Correlation of Radiographic Progression with the Cumulative Activity of Synovitis Estimated by Power Doppler Ultrasound in Rheumatoid Arthritis: Difference Between Patients Treated with Methotrexate and Those Treated with Biological Agents

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ABSTRACT. ***Objective.*** Our prospective study aimed to demonstrate that the cumulative synovial power Doppler (PD) ultrasound scores correlate with radiographic progression better than conventional measures in patients with rheumatoid arthritis (RA). We also investigated the difference between antirheumatic agents.

Methods. Sixty-nine patients with RA who had recently received either methotrexate (MTX; n = 23), tumor necrosis factor (TNF) antagonists (n = 28), or tocilizumab (TCZ; n = 18) were enrolled. Patients underwent clinical, laboratory, and ultrasonographic assessment at baseline, 12 weeks, and 24 weeks. Radiographic damage was evaluated using van der Heijde modified total Sharp score (TSS) at baseline and 24 weeks.

Results. Fifty-seven patients continued the same treatment regimen for 24 weeks and completed the study, and 21 patients (36.8%) showed radiographic progression during the study period. In all patients, ΔTSS significantly correlated both with cumulative 28-joint Disease Activity Score–C-reactive protein (DAS28-CRP; ρ = 0.342, p = 0.009) and cumulative total PD scores (ρ = 0.357, p = 0.006). In MTX-treated patients, cumulative total PD scores significantly correlated with ΔTSS (ρ = 0.679, p = 0.004), whereas cumulative DAS28-CRP did not (ρ = 0.487, p = 0.056). However, cumulative total PD scores did not correlate with ΔTSS in TNF antagonist–treated or TCZ-treated patients.

Conclusion. Our data confirm the evidence that synovial PD activity more accurately reflects active synovial inflammation (which actually causes joint destruction) than do conventional measures in patients treated with MTX. Our data also indicate that TNF antagonists can inhibit short-term radiographic progression in the presence of active synovitis. (J Rheumatol First Release Nov 1 2013; doi:10.3899/jrheum.130556)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ULTRASONOGRAPHY SYNOVITIS RADIOGRAPHY

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality[1,2]. Over the last decade, the use of disease-modifying antirheumatic drugs (DMARD), in particular methotrexate (MTX) and biological agents, has been shown to improve the clinical outcome of RA[3,4]. To maximize the efficacy and minimize the toxicity and cost of these drugs, accurate monitoring of synovial inflammation is necessary. Although conventional measures such as Disease Activity Score (DAS) have played important roles in clinical studies to establish modern therapeutic strategies for RA, these measures are not accurate enough to efficiently guide antirheumatic therapy in an individual patient.

Ultrasound (US) assessment is more sensitive than clinical joint examination in detecting synovial inflammation, and power Doppler (PD) US visualizes ongoing activity of synovitis[5,6,7,8,9]. Because US can be performed repeatedly at a relatively low cost, therapeutic strategies using US assessment to guide therapy are likely to be established[10]. However, a limited number of studies have demon-

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strated the advantage of US over conventional measures to detect synovitis, the actual cause of structural damage[11,12,13], and the advantage of US has not been compared among different treatment regimens. In our prospective study, we aimed to provide further evidence that the cumulative PD signals in synovial tissues correlate with joint damage progression better than conventional measures, and to explore whether the differences in antirheumatic agents influence the correlation.

MATERIALS AND METHODS

Patients. Patients with an established diagnosis of RA who required treatment with either MTX or a biological agent at the Department of Allergy and Clinical Immunology in Chiba University Hospital were consecutively recruited from January 2008 to December 2009. Sixty-nine patients were enrolled; all fulfilled the American College of Rheumatology (ACR) 1987 RA classification criteria[14]. Patients underwent clinical, laboratory, and US assessment at baseline and at 12 and 24 weeks of followup. Patients also underwent radiographic assessment at baseline and at 24 weeks. The study design was approved by the Ethical Committee of Chiba University and subjects' written informed consent was obtained according to the Declaration of Helsinki.

Clinical, laboratory, and radiographic assessment. Clinical evaluation included comprehensive history taking, routine physical examination, 28 swollen and tender joint counts, and visual analog scale for physician and patient global assessment. Laboratory tests included complete blood cell count, C-reactive protein (CRP), rheumatoid factor (RF), and anticyclic citrullinated peptide antibody (ACPA). Blood specimen was obtained on the day of clinical evaluation. Conventional radiographs of hands and feet were obtained and were read in chronological order by an independent observer who was blinded to patients' identity and clinical, laboratory, and US findings. Radiographic damage was assessed according to the van der Heijde and colleagues' modification of Sharp's method (vdH modified Sharp score)[15,16].

US examination. US was performed in a temperature-controlled room on the same day as clinical evaluation by 2 rheumatologists trained for musculoskeletal US, who were blinded to clinical information and laboratory data. A systematic multiplanar greyscale (GS) and PDUS examination of 28 joint regions (Appendix 1) was performed using either LOGIQ 7 Pro (GE Healthcare), LOGIQ E9 (GE Healthcare), Viamo (Toshiba Medical Systems Corporation), or HI VISION Avius (Hitachi Medical Corporation), depending on availability. The same machine was used for the same patient throughout the study period. For PDUS, pulse repetition frequency was adjusted to the lowest possible value for the anatomic area scanned and for the machine used, and low wall filters were used. Color gain was set just below the level at which color noise appeared.

US findings of GS synovitis and PD positivity were defined according to consensus definitions[17,18,19,20]. We employed the scoring system reported by Naredo, *et al*[13,21]. GS synovitis was graded semiquantitatively on a scale of 0–3 (Grade 0, absent; Grade 1, mild; Grade 2, moderate; Grade 3, marked) for synovial hypertrophy of articular recess, tendon sheath, and bursa. Intraarticular, tenosynovial, and intrabursal PD signals were graded on a semiquantitative scale of 0–3 [Grade 0, absent (no synovial flow); Grade 1, mild (3 or fewer isolated signals); Grade 2, moderate (> 3 isolated signals or confluent signal in less than half of the synovial area); Grade 3, marked (signals in more than half of the synovial area)]. The maximum grades for GS synovitis and synovial PD signal obtained from multiple synovial sites within a joint region were recorded as GS and PD scores for the joint region. Each patient's total GS and PD scores were calculated by summing the corresponding scores of all joint regions.

Intraobserver reliability of US assessment was evaluated by randomly selecting 4 images per each joint region from stored images of baseline US examination. Fifty-six images per sonographer were graded again for GS synovitis and synovial PD signal by the same sonographer under a blinded condition at the end of the study period. Interobserver reliability between sonographers was evaluated with the same sets of images (for a total of 102 images) graded by the other sonographer at the end of the study period.

Statistical analysis. Statistical analysis was performed using SPSS version 16.0J (IBM Japan). Normally distributed continuous data were summarized with means and SD or 95% CI and were analyzed using parametric tests (Student's t test). Non-normally distributed data were summarized with medians and interquartile ranges (IQR) and were analyzed using nonparametric tests (Mann-Whitney U test, Wilcoxon's signed-rank test, or Spearman's rank correlation coefficient). Categorical data were summarized with percentages analyzed using chi-squared test with continuity correction where necessary. P values < 0.05 were considered significant.

The sensitivity to change of clinical and US measures was evaluated using standardized response mean (SRM), which is the ratio of the mean changes to the SD of the changes. Usually, an SRM below 0.2 is considered nil and above 0.6 as relevant[22].

RESULTS

Patient demographics and clinical, laboratory, and radiographic data at baseline. The patient demographics and clinical, laboratory, and radiographic data at baseline are shown in Table 1. Median dose of oral prednisolone at baseline was 2 mg a week (IQR 0–9). Median maximum MTX dose prescribed during study period was 8 mg a week (IQR 6–10). TNF antagonists administered were either etanercept (ETA; 25 mg, twice a week; n = 10), infliximab (3 mg/kg, at 0, 2, 6, 14, 22 weeks; n = 9), or adalimumab (ADA; 40 mg, every other week; n = 9). Proportions of female patients, those with positive rheumatoid factor (RF), positive ACPA, corticosteroid use, and median vdH modified total Sharp scores (TSS) were higher in patients treated with biological agents as compared with those treated with MTX. Disease duration was also longer in those treated with biological agents. On the other hand, 28-joint Disease Activity Score-CRP (DAS28-CRP) and clinical disease activity index (CDAI) were comparable between different treatment groups.

Both total GS score and total PD score at baseline were significantly correlated with DAS28-CRP ($\rho = 0.400$, $p = 0.001$; $\rho = 0.592$, $p < 0.001$, respectively) and CDAI ($\rho = 0.473$, $p < 0.001$; $\rho = 0.639$, $p < 0.001$, respectively) at baseline.

Intraobserver and interobserver reliability of US assessment. Intraobserver and interobserver reliability of GS and PD scores were evaluated by calculating intraclass correlation coefficiency (ICC). As summarized in Appendix 2, ICC for intraobserver reliability of GS and PD scores were very high (0.93 and 0.97, respectively) and ICC for interobserver reliability of GS and PD scores were also high (0.85 and 0.89, respectively). These data suggest that the US data used for analyses were reproducible and reliable. There was no obvious difference in ICC among different US machines used for acquiring those images (data not shown).

Changes in conventional composite scores and US scores

Table 1. Patient demographics, and clinical, laboratory, radiographic, and ultrasound data at baseline, and in combined therapy.

	Total, n = 69	Antirheumatic Agent		
		MTX, n = 23	TNF Antagonist, n = 28	TCZ, n = 18
Age, yr, mean (SD)	54.9 (14.0)	52.5 (14.1)	54.7 (14.7)	58.3 (12.8)
Sex, female, n (%)	40 (73)	15 (64)	22 (78)	13 (75)
Disease duration, month, median (IQR)	35 (17–111)	18 (6–23)	67 (19–153)	84 (33–102)
RF positive, n (%)	56 (81)	17 (74)	24 (86)	15 (83)
ACPA positive, n (%)	50 (73)	13 (57)	23 (82)	14 (78)
CRP, mg/l, median (IQR)	12 (2–30)	17 (2–61)	8.5 (1–23.75)	11.5 (2–37)
DAS28-CRP, mean (SD)	4.4 (1.2)	4.6 (1.2)	4.2 (1.3)	4.4 (1.2)
CDAI, mean (SD)	22.5 (11.7)	23.3 (11.7)	22.4 (12.3)	21.7 (11.5)
vdH modified total Sharp score, median (IQR)	41 (22.5–72)	32 (17–55)	46 (32.25–76.5)	44.5 (24.5–74.25)
Total GS score, median (IQR)	25 (19–31)	21 (17–28)	27 (20–35)	27 (17–38)
Total PD score, median (IQR)	10 (7–14)	9 (8–14)	10 (7.25–16)	10 (5.75–16)
Corticosteroid treatment, n (%)	41 (59)	9 (39)	20 (71)	12 (67)
MTX treatment, n (%)	60 (87)	23 (100)	25 (89)	12 (67)

MTX: methotrexate; TNF: tumor necrosis factor; TCZ: tocilizumab; RF: rheumatoid factor; ACPA: anticyclic citrullinated peptide antibody; CRP: C-reactive protein; DAS: disease activity score; CDAI: Clinical Disease Activity Index; GS: greyscale; vdH: van der Heijde and colleagues' modification of Sharp's method; PD: power Doppler; IQR: interquartile range.

during treatment. Fifty-seven patients continued to take the same medication for 24 weeks and completed the study. Treatment regimen was changed in 3 patients (MTX 1, ADA 1, TCZ 1) before 12 weeks for insufficient efficacy. Treatment regimen was changed between 12 and 24 weeks in 7 patients (MTX 6, ETA 1) for insufficient efficacy and in 1 patient taking ADA for worsening of interstitial lung disease.

Changes in DAS28-CRP, total GS score, and total PD score during treatment are illustrated in Figure 1. The

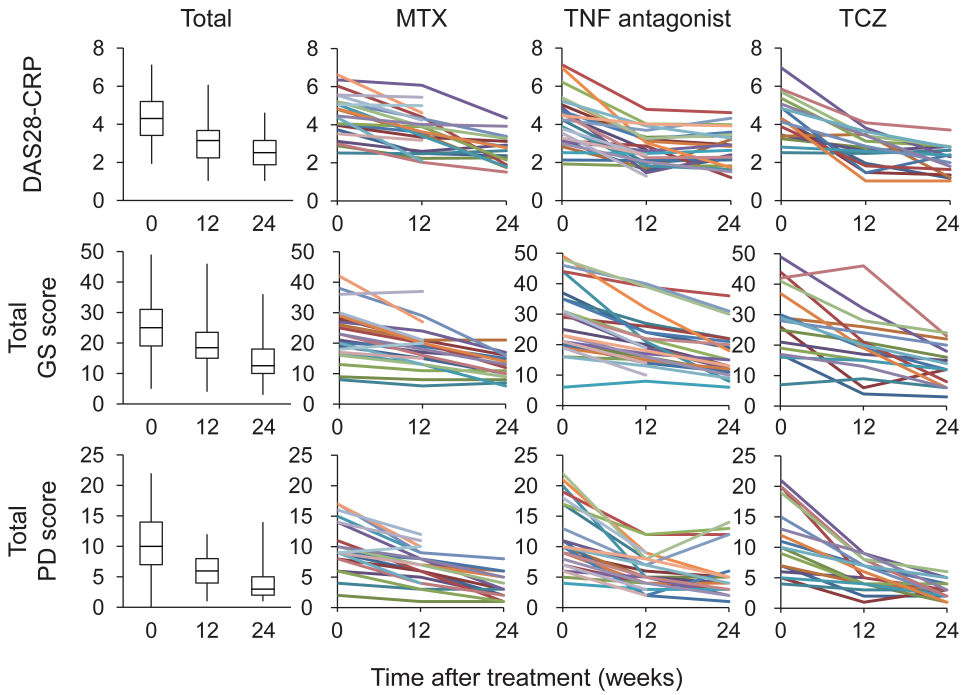

Figure 1. Changes in DAS28, total GS score, and total PD score during treatment. In the left column, data for all patients are shown in box plots (n = 66). A bar in the box represents median, a box represents an interquartile range, and a vertical bar represents a range between maximum and minimum values. In the right 3 columns, data for each treatment group are shown (MTX, n = 22; TNF antagonist, n = 27; TCZ, n = 17). Each line represents an individual patient. MTX: methotrexate; TNF: tumor necrosis factor; TCZ: tocilizumab; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; GS: greyscale; PD: power Doppler.

treatment response was generally good; 19 patients (27.5%) achieved European League Against Rheumatism (EULAR) good response and 27 patients (39.1%) achieved EULAR moderate response at 12 weeks. Changes in US scores between baseline and 12 weeks significantly correlated with those in DAS28-CRP and CDAI during the same period (Appendix 3). Although total PD score seems to respond most rapidly to potent therapy (Figure 1), SRM for PD score between baseline and 12 weeks were comparable to those for DAS28-CRP (Table 2). On the other hand, the absolute values of SRM for PD scores were greater than those for CDAI in all treatment groups. These results suggest that US measures, especially PD score, are at least as responsive to change of therapy as conventional composite measures.

Correlations between radiographic progression and disease activity measures. Appendix 4 shows the probability plot for radiographic progression during 6 months of the study period. Twenty-one patients (36.8%) experienced a radiographic progression of 1 point or greater.

To examine the longitudinal and cumulative effect of synovial inflammation assessed by different measures on joint damage progression, we calculated the total sum of each DAS during the study period (baseline, 12 weeks, 24 weeks) and analyzed the correlations between these cumulative values and the changes in the radiographic score during the same period (Figure 2). When analyzed for all patients (left column of Appendix 4), both cumulative DAS28-CRP scores and cumulative total PD scores significantly correlated with the changes in TSS (ΔTSS). Unexpectedly, strength and statistical significance of the correlations were equivocal between DAS28-CRP and total PD score. The correlation between cumulative total GS scores and ΔTSS was not statistically significant.

We performed the same analyses also in subgroups with different treatment regimens (Figure 2). In the MTX-treated group, cumulative total PD scores, but not GS scores or DAS28-CRP scores, significantly correlated with ΔTSS. However, the correlation between cumulative total PD scores and ΔTSS was not statistically significant in the groups treated with biological agents. Particularly in the TNF antagonist-treated group, radiographic progression was minimal [median 0 (IQR –1–0)] even though the cumulative values for total PD scores were comparable to the other groups.

We also compared these cumulative values between patients who experienced radiographic progression and those who did not. As shown in Figure 3, both cumulative DAS28-CRP and cumulative total PD scores were significantly greater in patients with no radiographic progression (ΔTSS < 0) than in those with progression (ΔTSS ≥ 1). P value for the difference was numerically smaller for cumulative total PD score [median 23 (IQR 20–32) vs median 17 (IQR 13–22.75), p = 0.004] than that for cumulative DAS28-CRP [median 11.7 (IQR 9.0–12.4) vs median 8.6 (IQR 7.4–11.0), p = 0.010]. Receiver-operating characteristic (ROC) analysis to identify patients with radiographic progression demonstrated the larger area under the curve for cumulative total PD score than that for cumulative DAS28 score, although the difference was not statistically significant (Appendix 5, left column).

In subgroup analyses for each treatment regimen (aure 3), cumulative total PD scores, but not cumulative DAS28-CRP or cumulative total GS scores, were significantly greater in patients with radiographic progression than those in patients with no radiographic progression in MTX-treated groups [median 23 (IQR 21–32) vs median 17 (IQR 10–20.5), p = 0.023]. However, the difference in cumulative total PD scores between groups with and without radiographic progression was not statistically significant in patients treated with biological agents [TNF antagonists, median 23 (IQR 17–35) vs median 19 (IQR 14–25), p = 0.209; TCZ, median 24 (IQR 19–30) vs median 14.5 (IQR 10.75–23.5), p = 0.133]. In addition, ROC analysis demonstrated the advantage of total PD score over DAS28-CRP in the prediction of radiographic progression only in MTX-treated patients (Appendix 5, right 3 columns).

Finally, we calculated the specificity, positive predictive value (PPV), and negative predictive value (NPV) for cumulative DAS28-CRP and cumulative total GS and PD scores to predict nonradiographic progression using the optimized cutoff point determined by the ROC analysis (Table 3). Total PD scores provided increased specificity, PPV, and NPV as compared with DAS28-CRP in the MTX-treated patients, whereas the predictive values of total PD score were not superior to DAS28-CRP in the biologics-treated patients.

Table 2. Standardized response means (SRM) for each measurement between baseline and 12 weeks.

Measurement	Total, n = 66	Antirheumatic Agent		
		MTX, n = 22	TNF Antagonist, n = 27	TCZ, n = 17
DAS28-CRP	–1.37	–1.36	–1.52	–1.49
CDAI	–1.20	–1.43	–1.24	–1.18
Total GS score	–1.17	–1.19	–1.48	–1.05
Total PD score	–1.37	–1.48	–1.53	–1.40

MTX: methotrexate; TNF: tumor necrosis factor; TCZ: tocilizumab; DAS28: 28-joint disease activity score; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; GS: greyscale; PD: power Doppler.

DISCUSSION

Dougados, *et al* conducted a prospective multicenter study to compare the US scoring systems and clinical examination and showed that the sensitivity to change of US is comparable to that of clinical examination by calculating SRM in patients treated with anti-TNF therapy[23]. In accordance with

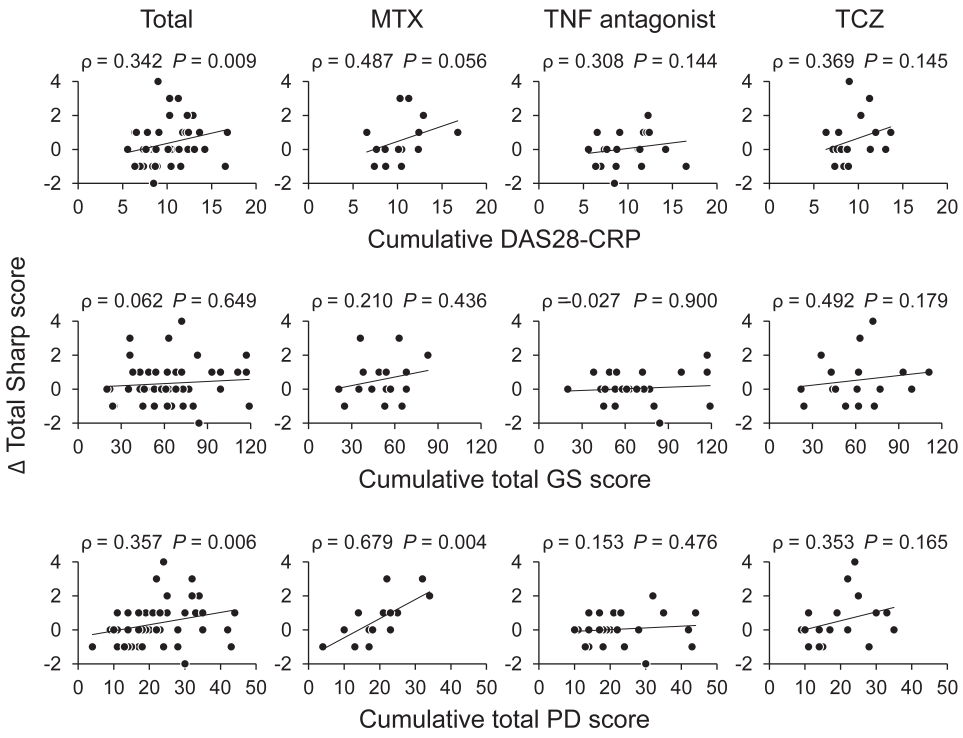

Figure 2. Correlation between cumulative disease activity scores and changes in radiographic damage during 24 weeks. In the left column, data for all patients are shown (n = 57). In the right 3 columns, data for each treatment group are shown (MTX, n = 16; TNF antagonist, n = 24; TCZ, n = 17). The Spearman's rank correlation coefficient and the corresponding p value are shown above each scatter plot. MTX: methotrexate; TNF: tumor necrosis factor; TCZ: tocilizumab; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; GS: greyscale; PD: power Doppler.

the report, the absolute values of SRM for US measures were not greater than those for DAS28-CRP in our study. Composite measures such as DAS28 consist of multiple components, which often simultaneously increase or decrease and amplify the change. Our data, together with the previous report, indicate that the major additional benefit of US as compared with the conventional measures in monitoring disease activity of RA is not the increased responsiveness to the change in the activity of synovitis.

Naredo, *et al* reported that the cumulative synovial PD activity during 12 months significantly correlated with radiographic progression (correlation coefficient 0.59, $p < 0.001$), while other measures such as DAS28 did not, in 38 patients with early RA who started therapy with conventional DMARD[11]. Although the high sensitivity of US in detecting the presence of synovitis had been reported by other research groups, the study by Naredo, *et al*, for the first time, to our knowledge, demonstrated that PDUS provides improved accuracy in the evaluation of pathogenic synovitis (which actually causes structural damage) and provided the evidence to support the use of PDUS in monitoring disease activity or evaluating response to therapy. Although the significant correlation of PDUS with radiographic progression has been shown in several other studies since then[8,12,13,24], no study, to our knowledge, has reproduced the superiority of PDUS to conventional measures in monitoring response to conventional DMARD at an individual patient level. Our data in the MTX-treated group add to the evidence provided by Naredo, *et al*, although our data were less powered, with a smaller sample size and a shorter observation period.

In the double-blinded randomized trials in early RA, TNF antagonists inhibited short-term radiographic progression in small joints even when disease activity did not sufficiently improve, while inhibition of structural damage was dependent on the clinical response in MTX arms[25,26,27,28]. Our study demonstrated for the first time the inhibition of radiographic progression that is independent of PD activity in patients with active RA treated with TNF antagonists. Because synovial PD signals more objectively and specifically represent inflammation than conventional measures do, the disease activity-independent inhibition of joint damage observed in our study could not be explained by a possibly high prevalence of noninflammatory conditions in those patients who did not sufficiently respond to TNF antagonists. Instead, the observation probably represents a property of TNF antagonists against structural damage that is independent of synovial inflammation, where the direct effect of TNF-α on the osteoclast differentiation could be involved[29,30,31,32,33,34]. Although a similar

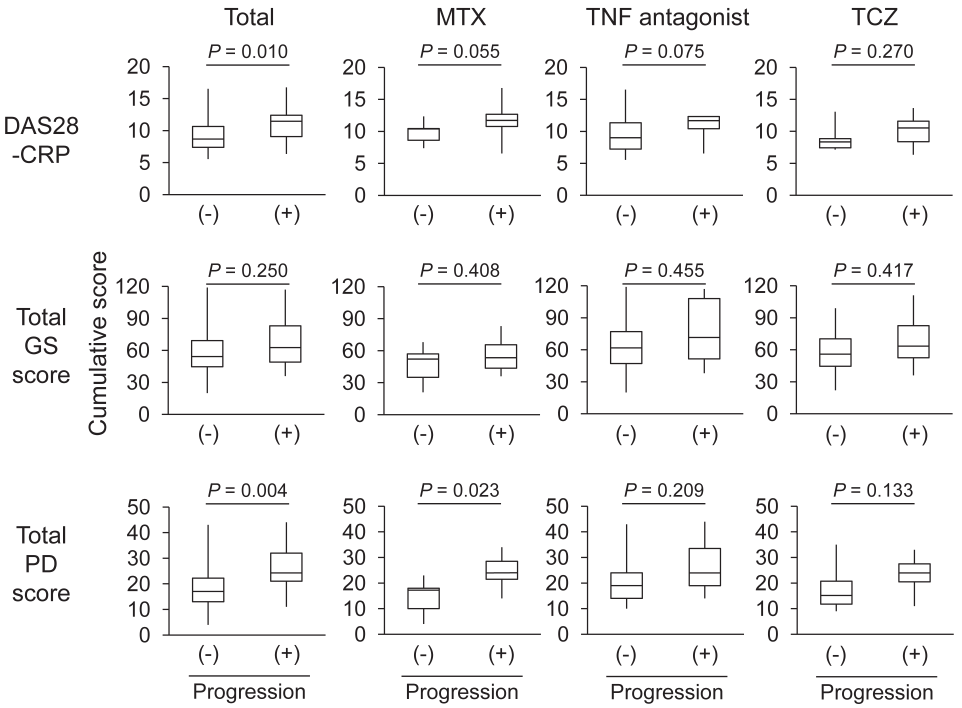

Figure 3. Difference in the cumulative disease activity scores between patients with and without radiographic progression during 24 weeks. In the left column, data for all patients are shown (n = 57). In the right 3 columns, data for each treatment group are shown (MTX, n = 16; TNF antagonist, n = 24; TCZ, n = 17). Radiographic progression is defined as a change of 1 point or greater in van der Heijde modified total Sharp score. The p value for Mann-Whitney U test is shown above each comparison. MTX: methotrexate; TNF: tumor necrosis factor; TCZ: tocilizumab; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; GS: greyscale; PD: power Doppler.

Table 3. Sensitivity, specificity, PPV, and NPV for the cumulative DAS28-CRP and total PD score to predict nonradiographic progression.

Treatment Regimen	Disease Activity Measures	Cutoff (average)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Total, n = 57	DAS28-CRP	< 9.0 (3.0)	64	81	85	57
	Total GS score	< 62 (20.7)	56	57	69	43
	Total PD Sore	< 21 (6.8)	69	76	83	59
MTX, n = 16	DAS28-CRP	< 10.8 (3.6)	89	71	80	83
	Total GS score	< 60 (20.0)	78	43	64	60
	Total PD Sore	< 20 (6.5)	89	86	86	89
TNF antagonist, n = 24	DAS28-CRP	< 11.9 (4.0)	88	71	88	71
	Total GS score	< 70 (23.3)	65	57	79	40
	Total PD Sore	< 21 (6.8)	65	71	85	46
TCZ, n = 17	DAS28-CRP	< 9.0 (3.0)	80	71	80	71
	Total GS score	< 62 (20.7)	60	71	75	56
	Total PD Sore	< 18 (6.0)	70	86	88	67

PPV: positive predictive value; NPV: negative predictive value; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; GS: greyscale; PD: power Doppler; MTX: methotrexate; TNF: tumor necrosis factor; TCZ: tocilizumab.

mechanism has been reported for interleukin 6 (IL-6)[35], the data of our small-scale study are insufficient to provide evidence for the inflammation-independent inhibition of radiographic progression by IL-6-blocking therapy.

Because antirheumatic therapy should be escalated or changed until the treatment goal is achieved according to the treat-to-target approach[36], appropriate definition of remission or acceptable minimal disease activity has

become increasingly important. Although the ACR/EULAR joint committee developed the new remission criteria based on the data from several cohorts, the provisional criteria demonstrate unsatisfactory accuracy to apply to the individual patient, with PPV and NPV of the criteria to predict nonprogression of radiographic damage being 77% and 49%, respectively, in patients treated with MTX[37]. Possible explanations for the low NPV would include a limited specificity of clinical examination in detecting synovitis, noninflammatory causes affecting patient global assessment, and nonrheumatic inflammation affecting CRP levels. The data from our study using cumulative values suggest that PDUS may provide remission criteria with an improved accuracy in MTX-treated patients.

Our data also suggest that the treatment target of RA should be modified to take into account the class of treatment. The data indicate that the optimized cutpoint for a certain measure should be determined differently for the different class of drug and that US may not provide additional benefit in evaluating disease activity to achieve structural remission in TNF antagonist-treated patients. Clinical remission or even low disease activity might be acceptable to prevent joint damage when the TNF antagonist is not intended to be discontinued. Indeed, the lack of additional benefit with US to predict joint damage progression in patients receiving a TNF antagonist was recently reported[38].

Our study has several limitations. First, this observational study was primarily designed to reproduce the more significant correlation of joint damage progression with cumulative PD signals than that with conventional measures in total patients. Therefore, the number of subjects was not large enough to provide the statistical power for exploratory subgroup analyses between treatment groups. A larger cohort would have provided more reliable data and allowed for more detailed comparisons. In fact, a multivariate regression model of a much larger cohort identified the cumulative PD activity as a significant predictor of radiographic progression in patients receiving a TNF antagonist, although the predictive value was not compared with that in non-TNF antagonist-treated patients[13]. Nevertheless, the comparison between conventional DMARD and TNF antagonists in the same study had not been reported and the difference demonstrated in our study seems to be meaningful especially when the treatment group with a larger number (i.e., greater statistical power) shows a nonsignificant result.

Second, because our study is not a controlled one, the direct comparison between treatment regimens is theoretically difficult. However, the much less radiographic progression in the presence of PD activity observed in the patients treated with TNF antagonists as compared to those treated with MTX was not likely due to the background difference, because the biologics-treated group had higher prevalence of known risk factors of radiographic progression such as positive RF and ACPA and advanced radiographic damage. In addition, the shorter disease duration and the less frequent use of corticosteroid in the MTX-treated group were not likely to be confounding factors because significant correlation was identified neither between disease duration and ΔTSS ($\rho = 0.080$, $p = 0.553$), between corticosteroid dose at baseline and ΔTSS ($\rho = 0.096$, $p = 0.475$), nor between corticosteroid dose and DAS28-CRP at baseline ($\rho = 0.012$, $p = 0.919$; data not shown).

Third, because this was a single-center study with Japanese patients under Japanese regulations (e.g., low dose of MTX approved by the government), our data may not be globally generalized. Although our data were not contradictory to the previously reported data, further investigation is needed to confirm the reproducibility and generalizability.

In addition, the machine difference between patients could have influenced our data. However, the machines were randomly assigned and we did not find any particular trend in the proportion of machines between treatment groups (data not shown). In our previous study, semiquantitative PD grades but not PD pixel counts were comparable between modern machines recommended by manufacturers for musculoskeletal US[39]. Our current study using several different machines is likely to reflect real-life practice and suggests that the data from previous studies could be used in daily practice.

Our data confirm the evidence that synovial PD activity more accurately reflects active synovial inflammation (which actually causes joint destruction) than conventional measures do in patients treated with MTX. Our data also support the notion that TNF antagonists could inhibit short-term radiographic progression in the presence of active synovitis in RA, and may provide information for the future development of an individualized strategy to prevent structural damage in RA patients receiving different classes of DMARD.

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APPENDIX 1. Intraarticular and periarticular synovial sites evaluated by ultrasound.

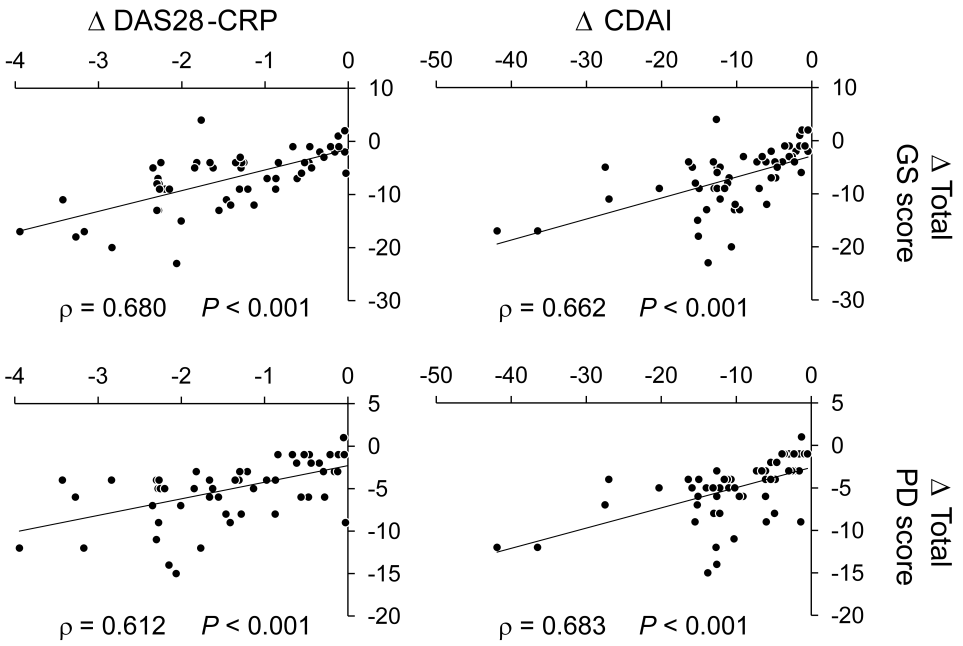
Joint Region	Joint/Tendon Sheath/Bursa	Scanned Site
Finger	IP, PIP (2–5), MCP (1–5)	Dorsal aspect
		Medial aspect (IP/PIP, MCP5)
		Lateral aspect (IP/PIP, MCP 1/2)
		Volar aspect
	Flexor digitorum tendon	Volar aspect
Wrist	Radiocarpal joint	Dorsal aspect
	Intercarpal joints	Dorsal aspect
	Distal radioulnar joint	Dorsal aspect
	Compartment II/IV/VI of extensor tendons	Dorsal aspect
Elbow	Humeroradial joint	Anterior aspect
		Lateral aspect
	Humeroulnar joint	Anterior aspect
		Lateral aspect
		Posterior aspect (Olecranon fossa)
	Olecranon bursa	Posterior aspect
Shoulder	Glenohumeral joint	Posterior aspect
	Long head of biceps tendon	Anterior aspect
	Subacromion/subdeltoid bursa	Anterior aspect
		Lateral aspect
Knee	Femorotibial joint	Anterior aspect
		(Suprapatellar recess)
		Medial aspect
		Lateral aspect
	Popliteal bursa (Baker's cyst)	Posterior aspect

IP: interphalangeal joint; PIP: proximal interphalangeal joint; MCP: metacarpophalangeal joint.

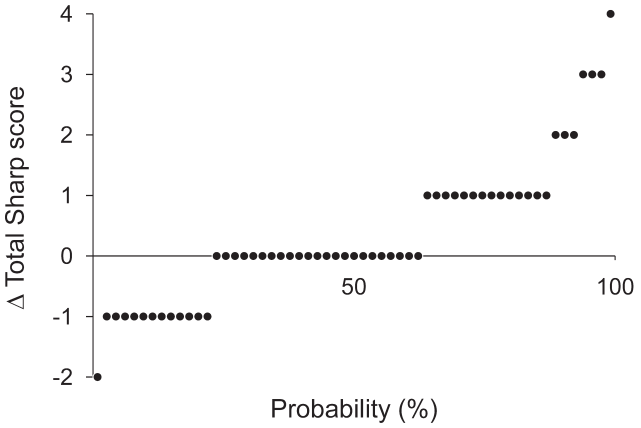
APPENDIX 2. Intraclass correlation coefficiency (ICC) for intraobserver and interobserver reliability.

	Intraobserver Reliability (ICC 95% CI)		Interobserver Reliability (ICC 95% CI)	
Joint Region	Greyscale	Power Doppler	Greyscale	Power Doppler
PIP (IP)	0.91 (0.87–0.95)	0.96 (0.94–0.99)	0.82 (0.75–0.89)	0.90 (0.87–0.93)
MCP	0.95 (0.92–0.98)	0.98 (0.97–0.99)	0.88 (0.86–0.90)	0.92 (0.88–0.94)
Wrist	0.91 (0.87–0.95)	0.96 (0.94–0.98)	0.81 (0.76–0.85)	0.88 (0.85–0.91)
Elbow	0.94 (0.91–0.97)	0.98 (0.96–0.99)	0.88 (0.86–0.90)	0.89 (0.85–0.93)
Shoulder	0.90 (0.87–0.93)	0.98 (0.97–0.99)	0.87 (0.83–0.90)	0.90 (0.87–0.93)
Knee	0.94 (0.91–0.97)	0.96 (0.94–0.98)	0.81 (0.76–0.85)	0.88 (0.84–0.91)
Total	0.93 (0.90–0.97)	0.97 (0.95–0.99)	0.85 (0.82–0.89)	0.89 (0.87–0.91)

PIP: proximal interphalangeal joint. IP: interphalangeal joint; MCP: metacarpophalangeal joint.



APPENDIX 3. Correlation between changes in composite scores and ultrasound scores during 12 weeks. Spearman's rank correlation coefficient and the corresponding p value are shown below each scatter plot. DAS28: 28-joint Disease Activity Score; CDAI: Clinical Disease Activity Index; GS: greyscale; PD: power Doppler.



APPENDIX 4. Probability plot for changes in the van der Heijde modified total Sharp score during 24 weeks. Each dot represents an individual patient.

APPENDIX 5. Areas under the ROC curves for the cumulative disease activity score to predict radiographic progression.

Disease Activity Measures	Total, n = 57	MTX, n = 16	Antirheumatic Agent TNF Antagonist, n = 24	TCZ, n = 17
DAS28-CRP	0.71 (95% CI 0.55–0.86)	0.79 (95% CI 0.53–1.06)	0.74 (95% CI 0.50–0.98)	0.67 (95% CI 0.38–0.96)
Total GS score	0.59 (95% CI 0.44–0.75)	0.64 (95% CI 0.36–0.92)	0.61 (95% CI 0.33–0.88)	0.62 (95% CI 0.34–0.91)
Total PD score	0.73 (95% CI 0.60–0.86)	0.84 (95% CI 0.64–1.04)	0.67 (95% CI 0.43–0.91)	0.73 (95% CI 0.47–0.98)

ROC: receiver-operating characteristic; MTX: methotrexate; TNF: tumor necrosis factor; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; GS: greyscale; PD: power Doppler; TCZ: tocilizumab.