantly associated with joint destruction (Table 2). Positive ACPA exhibited the strongest odds ratio (OR) with joint destruction, but due to smaller sample size (not all the RA patients were evaluated for ACPA positivity), it did not reach statistical significance. Nevertheless, because of the highest OR, we considered ACPA in the following regression analysis. Forward step-wise multivariate logistic regression analysis revealed SUMPD and observation period, and in analysis including ACPA, SUMPD and ACPA were identified as independent factors associated with future joint destruction in patient-based analysis (Table 2).

Joint-based analysis

To increase the detection power, we evaluated each joint independently, resulting in the analysis of 1,324 2nd and 3rd MCP joints from 331 patients. Among them, 1,308 joints were eligible for the analysis. Consistent with patient-based analysis, PD-positive joints showed significantly higher frequency of joint destruction (183/337 joints) than PD-negative joints (68/971 joints, $p < 0.0001$) (Figure 2A). Intensity of PD was slightly associated with the extent of joint damage (Figure 2B). As shown in a patient-based analysis, the correlation was stronger in the joints of ACPA-positive patients.

Table 2. Patient-based univariate and multivariate logistic regression analysis.

Univariate				
Variables	OR	95%CI		*P* value
Male	1.35	0.69	2.67	0.38
Age	0.99	0.98	1.01	0.46
SUMBS	**1.04**	**1.01**	**1.08**	**0.004**
Disease duration	1.01	0.98	1.04	0.64
Observation period	**1.21**	**1.10**	**1.32**	**<0.0001**
RF +	1.37	0.74	2.52	0.31
ACPA +	**2.16**	0.94	4.96	0.071
SUMPD	**1.36**	**1.24**	**1.50**	**<0.0001**
MTX +	1.31	0.75	2.29	0.34
Biologics +	1.40	0.87	2.26	0.17

Multivariate					Model including ACPA			
Variables	OR	95%CI		*P* value	OR	95%CI		*P* value
Male	1.27	0.60	2.67	0.53	1.15	0.41	3.17	0.79
Age	1.00	0.98	1.02	0.83	0.99	0.96	1.02	0.40
SUMBS	1.00	0.97	1.04	0.94	1.02	0.95	1.09	0.62
Observation period	**1.18**	**1.07**	**1.31**	**0.001**	**1.20**	**1.04**	**1.38**	**0.011**
ACPA +					**3.35**	**1.22**	**9.20**	**0.019**
SUMPD	**1.35**	**1.22**	**1.49**	**<0.0001**	**1.39**	**1.21**	**1.60**	**<0.0001**

SUMBS, sum of radiographic bone scores; RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibody; SUMPD, sum of power Doppler scores; MTX, methotrexate; OR, odds ratio; CI, confidence interval. "OR" indicates probability of joint destruction with or without the given variables. ORs in observation period, age, and disease duration indicate relative risk of joint destruction per year.
Sex and age were forcedly entered in the model.
Variables in bold are significant ones.

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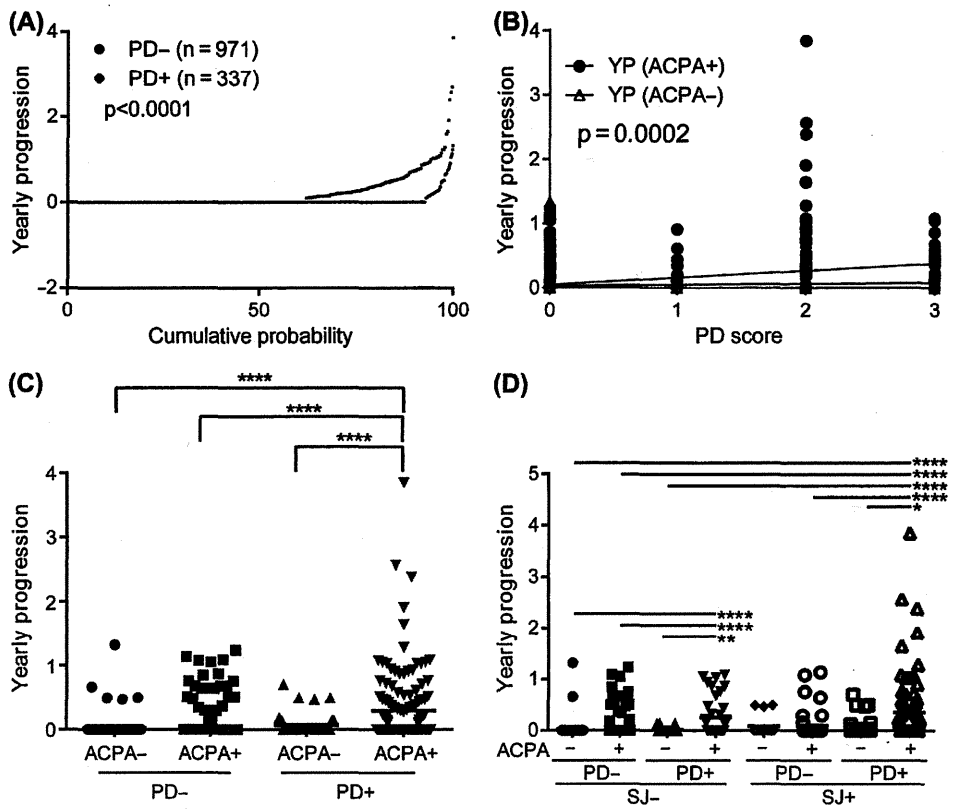

Figure 2. Joint-based analysis. (A) Cumulative probability plot of yearly progression (YP) between PD-negative (black dots) and -positive joints (red dots). (B) Correlation between PD score and yearly progression. *P* value within the graph indicates significant difference between slopes from ACPA-positive (closed circle and red line) and -negative (open triangle and black line) joints. (C) Comparison of groups categorized by (C) PD and ACPA; and (D) PD, ACPA, and swollen joint (SJ). ****$p<0.0001$, ***$p<0.001$, **$p<0.01$, and *$p<0.05$, corrected for multiple comparisons.

Next, we further categorized the data by ACPA positivity. The result showed that only PD-positive joints revealed significant joint destruction in the presence of ACPA compared with the other groups (Figure 2C). To estimate the relative risk, joint destruction was converted into binary state and the chi-square test was applied. PD-positive joints in ACPA-positive patients had OR of 18.1 (95% confidence interval [CI]: 6.91–47.5), compared with PD-negative joints in ACPA-negative patients. Positive predictive value of PD for joint destruction (PPV) was 0.380. Furthermore, the data were categorized by the presence of joint swelling. As expected, SJs showed higher rate of joint destruction ($p<0.0001$, data not shown). Then we categorized data by PD, ACPA, and SJ. The result showed that PD-positive joints in ACPA-positive patients had significantly more joint destruction even in clinically non-SJs (Figure 2D). On the other hand, risk of joint destruction is not increased in SJs without PD signal, irrespective of the presence or absence of ACPA.

Finally, we evaluated these variables on joint destruction. In univariate analysis, positive PD scores, joint swelling, longer observation period, and preexisting bone damage (score > 1 per joint at the baseline) were significantly associated with higher odds for joint destruction (Table 3). In multivariate analysis, positive PD, joint swelling, longer observation period, preexisting bone damage, and ACPA remained significant.

Discussion

In the current study, we evaluated the multiple factors linking progression of joint destruction and MSUS PD signals in more than 1,300 2nd and 3rd MCP joints from 331 patients. The study has one of the largest patient size and longest observation time in MSUS to date and therefore is robust in identifying weak factors. Among the variants we considered, PD remained the strongest predictor of the joint damage in 2nd and 3rd MCP joints. Other factors such as positivity for ACPA and joint swelling are also strongly associated with joint destruction in coordination with PD.

Citrullination of auto-antigens has been recognized as critical mechanisms underlying RA [28]. ACPA positivity is genetically determined since ACPA-positive and -negative RA patients show district genetic predispositions [29]. Moreover, ACPA-negative patients were suggested to have milder disease outcome [30]. In the current study, multivariate analysis was powered enough to show the independence of PD and ACPA for the joint destruction, implicating that "second hit" is required to establish PD positivity. Indeed, only PD-positive joints in ACPA-positive patients significantly developed joint destruction compared with the others (Figure 2C). Furthermore, we also showed independence of PD with SJ, which is often underestimated by physical examinations. Given that PD, ACPA, and joint swellings are independent risks for joint destruction, we suggest that ACPA-positive patients with SJs be further classified by PD positivity. PD- and ACPA-positive patients may represent "rapid progressor" who require prompt and intensive treatment strategy [31]. This idea needs to be validated through prospective studies.

RA patients usually develop arthritis in some, but not all, of the joints, which has long been an unanswered question. Consistent with previous prospective study [32], here we showed that baseline PD signals are associated with future radiographic progression of the particular joint. Since the longer observation period is the risk of joint destruction (Tables 1 and 2), it is likely that those PD-positive joints found at the time of the study entry are continuously inflamed during the course of the disease. On the other hand, most of the PD-negative joints do not develop joint destruction even in the long term, suggesting that affected joints may be determined at the early stage of RA, though effects of therapies should be considered. Indeed, previous report suggested that local swelling and tenderness predicts later joint damage in these joints after 8 years of T2T-treated patients [33]. These data support the rationale of local treatment strategy in some occasions.

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Table 3. Joint-based univariate and multivariate analysis by generalized linear mixed model.

Univariate				
Variables	OR	95%CI		*P* value
Male	0.60	0.20	1.84	0.37
Age	0.99	0.96	1.02	0.44
Disease duration	1.01	0.96	1.07	0.63
Right hand	1.00	0.64	1.57	1.00
MCP2	1.00	0.64	1.57	1.00
Observation period	**1.38**	**1.18**	**1.61**	**<0.0001**
Bone score +	**1.84**	**1.27**	**2.65**	**0.001**
RF +	1.69	0.62	4.63	0.31
ACPA +	**3.45**	0.98	12.2	0.055
Joint swelling +	**3.49**	**2.22**	**5.50**	**<0.0001**
PD +	**3.40**	**2.41**	**4.81**	**<0.0001**
MTX	1.58	0.63	3.99	0.33
Biologics	1.78	0.78	4.05	0.17

Multivariate								
					Model including ACPA			
Variables	OR	95%CI		*P* value	OR	95%CI		*P* value
Male	0.75	0.25	2.27	0.61	0.73	0.17	3.13	0.68
Age	0.99	0.96	1.02	0.55	0.98	0.94	1.02	0.32
Observation period	**1.30**	**1.11**	**1.51**	**0.001**	**1.34**	**1.08**	**1.65**	**0.007**
Bone score +	**1.54**	**1.08**	**2.21**	**0.019**	**1.70**	**1.01**	**2.86**	**0.045**
ACPA +					**4.58**	**1.24**	**16.9**	**0.023**
Joint swelling	**2.40**	**1.53**	**3.79**	**<0.0001**	**2.75**	**1.50**	**5.06**	**0.001**
PD +	**2.21**	**1.61**	**3.04**	**<0.0001**	**2.66**	**1.65**	**4.29**	**<0.0001**

MCP2, 2nd metacarpophalangeal joint; RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibody; MTX, methotrexate; PD, power Doppler; OR, odds ratio; CI, confidence interval. "OR" indicates probability of joint destruction with or without the given variables. ORs in observation period, age, and disease duration indicate relative risk of joint destruction per year. "Bone score +" indicates that the score was ≥ 1 in each joint.

Variables in bold are significant ones.

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It has been shown that the stronger the PD signal is, the more the joint destruct occurs [34], although our study failed to show strong connection between PD scores and yearly joint progression especially in ACPA-negative patients (Figure 2B). This result could be explained by the relatively long observation period in our study. As noted above, from the onset of the disease, the affected joint could be continuously or intermittently inflamed, and PD scores continuously change during the course of the disease [16].

A recent paper proposed that treatments based on PD positivity could lead to overtreatment especially for patients in remission [35]. Indeed, majority of PD positive joints did not cause joint destruction (PPV: 0.380) or few joints without PD signal lead to joint destruction in our own data, indicating that other critical factors are missing in our predictive model. Such risk factors include persistent synovitis [32,36], high RA disease activity, grayscale structural analysis, and extensor carpi ulnaris deterioration [37]. Moreover, not all of the inflamed synovia were anatomically assessable by MSUS.

We did not detect bone repair in our study. In the previous bone repair study of RA patients by Linden et al. [38], 32 joints showed bone repair, which was shown by reduction of Sharp–van der Heijde score, in 250 RA patients who were observed for average of 10.1 years. When limiting to MCP joints, 8 joints (0.32%) showed bone repair. Applying this statistics to our data, bone repair would be expected in 4 or 5 (4.24) of total 1324 MCP joints of patients enrolled in this study. In line with results from Linden et al., our previous analysis on bone repair showed 5 bone repairs in 2–3 MCP joints from 122 RA patients (1.02%) [39]. Based on these reports, bone repairs in ~10 MCP joints would be expected, although we did not detect them. Observation biases might contribute to the results, because Xp reader was not blinded to the date of Xp. In any event, underscoring bone repairs of few joints are unlikely to have a major impact on the conclusion of this study.

The additional important factor missing from the study is effects of specific treatments on PD and disease outcome. This study provides at least some evidence that in RA patients treated with MTX and biologics, PD positivity is associated with joint damage. However, recent study has shown that PD-positive joints under treatments with biologics do not necessary show joint destruction [40]. Since the current study is retrospective and not controlled for treatment regimen, it is hard to determine effects of specific treatments on joints destruction. Further prospective study with large patient size controlled for specific treatment is necessary to address this question.

In this study, the data were retrospectively collected in daily clinical settings. MSUS was preferentially conducted in patients with high-disease activity particularly when changing therapeutic agents including biologics were considered, potentially leading to selection biases in this study. However, the biases might miss patients at low risk, but not high risk for joint destruction.

Another drawback in this study is limited number of joints analyzed and therefore predictive factors other than 2nd and 3rd MCP joints are not shown. We selected 2nd and 3rd MCP joints from routinely examined joints including wrists and knees. In addition to high frequency of positive PD signals in available data, effects of complicated diseases such as OA on Xp findings is very little compared with those of the knee. Moreover, anatomical correspondence between MSUS and Xp is easier to determine in the MCP joints than wrists. These features of the MCP joints provide the advantage of analyzing accurate relationships between MSUS and Xp findings in this study. Thus, these 2nd and 3rd MCP joints have been included in various scoring systems developed in an attempt to improve the feasibility of MSUS routine screening [41].

Despite limitations, our data strongly suggest that not only PD positivity, but also ACPA and joints swelling need to be taken into account for more accurate prediction of destruction in a particular joint.

In conclusion, the present study confirmed the importance of PD signals in future joint damage in RA. Hopefully, along with ACPA, high disease activity, and other predictive factors, we can

manage to categorize RA patients who require intensive treatments in the near future.

Acknowledgements

We wish to thank Mr. Tom Kiper for his critical review in preparing the manuscript.

Conflict of interest

None.

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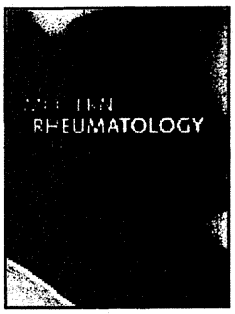

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ISSN: 1439-7595 (Print) 1439-7609 (Online) Journal homepage: http://www.tandfonline.com/loi/imor20

A novel 8-joint ultrasound score is useful in daily practice for rheumatoid arthritis

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To cite this article: Ryusuke Yoshimi, Atsushi Ihata, Yosuke Kunishita, Daiga Kishimoto, Reikou Kamiyama, Kaoru Minegishi, Maasa Hama, Yohei Kirino, Yukiko Asami, Shigeru Ohno, Atsuhisa Ueda, Mitsuhiro Takeno & Yoshiaki Ishigatsubo (2015) A novel 8-joint ultrasound score is useful in daily practice for rheumatoid arthritis, Modern Rheumatology, 25:3, 379-385

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ISSN 1439-7595 (print), 1439-7609 (online)

Mod Rheumatol, 2015; 25(3): 379–385
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DOI: 10.3109/14397595.2014.974305

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ORIGINAL ARTICLE

A novel 8-joint ultrasound score is useful in daily practice for rheumatoid arthritis

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Abstract

Objectives. To investigate the optimal number and combination of joints to be assessed by power Doppler ultrasonography (PDUS) in daily practice for rheumatoid arthritis (RA).
Methods. PDUS were performed in 24 joints, including all proximal interphalangeal, metacarpophalangeal (MCP), and bilateral wrist and knee joints in 234 patients with RA. PD signals were scored semiquantitatively from 0 to 3 in each joint, and total PD score-24 was calculated by summing them up as comprehensive assessment.
Results. Positive PD signals were more frequently found in bilateral wrist, knee, and the second and third MCP joints than the other joints. The individual PD scores of these 8 joints also showed higher correlation coefficients with total PD score-24 ($r_s \geq 0.4$). Among the sum PD scores of various selected joint combinations, the score of the combination of 8 joints (total PD score-8), including bilateral second and third MCP, wrist, and knee joints, showed the highest sensitivity and negative predictive value (98.1% and 96.2%, respectively). Total PD score-8 showed high correlation with the total PD score-24 ($r_s = 0.97, p < 0.01$).
Conclusions. Total PD score-8 is simple and efficient enough for monitoring disease activity and judging imaging remission of RA in daily practice.

Keywords

Power Doppler, Rheumatoid arthritis, Ultrasound

History

Received 30 June 2014
Accepted 6 October 2014
Published online 7 November 2014

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Since the advanced therapy including biologics has improved the management of rheumatoid arthritis (RA), earlier diagnosis and more stringent control of the disease activity is now realistic and required for prevention of joint destruction [1]. The new RA classification criteria designed for early classification have been proposed by American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2010 [2]. Although it has been verified to classify early RA more efficiently than the 1987 ACR classification criteria for RA [3], a substantial population still remains unclassified as RA by the 2010 RA classification criteria [2].

On the basis of the treat to target—T2T—concept, a current therapeutic goal regarding RA is to achieve clinical remission or low disease activity, which is determined by composite measures such as Disease Activity Score in 28 joints (DAS28), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) [1]. They include composite measures obtained by the physical examinations, that is, swollen joint count and tender joint count. However, some reports have shown that joint destruction progresses even after achieving clinical remission based on these criteria, reflecting the inadequate sensitivity of the conventional physical examination to detect synovitis [4,5].

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Musculoskeletal ultrasonography (US) has been established as a new imaging modality for assessing inflamed joints of patients with RA in the past decade [6–10]. Although the findings of US, directly visualizing and objectively quantifying synovial inflammation, shows favorable correlation with those of conventional physical examination, US is more sensitive and reliable for detecting synovitis in patients with RA [11–16]. Power Doppler (PD) US assists the diagnostic performance of 2010 RA classification criteria in the early recognition of RA [17,18]. Persistent PD signal-positive subclinical synovitis is associated with high risk of relapse and radiographic progression, even in patients who have clinical remission [15,16,19]. Thus, US contributes to a more accurate diagnosis and measure of disease activity in RA management than conventional clinical methods.

Despite the increasing use of US in RA, the joints to be tested for disease assessment remain undetermined. It is the rule that if more joints are examined, then more information is available. However, extensive US scanning on a large number of joints is ideal but not realistic in daily practice, because the procedure is time-consuming and impairs the feasibility. To this end, several studies have proposed different simplified scoring systems by examining limited number of joints, well correlated with clinical disease activity indices [20–23]. These data suggest that even a simplified US examination procedure, which is likely to be feasible in daily practice, is useful for the clinical assessment of RA. However, the sample size is too small to standardize the scoring system proposed by each study.

In this study, to establish efficient and feasible US assessment system in daily practice of RA, we determined an essential combination of US examining as few joints as possible, by retrospectively reviewing joint US findings in larger number of RA patients than the previous studies.

Patients and methods

Patients

Two hundred thirty-four RA patients, who fulfilled the 1987 ACR classification criteria or 2010 ACR/EULAR criteria for the classification of RA and received joint US examinations at the rheumatology clinic of Yokohama City University from May 2008 to April 2013, were evaluated retrospectively in this study [2,3]. The study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all patients before study enrollment. The design of the work was approved by the Institutional Review Board of Yokohama City University.

Clinical and laboratory assessment

Patients were evaluated clinically by attending rheumatologists who assessed 28 joints (bilateral glenohumeral, elbow, wrist, metacarpophalangeal (MCP), proximal interphalangeal (PIP) joints of the fingers, and knee joints) for tenderness and swelling. The patient global assessment (PGA; 10.0-cm visual analog scale) was rated individually by each patient. Serum concentrations of C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3), and rheumatoid factor (RF); and anti-cyclic citrullinated peptide antibody (ACPA) and erythrocyte sedimentation rate (ESR) were measured. Disease activity was assessed by both DAS28-ESR and DAS28-CRP because some cases showed a large discrepancy between DAS28-ESR and DAS28-CRP [24–26], which could be caused by confounding factors such as age, sex, fibrinogen levels, hypergammaglobulinemia, RF, and anemia [27,28]. A patient was considered to be in clinical remission if DAS28-ESR was <2.6 or DAS28-CRP was <2.3.

US assessment

Musculoskeletal US was performed by experienced rheumatologists (RY, DK, KM, MH, and YK). They were blind to the clinical, laboratory, and radiographic findings. An Aplio SSA-700A (Toshiba, Tokyo, Japan) with 12-MHz (or 7.5-MHz in some knee joint assessments) linear array transducers was used in this study. The ultrasound scanning method, including parameter settings, has been described previously [29–32]. Of the 28 joints defined in DAS28, 24 (excluding bilateral glenohumeral and elbow joints) were assessed by US. Bilateral glenohumeral and elbow joints were excluded from the US assessment because the methods for assessing and evaluating these joints have not been well established. The joints were scanned longitudinally and transversally from the dorsal view. PD imaging was performed by selecting a region of interest that included the bony margins and synovial site. PD signals in each joint were graded on a semiquantitative scale of 0–3 (0: absent [no synovial flow], 1: mild [single-vessel signal or isolated signals], 2: moderate [confluent signals in less than half of the synovial area], and 3: marked [signals in more than half of the synovial area]), corresponding to the maximum score obtained from the synovial sites evaluated in each joint [11]. Wrist joints were assessed in three divided portions, that is, radial, medial, and ulnar portions, and the highest score was termed as the wrist PD score. Knee joints were examined by suprapatellar, lateral, and medial longitudinal scanning at the neutral supine position [33]. In wrist and knee, the highest PD score was used in the multiple scanning. The intraobserver and interobserver reliabilities were previously described [34]. Total PD score-24 was calculated by summing up individual joint scores as comprehensive assessment. A patient was considered to have active synovitis if the total PD score-24 was ≥ 1. We examined correlations of total PD score-24 with individual joint PD scores and the sum PD scores of 9 sets of arbitrarily selected joint combinations. The sensitivity and negative predictive value (NPV) of individual sets of selected joint examination for the detection of active synovitis were also evaluated.

Statistical analysis

The data are reported as mean ± standard deviation (SD) in demographic, clinical, and laboratory features, and mean ± standard error (SE) in PD score. Normally distributed continuous data were analyzed using the non-paired *t*-test. Unpaired non-normally distributed and ordinal data were analyzed using Mann–Whitney *U* test. Paired non-normally distributed and ordinal data were analyzed using Wilcoxon signed-rank test. Categorical data were analyzed using the Fisher's exact probability test. Analysis of variance was used to determine whether there are any significant differences between the three independent groups. All correlations among US variables were assessed using Spearman's rank correlation test. For this analysis, a Spearman's correlation coefficient (r_s) of >0.7 was considered high, an r_s of 0.4–0.7 was considered moderate, and an $r_s<0.4$ was considered weak. Correlations between DAS28 and US variables were evaluated by Pearson's correlation coefficient. p values of less than 0.05 were considered statistically significant.

Results

Patient characteristics

Demographic, clinical, and laboratory feature of 234 RA patients in this study are shown in Table 1. RF was positive in 182 patients (77.8%), negative in 33 patients (14.1%), and not available in 19 patients (8.1%). ACPA was measured in 85 patients, among whom 68 patients (80.0%) had positive values. Patients were distributed in all clinical stages of the study, and stage II was the most frequent (Figure 1a). DAS28-ESR and DAS28-CRP scores were 3.54±1.63 (range 0.10–8.39) and 3.04±1.52 (range 0.96–8.15), respectively, ranging from remission to high disease activity (Figure 1a). The rate of patients with moderate or high disease activity was comparable with that of patients with low disease activity or remission according to DAS28-CRP (48.7% vs 46.2%).

One hundred seventy-six patients were treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) including methotrexate (MTX), sulfasalazine (SASP), tacrolimus (TAC), bucillamine (BUC), leflunomide (LEF), mizoribine (MZB), azathioprine (AZP), and gold sodium thiomalate (GST). One hundred forty-two patients (60.7%) were taking MTX (median dose: 8 mg/week) and 30 (12.8%) were taking SASP. Ninety-four patients (40.2%) received treatment with biologics (in combination with or without MTX), including etanercept (ETN), tocilizumab (TCZ), infliximab (IFX), adalimumab (ADA), and abatacept (ABT). All these biologics were used according to the dosages approved for the treatment of RA. A total of 101 patients (43.2%) were treated with prednisolone (PSL) at median dosage of 4.5 mg/day. Twenty-two patients were drug-free.

Average PD score in each joint site

We investigated the average PD score of 468 joints per each joint site. In wrist and knee, the highest PD score was used in multiple scanning. As shown in Figure 1b, there was no significant difference in PD score among radial (0.56 ± 0.91), medial (0.73 ± 0.98), and ulnar portions (0.64 ± 0.96, $p=0.063$). However, the PD score by the total assessment, which was determined by the highest score of three portions, was significantly higher than

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Table 1. Demographic, clinical, and laboratory features of 234 patients with RA.

Variables	Values
Age (years)	59.2 ± 13.8[a]
Sex	Male: 36 cases, female: 198 cases
Stage	I: 56 cases, II: 82 cases, III: 40 cases, IV: 56 cases
DAS28-ESR	3.54 ± 1.63[a]
	(HDA: 41 cases, MDA: 68 cases, LDA: 29 cases, remission: 80 cases, unknown: 16 cases)
DAS28-CRP	3.04 ± 1.52[a]
	(HDA: 60 cases, MDA: 54 cases, LDA: 19 cases, remission: 89 cases, unknown: 12cases)
Swollen joint count	2 (0–5)[b], unknown: 3 cases
Tender joint count	1 (0–5)[b], unknown: 3 cases
PGA (mm)	30 (10–50)[b], unknown: 12 cases
ESR (mm/h)	26.8 ± 27.0[a], unknown: 4 cases
CRP (mg/dl)	0.84 ± 1.70[a]
MMP-3 (ng/ml)	124 ± 118[a], unknown: 22 cases
RF	+: 182 cases, -: 33 cases, unknown: 19 cases
Treatment	Biologics: 94 cases
	(ETN 32 cases, TCZ 25 cases, IFX 23 cases, ADA 12 cases, ABT 2 cases)
	csDMARDs: 176 cases
	(MTX 142 cases [8 (6–10)[b] mg/week], SASP 30 cases, TAC 10 cases, BUC 9 cases, LEF 5 cases, MZB 5 cases, AZP 2 cases, GST 1 case)
	Steroid: 101 cases [PSL 4.5 (2.5–6)[b] mg/day]
	Drug-free: 22 cases

HDA high disease activity, *MDA* moderate disease activity, *LDA* low disease activity, *PGA* patient global assessment, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *MMP-3* matrix metalloproteinase-3, *RF* rheumatoid factor, *ETN* etanercept, *TCZ* tocilizumab, *IFX* infliximab, *ADA* adalimumab, *ABT* abatacept, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *MTX* methotrexate, *SASP* salazosulfapyridine, *TAC* tacrolimus, *BUC* bucillamine, *LEF* leflunomide, *MZB* mizoribine, *AZP* azathioprine, *GST* gold sodium thiomalate, *PSL* prednisolone

[a]The data are shown as the mean ± standard deviation (SD).

[b]Values are the median (interquartile range).

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that in any of the sole portions ($p = 7.6 \times 10^{-7}$, 9.8×10^{-3}, and 1.2×10^{-4}, respectively).

As shown in Figure 1c, the highest average was observed in wrist joints (0.87 ± 1.02), followed by knee, second MCP, and third MCP joints (0.28 ± 0.66, 0.20 ± 0.59, and 0.13 ± 0.49, respectively). Other MCP joints and all PIP joints had lower PD score averages. There was no significant difference in average PD scores between the left and right in each joint except for the fourth PIP joints ($p = 0.039$; Figure 1d). However, the PD scores revealed low concordance between the corresponding left and right joints in individual patients ($\kappa < 0.4$), indicating that the unilateral examination is inappropriate for assessing the disease activity of RA (Supplementary Table 1 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.974305).

Correlation coefficient between total PD score-24 and PD score in each joint site

To determine the contribution of PD score in each joint site to the total PD score-24, we next investigated the correlation between

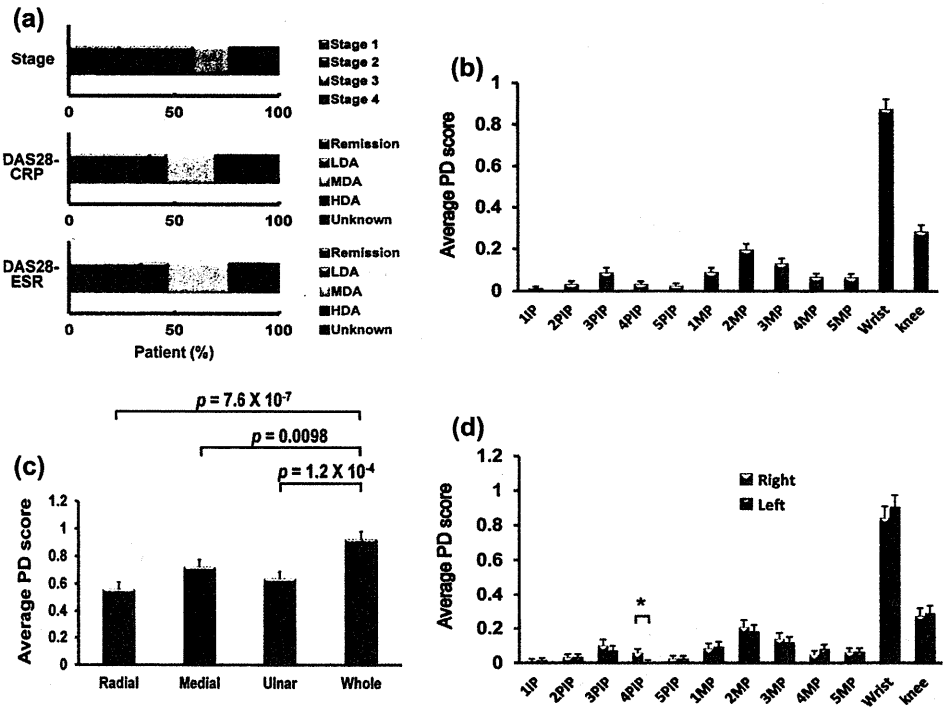

Figure 1. Average PD score in each joint site. (a) Clinical stage and disease activities based on DAS28-CRP or DAS28-ESR of 234 patients. *LDA*, low disease activity; *MDA*, moderate disease activity; *HDA*, high disease activity. (b) Average PD scores in three portions of wrist joints ($n = 372$). (c) Each joint site includes bilateral joint data ($n = 468$). (d) Left and right joint sites are indicated separately ($n = 234$). There was no significant difference in average PD scores between left and right except for the fourth PIP joint (*, $p = 0.039$). Data are given as the mean ± SE.

Mod Rheumatol, 2015; 25(3): 379–385

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them. Similar to the average PD score, wrist showed the highest Spearman's correlation coefficient ($r_s = 0.73$ and 0.72 in right and left, respectively; Figure 2a). Besides wrist, the joint sites which showed the moderate correlation ($r_s > 0.4$) included knee ($r_s = 0.49$, 0.43), second MCP ($r_s = 0.45$, 0.47), and third MCP ($r_s = 0.42$, 0.40) joints. Other MCP joints and all PIP joints showed only weak correlations with total PD score-24 ($r_s < 0.4$). Multiple linear regression analysis, which included all joints other than the two lowest r_s joints, the first interphalangeal and fifth PIP joints, as predictors, revealed that the wrist, knee, and the second and third MCP joints showed higher standardized coefficients (β) than the others (Table 2). The adjusted coefficient of determination (R^2) reached 0.9 with these four predictors (Table 3).

The 8-joint PDUS synovitis assessment

Based on the contribution of individual joints to total assessment, we examined whether the selected 8 joints including bilateral wrist, knee, and second and third MCP joints can represent the total US assessment with validity equivalent to that of the 24-joint assessment. As a result, diagnostic concordance between the detection of PD signals in the reduced 8 joints (total PD score-8) and comprehensive assessment (total PD score-24) was shown in 231 cases (98.7%), including 76 patients in US remission (Table 4). Only three patients (1.9%) had negative total PD score-8 among 158 patients having positive total PD score-24. The sensitivity and NPV of total PD score-8 for detecting active synovitis were 98.1% and 96.2%, respectively. The total PD score-8 correlated well with the total PD score-24 ($r_s = 0.97$, $p < 0.01$; Figure 2b, *left upper panel*).

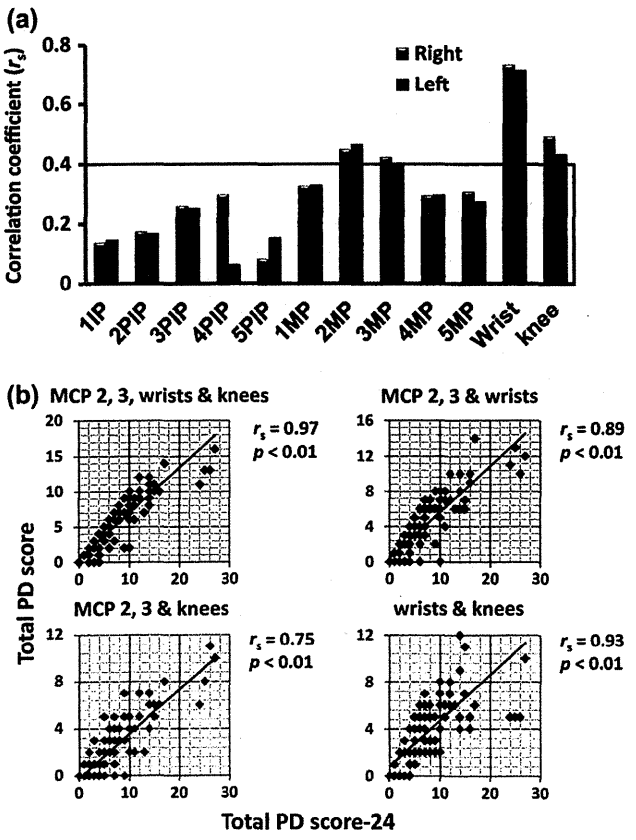

Figure 2. Spearman's correlation coefficient between total PD score-24 and PD score in each joint site or total PD scores of various joint combinations. (a) Spearman's correlation coefficient (r_s) between total PD score-24 and PD score in each joint site. Left and right joint sites are indicated separately ($n = 234$). (b) Correlation diagrams between total PD score-24 and total PD scores from different joint combinations ($n = 234$). The left upper diagram shows the correlation between total PD score-24 and total PD score-8.

Table 2. Predictors from stepwise linear regression analysis of total PD score-24.

Predictors	β	Partial R^2	p value	Model
Wrist	0.366	0.949	<0.001	Adjusted $R^2 = 0.994$
Knee	0.249	0.903	<0.001	$F = 4042$
MCP 2	0.219	0.854	<0.001	$p < 0.001$
MCP 3	0.163	0.696	<0.001	
PIP 3	0.154	0.762	<0.001	
MCP 1	0.140	0.701	<0.001	
MCP 5	0.123	0.590	<0.001	
MCP 4	0.106	0.498	<0.001	
PIP 2	0.093	0.575	<0.001	
PIP 4	0.064	0.348	<0.001	

β standardized coefficient, R^2 coefficient of determination, *MCP* metacarpophalangeal, *PIP* proximal interphalangeal

More simplified models for reduced PDUS assessment

To make US assessment simpler, different models for further reduced PDUS assessment based on the most frequently involved joints at baseline were investigated (Table 5 and Figure 2b). Comparison with other sets of joint combinations revealed that the wrist and knee joints had stronger impacts on correlation and other parameters. When we removed wrist joints from the 8-joint assessment, the correlation coefficient with total PD score-24 was greatly reduced from 0.97 to 0.75. Furthermore, the sensitivity for detecting active synovitis was also greatly decreased from 98.1% to 51.9%. All the models which did not include the assessment of wrists showed very low sensitivities, NPVs, and correlation coefficients. By removing knee joints from the 8-joint assessment, the correlation coefficient with total PD score-24 was reduced to 0.89, and the sensitivity was decreased to 88.0%. If the third MCP joints were omitted from the 8-joint assessment, NPV became fewer than 95%. Without including the assessment of both second and third MCP joints, NPV was reduced to 93.8%.

Correlation between PDUS parameters and clinical disease activity indices

Finally, we evaluated the correlation between PDUS parameters and clinical disease activity indices. Total PD score-24 positively correlated with DAS28-CRP ($r = 0.61$, $p = 9.7 \times 10^{-24}$) and DAS28-ESR ($r = 0.59$, $p = 3.2 \times 10^{-22}$) (Figure 3a). Similarly, total PD score-8 positively correlated with DAS28-CRP ($r = 0.60$, $p = 3.6 \times 10^{-23}$) and DAS28-ESR ($r = 0.59$, $p = 4.8 \times 10^{-22}$) (Figure 3b). There was no significant difference between total PD score-24 and total PD score-8 in correlation coefficients with DAS28-ESR ($p = 1.0$) and DAS28-CRP ($p = 1.0$).

Discussion

This study demonstrates that the selected 8 joints, including the bilateral wrist, knee, and the second and third MCP joints, are efficient enough for monitoring activity of RA in daily practice. We selected the 8 joints on the basis of the following reasons. First, our study shows that PD signal is observed dominantly in wrist, knee, and the second and third MCP joints without laterality. Second, the PD score of each joint site correlates well with the total PD score of comprehensive 24-joint assessment in wrist, knee, and the second and third MCP joints. These results indicate that the selected 8 joints contribute more to RA disease activity than the other joints. Indeed, our data showed that total PD score of the selected 8-joint assessment correlates well with that of 24 joints as the comprehensive assessment and maintains the comparable sensitivity.

Table 3. Models from stepwise linear regression analysis of total PD score-24.

Models	Adjusted R^2	F value	p value
Wrist	0.538	272.1	<0.001
Wrist, MCP3	0.759	367.5	<0.001
Wrist, MCP 3, knee	0.840	408.8	<0.001
Wrist, MCP 3, knee, MCP 2	0.900	527.2	<0.001
Wrist, MCP 3, knee, MCP 2, MCP 1	0.936	687.7	<0.001
Wrist, MCP 3, knee, MCP 2, MCP 1, MCP 5	0.957	872.6	<0.001
Wrist, MCP 3, knee, MCP 2, MCP 1, MCP 5, PIP 3	0.976	1372	<0.001
Wrist, MCP 3, knee, MCP 2, MCP 1, MCP 5, PIP 3, PIP 2	0.987	2268	<0.001
Wrist, MCP 3, knee, MCP 2, MCP 1, MCP 5, PIP 3, PIP 2, MCP 4	0.991	2933	<0.001
Wrist, MCP 3, knee, MCP 2, MCP 1, MCP 5, PIP 3, PIP 2, MCP 4, PIP 4	0.994	4042	<0.001

R^2 coefficient of determination, *MCP* metacarpophalangeal, *PIP* proximal interphalangeal

A variety of US assessment methods in RA have been proposed and used in published studies [35]. Nonetheless, the appropriate combination of joint scans with US for assessing the diagnosis and monitoring of RA remains uncertain. Because a comprehensive assessment of all accessible joints is time-consuming, establishment of simplified assessment method is needed. Several groups have proposed simplified US assessments in their own way. Iagnocco et al. chose the second and fifth MCP, the PIP, wrist, and knee joints to evaluate the response to treatment with ADA and ETN [36,37]. The simplified score showed good correlation with clinical disease activity indices.

Naredo et al. selected a 12-joint model including bilateral elbow, wrist, and the second and third MCP, knee, and ankle joints [20]. One hundred sixty patients with RA were enrolled in the study, and the 12-joint PDUS parameters correlated with the comprehensive 44-joint PDUS parameters. A process of data reduction was based on the frequency of involvement of synovial sites in synovitis and PD signal. They also suggest that in remission the assessment of 20 joints, including bilateral wrist, second-to-fifth MCP, ankle, and second-to-fifth metatarsophalangeal (MTP), can be highly sensitive, from the analysis of 41 patients in DAS28-based remission [38]. By applying a similar process in this study with the larger group of patients with RA as compared with their study, we confirmed that the reduced joint assessment is as effective as the comprehensive assessment, consistent with their results, in the larger population.

Backhaus et al. evaluated a novel US score "German US7" by examining the wrist, the second and third MCP, the second and third PIP, and the second and fifth MTP joints of the clinically dominant side [21]. One hundred and nine RA and eleven psoriatic arthritis patients were enrolled in this study, and a significant correlation between changes in the US parameters and the DAS28 was observed after six months of therapy. Our results showed that there was no significant bilateral difference in the detection of PD signals. Thus, although "German US7" can be a valuable tool for monitoring inflamed joint activity, its sensitivity could not be very high because only the dominant side of the body was examined.

Perricone et al. also adopted a process for simplification of US assessment, which is similar to that adopted by Naredo et al. and us [22]. Forty-five patients with RA were evaluated, and reduced 6-joint US assessment was compared with the 12-joint score suggested by Naredo et al. The 6-joint assessment, including the assessment of bilateral wrist, knee, and the second MCP joints, was able to detect 100% of patients with PD signals in the 12 joints, and the correlation between the 12-joint and 6-joint US score was high ($r = 0.943$). However, the sample size was quite small, and the patient's background was not generalized in that all the participants started anti-tumor necrosis factor therapy. Another group has suggested a different 6-joint assessment, which includes the assessment of bilateral wrist and second and third MCP joints, using a similar study, in which 22 RA patients were enrolled [23].

To the best of our knowledge, this is the largest study comparing limited number of joint PDUS assessments with a comprehensive assessment in RA. Two-hundred thirty-four patients were enrolled in this study, including patients in all clinical stages and in all disease activity levels receiving various therapies. The size of the study and wide variety of patient backgrounds can offer generalized optimization for selecting the site and number of joints to be examined by US. Furthermore, the high correlation of total PD score-8 with the score from the comprehensive assessment indicates that it is efficient for monitoring disease activity of RA.

Synovial hypertrophy and synovial fluid assessed by gray-scale (GS) images were not taken into consideration in this study. A recent study from a Japanese group has identified synovial hypertrophy as an independent and significant factor influencing the assessment of synovial inflammation by multiple linear regression analysis, though the contribution was much less than that of PD [39]. In our additional analysis of the studied patient group, GS findings in the selected 8 joints well correlated with those in 24 joints as shown in the PD signals. Abnormal GS findings were found in the selected 8 joints in 98.2% of patients having one or more positive GS findings in 24 joints. These data also suggest

Table 4. Binary classification.

		Total PD score-24	
		PD (+)	PD (−)
Total PD score-8	PD (+)	155	0
	PD (−)	3	76

The existence of active synovitis was determined by total PD score-24 as a gold standard. $n = 234$.
PD (+) total PD score ≥ 1, *PD (-)* total PD score = 0.

Table 5. Sensitivity, NPV, and correlation coefficient in various joint combinations.

Joint combination	Joint number	Sensitivity (%)	NPV (%)	r_s[a]
Bilateral MCP 2, 3, wrists & knees[b]	8	98.1	96.2	0.97
Bilateral MCP 2, wrists & knees	6	97.5	95.0	0.96
Bilateral wrists & knees	4	96.8	93.8	0.93
Bilateral MCP 2, 3 & wrists	6	88.0	80.0	0.89
Bilateral wrists	2	86.1	77.6	0.84
Bilateral MCP 2, 3 & knees	6	51.9	50.0	0.75
Bilateral knees	2	38.0	43.7	0.55
All MCPs	10	34.8	42.5	0.69
All PIPs	10	22.8	38.4	0.52

NPV negative predictive value, *MCP* metacarpophalangeal, *PIP* proximal interphalangeal
[a] Spearman's rank correlation coefficients between total PD score-24 and sum PD scores of the different joint combination ($p < 0.01$ for all the correlations).
[b] Total PD score-8.

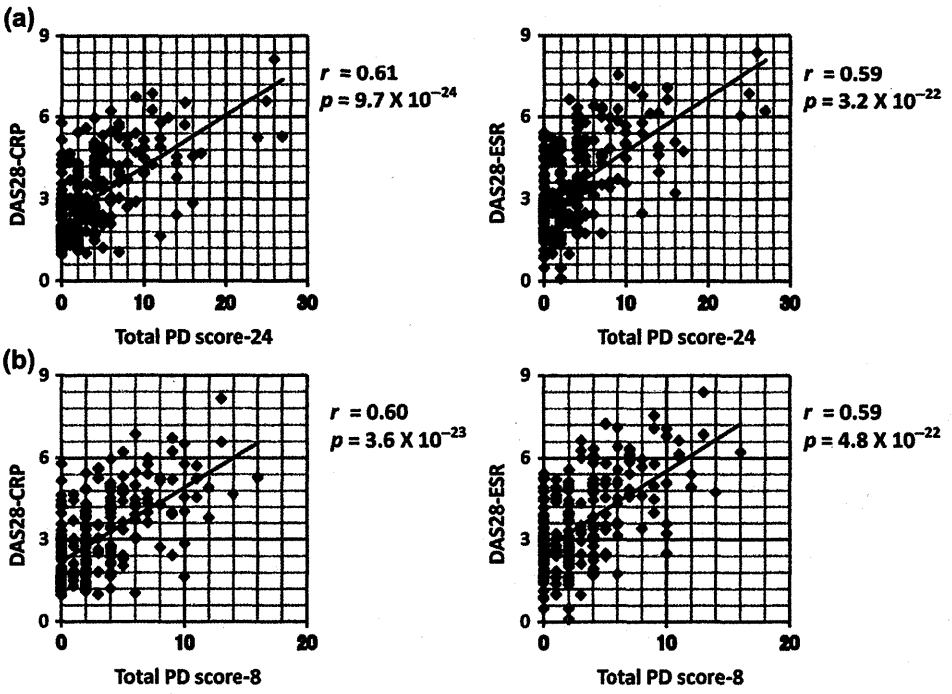

Figure 3. Correlation between PDUS parameters and clinical disease activity indices. (a) Correlation diagrams between total PD score-24 and DAS28-CRP ($n = 222$), or DAS28-ESR ($n = 218$). (b) Correlation diagrams between total PD score-8 and DAS28-CRP ($n = 222$), or DAS28-ESR ($n = 218$).

that the selected 8-joint assessment efficiently covers positive findings of the comprehensive 24-joint assessment regarding synovial hypertrophy as well as PD signal.

Both total PD score-24 and total PD score-8 correlate well with the composite measures, DAS28-ESR and DAS28-CRP, in this study. Naredo et al. reported that PDUS parameters of 44-joint assessment and simplified 12-joint assessment correlate with DAS28 ($r = 0.55$ and 0.53, respectively) [20]. The other group also showed the good correlation between US count by 6-joint assessment and DAS28 ($r = 0.535$) [22]. The levels of correlation coefficients in our study were the same or more than those in the other studies. On the other hand, our previous report has shown that the US score is often dissociated with the composite measures in patients in DAS28-based clinical remission [10]. Because persistent PD-signal-positive synovitis is associated with high risk of radiographic progression even in patients who have clinical remission [15,16,19], PDUS is essential for assessing "true remission," especially after achieving "clinical remission" based on the composite measures.

There were some limitations in this study. First, as this is a retrospective study, some errors due to bias and confounding might not have been prevented in data selection and analysis. Second, we examined 24 joints which have commonly been assessed and methodologically established in daily practice as the comprehensive assessment. Other joint sites, such as shoulder, elbow, ankle, and MTP, were not included in the study because the joint sites were not defined in DAS28 and/or the assessment methods for these joints have not been established enough so far. As MTP joints are prone to be involved clinically in RA, a more comprehensive assessment including these joint sites should be adopted in the future study. Although only 3 of 158 patients (1.9%) had positive total PD score-24 in spite of having negative total PD score-8 in the present study, the 8-joint assessment potentially leads to over- and underestimation in a part of patients. To this end, additional scanning of symptomatic and/or physically abnormal joints may be practical and helpful.

In conclusion, our proposed 8-joint PDUS assessment seems to be valid and feasible in daily clinical practice and can be recommended for the diagnosis and disease activity assessment in RA.

Acknowledgments

We thank all the colleagues in our laboratories for kind cooperation in this project. We also thank Mr. Tom Kiper for his review of the manuscript. This work was supported by the Japan Rheumatism Foundation (R. Y.).

Conflict of interest

None.

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Supplementary material available online

Supplementary Table 1.

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EXTENDED REPORT

Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study)

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Handling editor Tore K Kvien

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2015-208426).

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Received 14 August 2015
Revised 26 October 2015
Accepted 24 November 2015

ABSTRACT

Objective To compare the efficacy and safety between tocilizumab added to methotrexate and tocilizumab switched from methotrexate in patients with active rheumatoid arthritis (RA).

Methods This is a 2-year randomised, controlled study. RA patients with moderate or high disease activity despite methotrexate were randomly assigned either to tocilizumab added to methotrexate (add-on) or tocilizumab switched from methotrexate (switch). The primary endpoint was the DAS28 remission rate at week 24. Secondary objectives included other clinical efficacy indices, radiological outcomes assessed with the van der Heijde-modified total Sharp scoring system (mTSS), and safety.

Results Of 223 randomised patients, 83% completed 52 weeks. DAS28 remission rates at week 24 were 70% for add-on and 55% for switch (p=0.02), but they became comparable at week 52 (72% vs 70%, p=0.86). Structural remission rates (mTSS≤0.5) at week 52 were not different (66% vs 64%, p=0.92). However, clinically relevant radiographic progression rates (CRRP; mTSS≥3) tended to be higher with the switch than with the add-on (15% vs 7%, p=0.07). Radiographic progression in the CRRP patients was larger with the switch than with the add-on (9.0/year vs 5.0/year, p=0.04). The difference in the mean C-reactive protein of the CRRP patients was significant for the first 24 weeks (1.56 vs 0.49, p=0.001) but not for the following 28 weeks (0.10 vs 0.04, p=0.1). Overall safety was preferable in the switch group.

Conclusions In RA patients with inadequate response to methotrexate, tocilizumab added to methotrexate more rapidly suppressed inflammation than tocilizumab switched from methotrexate, leading to superior clinical efficacy and prevention of joint destruction.

Trial registration number NCT01120366.

To cite: Kaneko Y, Atsumi T, Tanaka Y, *et al*. *Ann Rheum Dis* Published Online First: [*please include* Day Month Year] doi:10.1136/annrheumdis-2015-208426

INTRODUCTION

The advent of intermittent methotrexate (MTX) and various biologic agents has had such an impact on the treatment of rheumatoid arthritis (RA) that a paradigm shift has emerged towards earlier and more aggressive intervention with the goal of remission.[1–3] MTX is an anchor drug in the management of RA because of its long-term effectiveness and safety profile,[4] but in patients who have responded insufficiently to MTX, adjustment of treatment should be considered, including the introduction of another conventional disease-modifying anti-rheumatic drug (DMARD) or a biological DMARD according to the absence/presence of poor prognostic factors.[1]

When starting a biological DMARD in MTX-insufficient responders with poor prognostic factors, there are two strategies: one is combining a biological DMARD with MTX, and the other is switching to a biological DMARD from MTX. While majority of clinical studies provide the favourability of a combination therapy, the switch to a monotherapy is debate for interleukin-6 (IL-6) blocking.

Regarding tumour necrosis factor (TNF) inhibitors, results from many clinical studies have suggested that the use of TNF inhibitors in combination with MTX is superior to TNF inhibitor monotherapy, and that adding TNF inhibitors to MTX is better than replacing MTX with TNF inhibitors in efficacy, while the safety is comparable among the groups.[5–7]

Tocilizumab (TCZ), humanised antihuman IL-6 receptor monoclonal antibody, has been proven to be efficacious in RA patients, and its efficacy has been well validated, both as a combination therapy with MTX and as monotherapy. TCZ monotherapy has been shown to be more efficacious than MTX monotherapy in MTX-naïve patients, in patients with an inadequate response to MTX and in patients with a history of MTX treatment more than 6 months before.[8–10] Therefore, a question arises if addition of TCZ to MTX or a switch from MTX to TCZ is comparable.

The ACT-RAY study was designed as a 3-year trial to compare adding TCZ to switching to TCZ

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in inadequate responders to MTX. In that study, no clinically relevant superiority of the addition of TCZ to MTX over the switch to TCZ monotherapy was proven, but there was a modest difference favouring the addition strategy in achieving low disease activity at week 24 and in suppressing radiographic progression at week 52.[11 12]

The present 2-year study, the Success of Tocilizumab in RA Patients With Remission Induction and Sustained Efficacy After Discontinuation (SURPRISE) study, was planned to evaluate the efficacy and safety profile of adding TCZ to MTX or switching MTX to TCZ in patients with moderate or high disease activity despite MTX treatment during the first 52 weeks and subsequently to determine if maintenance of remission after discontinuation of TCZ is possible between weeks 52 and 104. The first-year results are reported here.

SUBJECTS AND METHODS

Study design and participants

n this randomised, controlled study, patients with RA diagnosed according to the 1987 American College of Rheumatology (ACR) criteria less than 10 years before, aged between 20 and 75 years, with moderate or high disease activity at baseline visits, were enrolled between November 2009 and March 2012. Moderate or high disease activity was defined as a disease activity score in 28 joints (DAS28; on the basis of the erythrocyte sedimentation rate, ESR) of more than 3.2. Participants had to have been receiving stable doses of ≥6 mg/week of MTX for treatment of RA for at least 8 weeks before enrolment.[9] Patients were excluded if they had previously taken or were taking any biologic treatment, leflunomide within 12 weeks of baseline, tacrolimus within 4 weeks, or any other conventional DMARDs other than MTX within 8 weeks. Patients taking prednisolone (or equivalent) at a dose of more than 10 mg/day were excluded.

This report covers the planned analysis of the first 1 year of a 2-year study (NCT01120366, UMIN000002744). This study was approved by the ethics committee at each site and conducted in accordance with the Declaration of Helsinki. All participants gave their written, informed consent.

Study treatment

Patients were randomly assigned by a centralised system in a 1:1 ratio to one of two open-label treatment groups: TCZ added to MTX (ADD-ON group) or TCZ switched from MTX (SWITCH group). TCZ was administered at a dose of 8 mg/kg intravenously every 4 weeks, and MTX was maintained at the same dose as the baseline unless a clinically relevant adverse event (AE) occurred.

Collected patient data and assessments

Data collected at baseline included demographics and disease characteristics. The following parameters were assessed at baseline and at weeks 4, 12, 24, and 52: tender joint count, swollen joint count, health assessment questionnaire-disability index, patient global assessment using a visual analogue scale (VAS), evaluator global assessment using a VAS, C-reactive protein (CRP), ESR and matrix metalloproteinase-3. Radiographs of the hands and feet were obtained at baseline and at week 52. Each radiograph was assessed applying the van der Heijde-modified total Sharp scoring system (mTSS) by two independent readers who were blinded to treatment assignment and the patient's clinical status. At each visit, patients were monitored for physical signs, laboratory tests, and AEs.

Statistical analysis

The primary outcome of this study was defined as the percentage of patients in remission according to the DAS28-ESR at week 24. With the assumption that DAS28-ESR remission would be achieved by 50% of patients in the ADD-ON group and 45% in the SWITCH group, 133 patients per treatment group were calculated as necessary for more than 80% power to prove the null hypothesis of no difference between the treatment arms with a non-inferiority margin of 10%. A two-sided statistical test of no difference at the 5% significance level was used. As a sensitivity analysis, the percentage of patients in remission according to the simplified disease activity index (SDAI) and clinical disease activity index (CDAI) in substitution for the DAS28 was further analysed.

Efficacy analyses were conducted in the full analysis population with the last-observation-carried-forward method. Safety endpoints including the incidence of AEs, serious AEs, infections, and specific laboratory abnormalities were analysed in all treated patients.

All analyses of proportions were analysed for treatment differences with the χ^2 test, and continuous variables were compared with Student's t test.

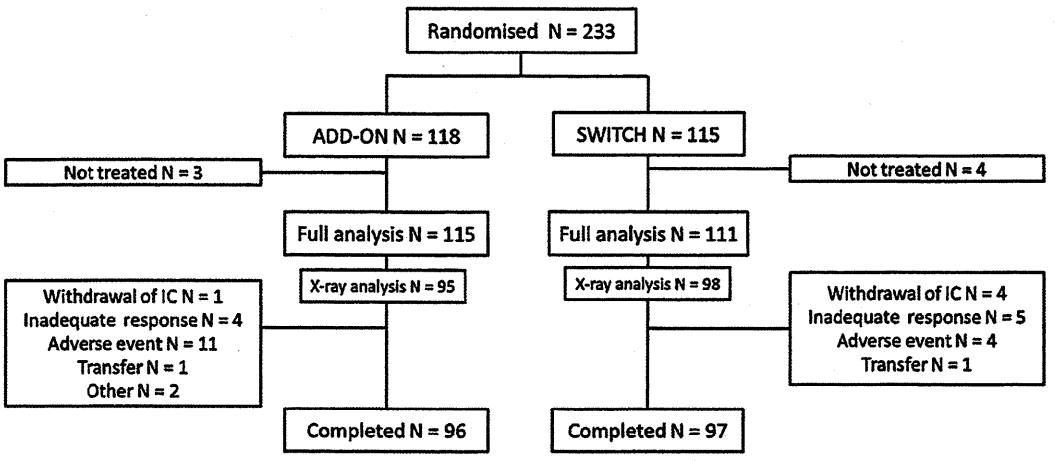

Figure 1 Patient disposition and study flow chart. IC, informed consent.

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RESULTS

Patient flow and baseline characteristics

Figure 1 shows patient disposition through the 52 weeks. A total of 223 patients eligible for this study were randomised to TCZ added to MTX (ADD-ON, N=118) or TCZ switched from MTX (SWITCH, N=115). Of all of the patients randomly assigned, three patients in the ADD-ON group and four in the SWITCH group were not treated with TCZ and excluded from the analysis. Overall, 115 in the ADD-ON group and 111 in the SWITCH group who received at least one injection of TCZ were analysed for efficacy and safety as the full analysis population. The number of patients in the analysis did not reach the sample size defined in the protocol to prove the inferiority of switch strategy to add-on. There were no statistically or clinically significant differences between the two groups in baseline characteristics, except for the swollen joint count in the 66 joints (table 1).

Twenty patients in the ADD-ON group and 13 in the SWITCH group lacked X-rays of the hands and feet at baseline or week 52 and were excluded from the radiographic analysis. The baseline characteristics did not differ significantly between the patients who underwent radiographic evaluation and those who did not (data not shown).

Clinical efficacy

The main efficacy results at weeks 24 and 52 are summarised in figure 2 and online supplementary table. DAS28-ESR remission rates were significantly higher in the ADD-ON group than in the SWITCH group at weeks 4 and 24 (primary endpoint), but they became comparable at week 52 (figure 2A). Remission rates according to the SDAI and the CDAI were not significantly different between the two groups but showed a similar tendency (see online supplementary figure A, B). For other endpoints, including Boolean remission and ACR20/50/70, the differences between the two treatment groups were not significant, but there was a trend towards superiority of TCZ added to MTX to TCZ switched from MTX (figure 2B, C, see online supplementary table). Although the week 8 visit was not compulsory, data were collected for 55% of the patients and analysed. The DAS28-ESR remission rate was also significantly higher in the ADD-ON group at week 8 (see online supplementary figure C), and this

Table 1 Baseline patient characteristics

	ADD-ON (N=115)	SWITCH (N=111)	p Value
Age, years	55.8 (11.7)	56.3 (2.7)	0.60
Female, N (%)	100 (87.0)	96 (86.5)	1.00
Weight, kg	55.5 (10.8)	54.2 (9.6)	0.41
Disease duration, years	3.6 (3.2)	3.8 (3.1)	0.38
Methotrexate dose, mg/week	8.6 (2.5)	8.4 (2.0)	0.88
Methotrexate duration, months	21.1 (28.5)	20.6 (24.6)	0.88
Prednisolone use, N (%)	41 (35.7)	41 (36.9)	0.84
Prednisolone dose, mg/day	4.3 (2.1)	5.0 (2.8)	0.31
TJC28	7.1 (5.3)	7.2 (6.0)	0.65
SJC28	6.3 (4.2)	7.2 (4.9)	0.23
TJC68	9.6 (7.5)	10.1 (9.0)	0.93
SJC66	7.6 (5.3)	9.9 (7.6)	*0.02**
CRP, mg/dL	1.2 (1.5)	1.8 (2.6)	0.58
ESR, mm/h	40.8 (28.0)	44.7 (29.6)	0.27
PGA, mm	46 (23)	51 (24)	0.15
EGA, mm	46 (21)	47 (21)	0.47
DAS28-ESR	5.1 (1.1)	5.3 (1.2)	0.29
SDAI	23.9 (10.9)	26.1 (13.4)	0.32
CDAI	22.6 (10.4)	24.2 (12.2)	0.40
HAQ-DI	1.0 (0.7)	1.0 (0.7)	0.42
MMP-3, mg/dL	172.1 (152.4)	190.4 (199.1)	0.96

*p<0.05.
CDAI, clinical disease activity index; CRP, C-reactive protein; DAS28, disease activity score for 28 joints; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire disability index; MMP, matrix metalloproteinase; PGA, patient global assessment; SDAI, simplified disease activity index; SJC, swollen joint count; TJC, tender joint count.

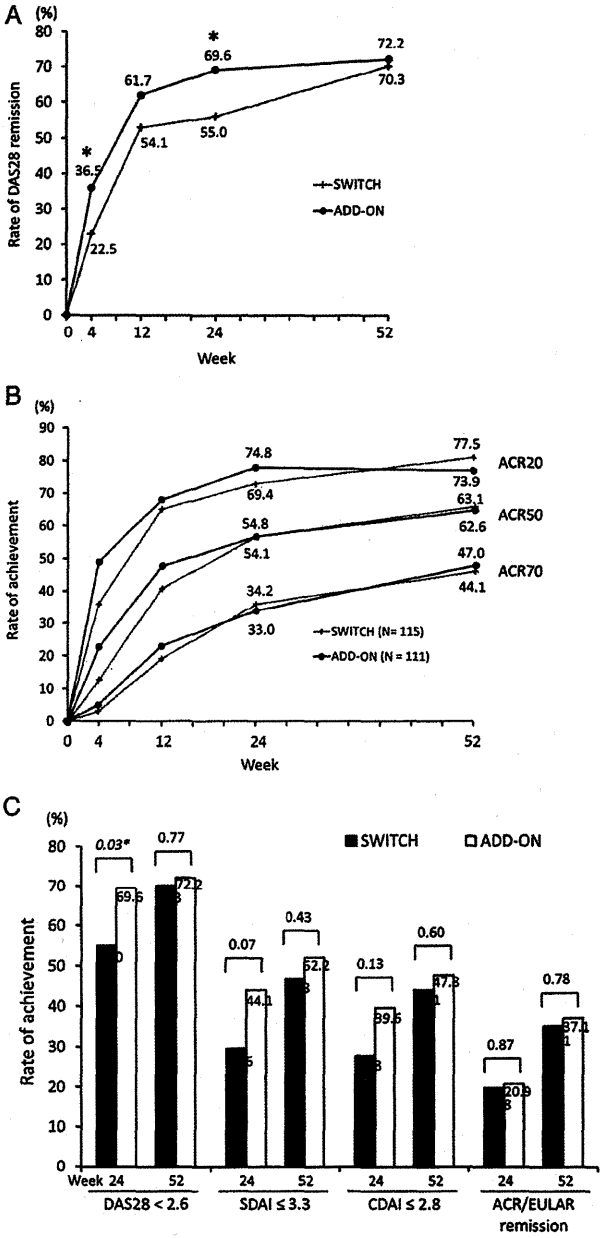

Figure 2 Clinical efficacy results. Results over time for (A) percentage of patients achieving DAS28 remission, (B) percentage of patients achieving ACR20/50/70, (C) patients achieving remission according to DAS28, SDAI, CDAI and ACR/EULAR Boolean defined criteria at weeks 24 and 52. DAS28, disease activity score for 28 joints; ACR, American College of Rheumatology; SDAI, simplified disease activity index; CDAI, clinical disease activity index; EULAR, European League against Rheumatism. *p<0.05.

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corroborated the finding that TCZ added to MTX was favourable for the 24 weeks. The clinical efficacy of TCZ switched from MTX could catch up by week 52.

Structural outcome

At week 52, structural remission, defined as a change in mTSS from baseline ≤0.5, was achieved in 63 patients (66%) in the ADD-ON group and in 63 (64%) in the SWITCH group (p=0.92), and there was no significant difference in the median change (0 in both groups) between the two groups. Clinically relevant radiographic progression (CRRP), defined as change in mTSS from baseline ≥3, was observed in 7 patients (7%) in the ADD-ON group and 15 (15%) in the SWITCH group. Although the percentages of CRRP were not significantly different between the two groups (p=0.07), the mean change in mTSS in CRRP patients was significantly larger in the SWITCH group than in the ADD-ON group (9.0/year vs 5.0/year, p=0.04, figure 3A).

To examine the relationship between the achievement of DAS28-ESR remission at week 24 and the CRRP (figure 3B), the patients were divided into four groups: remission at both weeks 24 and 52 (68 in the ADD-ON group and 50 in the SWITCH group); remission at week 24 but non-remission at week 52 (6 in both groups); non-remission at week 24 but remission at week 52 (9 in the ADD-ON group and 23 in the SWITCH group); and non-remission at weeks 24 and 52 (12 in the ADD-ON group and 19 in the SWITCH group). The proportion of CRRP patients was the lowest in the group with remission at both weeks 24 and 52, and significantly less than the group with non-remission at week 24 but remission at week 52 and the group with non-remission at weeks 24 and 52 (5.9% vs 18.8%, p=0.02; 5.9% vs 25.8%, p=0.001, respectively). The group with remission at week 24 but non-remission at week 52 showed a comparable percentage of CRRP patients as the group with remission at both weeks 24 and 52, implying that non-remission at week 24 contributed chiefly to rapid radiological progression. In addition, the CRRP patients included nearly twice as many SWITCH patients as ADD-ON patients, supporting the idea that the add-on strategy is a good strategy for preventing radiological progression.

Inflammation status using CRP was further analysed through the study of the CRRP patients, who had higher disease activity than those who responded well to TCZ (figure 3C). The mean CRP of the CRRP patients for 52 weeks was much higher in the SWITCH group than in the ADD-ON group (1.27 vs 0.37, p=0.03). The difference in the mean CRP between the two groups was significant for the first 24 weeks (1.56 vs 0.49, p=0.001) but not for the second 28 weeks (0.10 vs 0.04, p=0.1), suggesting that less radiographic progression in TCZ added to MTX was attributable to the degree inflammation was suppressed during the first 24 weeks of the study.

Safety

The safety results are presented in table 2. Overall, the number of patients with at least one AE was greater in the ADD-ON group than in the SWITCH group (60.0% vs 45.0%, p=0.02), but the percentage of patients with at least one serious AE was comparable in the two treatment groups (13.9% vs 8.1%, p=0.20). AEs occurring more in the ADD-ON group than in the SWITCH group were infections, gastrointestinal disorders, and liver dysfunction. Eleven patients (9.6%) in the ADD-ON group and 4 (3.6%) in the SWITCH group were withdrawn from the study because of AEs (p=0.11). There was one death from interstitial pneumonitis in the ADD-ON group in this 1-year observation period.

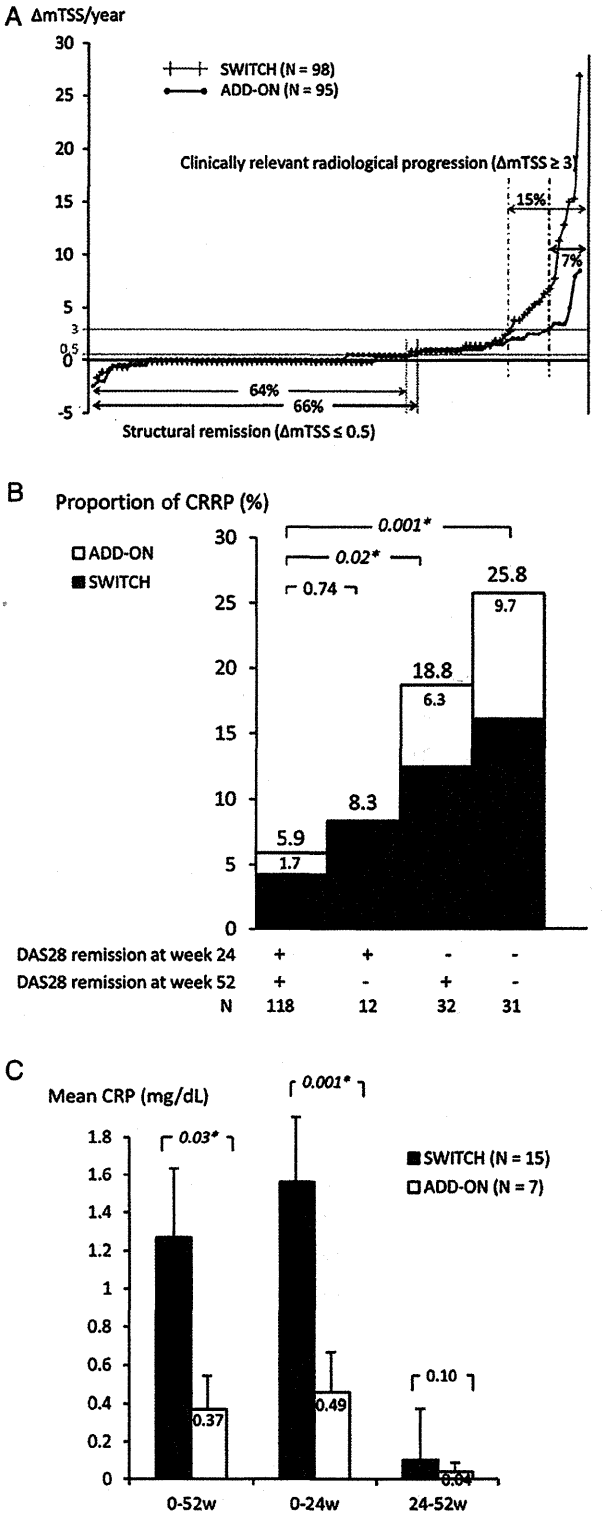

Figure 3 Structural outcome. (A) Cumulative probability plot of change from baseline to week 52 in van der Heijde-modified total Sharp scoring system (mTSS). (B) Percentage of patients with CRRP. (C) Mean CRP. CRRP, clinically relevant radiographic progression; DAS28, disease activity score for 28 joints; CRP, C-reactive protein. *p<0.05.

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Table 2 Adverse events by group

	ADD-ON (N=115)		SWITCH (N=111)	
	AE	SAE	AE	SAE
Total patients with ≥1 AE or ≥1 SAE	**69, 60.0%**	**16, 13.9%**	**50, 45.0%**	**9, 8.1%**
Infections and infestations	47, 40.9%	6, 5.2%	25, 22.5%	7, 6.3%
Bacterial pneumonia	2, 1.7%	2, 1.7%	3, 2.7%	1, 0.9%
Nasopharyngitis	10, 8.7%	0	3, 2.7%	1, 0.9%
Gastrointestinal disorders	29, 25.2%	1, 0.9%	14, 12.6%	2, 1.8%
Hepatobiliary disorders	22, 19.1%	1, 0.9%	5, 4.5%	1, 0.9%
Liver function disorders	15, 13.0%	1, 0.9%	3, 2.7%	0
Respiratory, thoracic and mediastinal disorders	14, 12.2%	1, 0.9%	5, 4.5%	0
Laboratory test abnormalities	18, 15.7%	0	9, 8.1%	0
Metabolism and nutrition disorders	9, 7.8%	0	7, 6.3%	0
Skin and subcutaneous tissue disorders	7, 6.1%	0	7, 6.3%	2, 1.8%
Injury, poisoning, and procedural complications	7, 6.1%	4, 3.5%	2, 1.8%	1, 0.9%
General disorders and administration site conditions	4, 3.5%	0	1, 0.9%	0
Neoplasms benign, malignant, unspecified	2, 1.7%	2, 1.7%	1, 0.9%	0
Eye disorders	3, 2.6%	0	0	0
Musculoskeletal and connective tissue disorders	2, 1.7%	1, 0.9%	1, 0.9%	0
Blood and lymphatic system disorders	2, 1.7%	1, 0.9%	1, 0.9%	0

AE, adverse event; SAE, serious adverse event

DISCUSSION

This study compared two different strategies in patients with RA with inadequate responses to MTX, and the results suggest that TCZ added to MTX is clinically and radiographically superior to TCZ switched from MTX. The switch strategy was able to catch up later to the add-on protocol with respect to clinical efficacy, but the structural damage progressed more in a year with the switch therapy.

TCZ monotherapy as well as TCZ in combination with MTX has been proven to be more efficacious than MTX monotherapy.[8–10 13 14] The ACT-RAY study comparing the efficacy and safety of TCZ in combination with MTX with TCZ monotherapy in a similar fashion to the present study showed no clinically relevant superiority of the add-on strategy over the switch strategy at 1 year and suggested that TCZ monotherapy is a valuable treatment in RA patients with inadequate response to MTX.[11 12] However, a modest difference favouring the add-on strategy in achieving low disease activity at week 24 and in suppressing radiographic progression at week 52 was observed. The present study underlined the trends showing the clinical superiority of the combination therapy for the first half of the follow-up period and radiological superiority at 1 year. The mean disease duration in the SURPRISE study (3.6–3.8 years) was shorter than that in the ACT-RAY study (8.2–8.3 years). In the ACT-RAY study, conventional DMARDs were added in a patient with a DAS28 >3.2 at week 24. Those differences in patient background and study protocol between the two studies could generate more notable advantageous results of add-on strategy in our study. The CHARISMA study, in which the combination therapy of TCZ was compared with TCZ monotherapy as a part of a dose-finding phase 2 trial in RA patients who had an incomplete response to MTX, also implied that combination therapy was superior to monotherapy;[15] DAS28 remission rates at week 16 in that study were 34% for combination therapy and 17% for monotherapy. We assume that stopping MTX in conjunction with starting TCZ could transiently increase disease activity, since MTX might have worked to downregulate inflammation to some extent despite the inadequacy.

Importantly, the worse disease activity in patients with TCZ switched from MTX in the first 24 weeks impacted radiological outcomes at week 52, despite comparable clinical efficacy at week 52. This finding was observed in another trial conducted in Japan in which patients completing a 26-week, randomised, placebo-controlled trial of adalimumab received open-label adalimumab in the following 26 weeks. This study showed that the accrual of significant structural damage during 26-week placebo therapy contributed to the persistence of differences in radiographic progression at week 52.[16] Taking those findings together with the irreversible nature of the structural damage, TCZ added to MTX was better than TCZ switched from MTX.

Despite the clinical and radiological superiority of TCZ added to MTX, TCZ switched from MTX showed favourable safety outcomes. While serious AEs were comparable between the two study treatments, AE rates were higher with the add-on strategy than with the switch strategy. In particular, the add-on strategy resulted in a higher proportion of patients with hepatic disorder. This was also observed in other TCZ studies,[11–13 17] suggesting that the combination of TCZ and MTX might have a synergistic effect on the liver. Nevertheless, the regimen in the combination group in the present study was well tolerated.

The fact that the clinical efficacy of SWITCH eventually caught up to that of ADD-ON would be provoking a new strategy: stopping or decreasing MTX after TCZ has made a sufficient contribution. Aside from the fact that stopping MTX is sometimes necessary because of liver injury or gastrointestinal discomfort, the lymphoproliferative disorder related to long-term use of MTX increasingly poses a serious problem leading us to surmise that minimising the use of MTX is preferable.[18–20] This should be further examined in future studies.

The present study has several limitations. First, this study was not double-blind, and it cannot be ruled out that knowing the treatment might affect the clinical evaluation. However, since an objective index such as the mTSS that was assessed by

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independent blinded readers could detect a difference between the two groups, this effect was likely minimal. Second, the number of patients enrolled in this study did not reach the sample size defined in advance to prove non-inferiority of TCZ switched from MTX to TCZ added to MTX. Although the add-on strategy was significantly superior to the switch strategy on the primary endpoint using the DAS28, the superiority in the sensitivity analysis using the SDAI and the CDAI was limited because of the insufficient power. Third, the dose of MTX used in this study was lower than that used in Western countries, as in the ACT-RAY study. Since the lower dose of MTX would have tended to decrease the difference between the two groups, this did not appear to have affected the results of the study. In addition, it has been reported[21] that concentration of MTX polyglutamates, a potential marker for MTX use, in red blood cells was relatively higher in a Japanese study than in a study from the USA, suggesting that a lower dose of MTX may be sufficient in Japanese patients.

In conclusion, in RA patients with inadequate response to MTX, TCZ added to MTX suppresses inflammation more than TCZ switched from MTX, leading to superior clinical efficacy and prevention of joint destruction. While meaningful clinical and radiographic responses were achieved with both strategies, patients could benefit from combination therapy more than monotherapy, although precautions against AEs are necessary.

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Acknowledgements The authors acknowledge and thank all the investigators and participants in this study.

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

Funding Specified Nonprofit Corporation Advanced Clinical Research Organization.

Competing interests YK has received lecture fees from AbbVie GK, Eisai Co, Chugai Pharmaceutical Co, Eli Lilly Japan K.K., Mitsubishi-Tanabe, Bristol–Myers K.K., Astellas Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Pfizer, Janssen, Santen, Kyowa Hakko Kirin and UCB Japan. TA has received research grants or lecture fees from Eisai Co, Chugai Pharmaceutical Co, Novartis, Mitsubishi-Tanabe, Teijin, Astellas, Takeda, Novo Nordisk, Abbvie GK, Pfizer and Bristol–Myers K.K. YT has received consulting fees, speaking fees and/or honoraria from Abbvie GK, Daiichi-Sankyo, Chugai Pharmaceutical Co, Takeda, Mitsubishi-Tanabe, Bristol–Myers K.K., Astellas, Eisai Co, Janssen, Pfizer, Asahikasei Pharma Corp., Eli Lilly Japan K.K., GlaxoSmithKline, UCB Japan, Teijin, MSD and Santen and has received research grants from Mitsubishi-Tanabe, Takeda, Chugai Pharmaceutical Co, Astellas, Eisa Co. i, Taisho-Toyama, Kyowa-Kirin, AbbVie GK and Bristol–Myers K.K. KA has received research grants from Chugai Pharmaceutical Co. and Astellas, and has received lecture fees from Abbvie GK, Astellas, Bristol–Myers K.K., Chugai Pharmaceutical Co and Pfizer. SH has received lecture fees from AbbVie GK, Eisai Co an Bristol–Myers K.K. YM has received research grants or lecture fees from Japan Blood Products, Taisho Toyama, Nippon Kayaku, Takeda Pharma, AbbVie GK, Janssen Pharma. and UCB Japan, Astellas, Chugai Pharmaceutical Co, Ono, Mitsubishi-Tanabe, Teijin and Eisai Co. SH has received lecture fees from AbbVie GK, Eisai and Bristol-Myers K.K. ET has received lecture fees or consulting fees from Abbvie GK, Eisai Co, Chugai Pharmaceutical Co, Bristol–Myers K.K., Astellas Pharmaceutical, Pfizer, Takeda Pharmaceutical and Santen Pharmaceutical. HY has received research grants or lecture fees from AbbVie GK, Bristol-Myers K.K., Chugai Pharmaceutical Co, Eisai Co, Mitsubishi-Tanabe, Astellas, Pfizer, Takeda, UCB Japan and Nippon Shinyaku. KY has received consultancy fees from Abbott, Bristol-Myers K.K., Chugai Pharmaceutical Co, Eisai Co, Mitsubishi-Tanabe, Pfizer, Roche and UCB Pharma, and has received research grants from AbbVie GK, Eisai Co, Mitsubishi-Tanabe, Pfizer, Santen and UCB Japan. TT has received research grants or lecture fees from Astellas Pharma, Bristol-Myers K.K., Chugai Pharmaceutical Co, Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd., AbbVie GK, Asahikasei Pharma Corp., Taisho Toyama Pharmaceutical Co., Ltd., SymBio Pharmaceuticals Ltd., Janssen Pharmaceutical K.K., Celtrion, Nipponkayaku Co. Ltd. and UCB Japan, and consultant fees from Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., Asahi Kasei Medical K.K., Abbvie GK, Daiichi Sankyo Co., Ltd., Bristol–Myers K.K. and Nipponkayaku Co. Ltd.

Patient consent Obtained.

Ethics approval Ethics Committee at each site.

Provenance and peer review Not commissioned; externally peer reviewed.

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