Ultrasonography predicts achievement of Boolean remission after DAS28-based clinical remission of rheumatoid arthritis

Ryusuke Yoshimi¹, Maasa Hama¹, Kaoru Minegishi¹, Daiga Kishimoto¹, Toshiyuki Watanabe¹, Reikou Kamiyama¹, Yohei Kirino¹, Yukiko Asami¹, Atsushi Ihata¹, Shinichiro Tsunoda¹,², Atsuhisa Ueda¹, Mitsuhiro Takeno¹, and Yoshiaki Ishigatsubo¹

¹Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan and ²Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

Abstract

Objective. To determine whether ultrasonography (US) predicts Boolean remission in rheumatoid arthritis (RA) patients who had achieved disease activity score in 28 joints (DAS28)-based remission criteria.

Methods. Thirty-one RA patients in DAS28-based clinical remission were recruited. US semiquantitatively determined Gray scale (GS) and power Doppler (PD) signal scores in the bilateral wrists and all metacarpophalangeals and proximal interphalangeals. Total GS score and total PD score were calculated as the sum of individual scores for each joint.

Results. Among 22 RA patients, who maintained DAS28 remission for 2 years, 16 met Boolean remission criteria at the end of study. Both total GS and total PD scores at baseline were significantly lower in Boolean remission group than non-remission group. There was no significant difference in other baseline parameters, including duration of disease, duration of remission, mTSS, and disease activity composite parameters between the two groups. Among the factors for Boolean remission criteria at 2 years, patient global assessment score was associated with total GS score at the entry, while swollen joint count was related to total PD score.

Conclusions. Null or low grade of GS and PD findings in US are associated with achieving Boolean remission. Thus, US is essential for assessment and prediction of ‘deeper remission’ of RA.

Introduction

As therapy advancement has improved the management of rheumatoid arthritis (RA), “clinical remission” has become a realistic goal in daily practice during the past decade [1]. Because different sets of remission criteria for RA have been proposed, the quality of clinical remission relies on which criteria are applied. Although disease activity score in 28 joints (DAS28) have been widely used not only in clinical trials but also daily practice [2], several reports have shown that radiographic damage progresses even in some patients who met the DAS28-defined remission [3,4], suggesting that the remission criteria are not necessarily adequate as a clinical goal. To this end, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) recently proposed a simplified disease activity index (SDAI) and the Boolean-based definition to determine clinical remission in clinical trials and daily practice [5]. As joint progression in persistent remission has been shown to be reduced by stringency of remission, development of predictive factors for achieving deeper remission is expected.

Musculoskeletal ultrasonography (US) has been established as a new imaging modality for assessing inflamed joints of patients with RA during the past decade [6–9]. US, which is capable of directly visualizing and objectively quantifying synovial inflammation, is more sensitive and reliable than physical examination for detecting subclinical synovitis in RA [10–15]. Persistent power Doppler (PD) signal-positive synovitis is associated with high risk of relapse and radiographic progression even in patients who are classified as clinical remission [14–16].

There is still controversy over the association between detection rate of US findings and stringency of remission criteria. While a couple of studies have demonstrated that PD-positive synovitis is more commonly found in patients in DAS28 remission than those in more stringent new ACR/EULAR criteria [17,18], another study has shown that the prevalence of PD signals is comparable between the two sets of remission criteria [19]. Thus it is unclear whether US findings predict subsequent deepening of the degree of remission, which should be encouraged for tight control.

We examined US findings in patients achieving persistent DAS28 remission and subsequently monitored the patients for 2 years to ask whether baseline US findings predict future achievement of Boolean remission.

Patients and methods

Patients and treatment

Thirty-one RA patients were included in this longitudinal study. All patients fulfilled the 1987 American Rheumatism Association...
revised criteria for the classification of RA and clinical remission criteria using DAS28-erythrocyte sedimentation rate (ESR) or DAS28-C-reactive protein (CRP) for at least 2 months [2,20]. Patients were recruited at the rheumatology outpatient clinic of Yokohama City University from July, 2008 to April, 2009. Twenty-eight patients were treated with conventional disease-modifying antirheumatic drugs (DMARDs) including methotrexate (MTX; mean dose 6.7 ± 2.2 mg/week), sulfasalazine and tacrolimus. Thirteen patients received treatment with biologics (in combination with MTX). Nine of them received etanercept and four patients were treated with infliximab. All these TNF inhibitors were used according to the dosages approved for the treatment of RA. Nine patients were treated with prednisolone (PRL) at dosages of 1–5 mg/day (mean dose 2.4 ± 1.2 mg/day). In principle, therapy was not modified during the study, unless the patients had a clinical flare-up. 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

At each visit (one- to three-month intervals), patients were evaluated clinically by 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 for each patient. Serum concentration of CRP, ESR, matrix metalloproteinase-3 (MMP-3) and rheumatoid factor (RF) were measured. Disease activity was assessed both by DAS28-ESR and by DAS28-CRP [21] because some cases showed large discrepancy between DAS28-ESR and DAS28-CRP [22,23], which could be caused by confounding factors such as age, sex, fibrinogen levels, hypergammaglobulinemia, RF and anemia [24,25]. A patient was considered to be in clinical remission if DAS28-ESR was less than 2.6 or DAS28-CRP was less than 2.3. Boolean remission criteria, which required a score of 1 or lesser for individual core set measures, comprising tender joint count (TJC), swollen joint count (SJC), CRP level (in mg/dl), and PGA (in cm), was also used for assessment of disease activity [5].

US assessment

Musculoskeletal US was performed at entry by experienced rheumatologists. They were blind to the clinical, laboratory, and radiographic findings. An Aplio SSA-700A (Toshiba, Tokyo, Japan) with 12-MHz linear array transducers was used in this study. The ultrasound scanning method, including parameter settings, has been described previously [26–29]. Of the 28 joints, 22 (excluding bilateral glenohumeral, elbow, and knee joints) were assessed by US to be compared with hand X-ray films. 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 scored semiquantitatively from 0 to 3 (0: none; 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 [10]. For PIP and MCP joints, gray scale (GS) images were scored semiquantiatively from 0 to 3 (0: none [no synovial thickening]; 1: mild [filling the angle between the periarticular bones without bulging over the line linking tops of the bones]; 2: moderate [synovial thickening bulging over the line linking tops of the periarticular bones but without extension along the bone diaphysis]; and 3: severe [synovial thickening bulging over the line linking tops of the periarticular bones and with extension to at least one of the bone diaphyses]) in each joint according to the definition by Szkudlarek et al. [30]. For wrists, GS images were scored semiquantitatively from 0 to 3 (0: none; 1: mild; 2: moderate; and 3: severe) on subjective appraisal. Total PD and GS scores were calculated as the sums of individual scores for each joint at each examination. The intraobserver and interobserver reliabilities were described previously [31].

Radiographic assessment

A rheumatologist who was unaware of the clinical and ultrasound findings measured structural damage of the hands at baseline and at 2 years by using the van der Heijde modification of the Sharp score (mTSS) excluding the evaluation of foot joints. The mTSS (with a maximum possible score of 280) was composed of the erosion score (maximum possible 160) plus the joint space narrowing score (maximum possible 120) [32]. The intraobserver intraclass correlation coefficient for the mTSS of each joint was described previously [16].

Statistical analysis

The data are reported as mean ± standard deviation (SD). Normally distributed continuous data were analyzed using the non-paired t-test. Non-normally distributed and ordinal data were analyzed using Mann–Whitney U test. Categorical data were analyzed using the Fisher’s exact probability test. Receiver operating characteristic (ROC) analysis was used to determine the cutoff point with maximum sensitivity and specificity in total GS score and total PD score. The calculation of the CI of the area under the curve (AUC) was performed using the method of DeLong et al. [33]. p Values less than 0.05 were considered to be statistically significant.

Results

Patient characteristics

Among 31 patients, 22 patients maintained clinical remission during the 2-year follow-up, while four dropped out and five had clinical flare-ups during the study (Figure 1a). The main baseline clinical, laboratory and US characteristics of the clinical remission cohort are detailed in the previous paper [16]. At the entry, 11 patients had achieved Boolean remission criteria (50%). After the 2-year follow-up, 16 of 22 patients who maintained clinical remission met the Boolean remission criteria (73%), including 10 of 11 patients who had met the Boolean remission criteria at the entry (Figure 1a and Table 1). There was no significant difference in age, sex, disease duration, remission duration, clinical stage, and mTSS at study entry between patients achieving the Boolean remission at the endpoint and the others (Table 1).

There was no significant difference in therapeutic regimens between the two groups, except higher frequency of PSL usage in the Boolean remission group (44%) than non-Boolean remission group (17%). As shown in Figure 1b, no significant difference was found in usage of DMARDs including biologics and MTX ($\chi^2 = 1.59, p = 1.00$). Biologics and MTX were given to 44% and 100% of the Boolean remission group and 50 and 81% of non-Boolean remission group, respectively. No significant difference was found in doses of MTX between the two groups (Boolean remission 6.31 ± 2.05 mg/week vs. non-Boolean remission 7.08 ± 2.05 mg/week, $p = 0.66$). The similar results were also seen when we included the cases with DAS28-based clinical relapse during
**Figure 1.** Patient characteristics. (a) Patient disposition of the study. (b) Therapeutic regimen of 22 patients who maintain DAS28 remission for 2 years.

**Table 1.** Baseline demographic, clinical, US, and laboratory features of patients in Boolean remission group and non-Boolean remission group.

| Baseline variable         | Boolean remission at the endpoint (n = 16) | Non-Boolean remission at the endpoint (n = 6) | p value |
|---------------------------|--------------------------------------------|------------------------------------------------|---------|
| Age (year)                | 57.3 ± 11.3a                               | 55.3 ± 11.9a                                  | 0.74    |
| Sex                       | M: 4, F: 12                                | M: 0, F: 6                                    | 0.54    |
| Duration of RA (month)    | 87.9 ± 50.7b                               | 70.3 ± 22.8b                                  | 0.96    |
| Duration of remission (month) | 21.5 ± 19.0a                     | 17.8 ± 13.8a                                  | 0.93    |
| Stage                     | I: 5, II: 7, III: 2, IV: 2                 | I: 0, II: 4, III: 1, IV: 1                    | 0.28    |
| nTSS                      | 12.4 ± 11.9a                               | 33.8 ± 33.4a                                  | 0.14    |
| Total PD score            | 1.06 ± 1.14a                               | 6.33 ± 6.99a                                  | 0.020*  |
| Total GS score            | 7.75 ± 6.02a                               | 16.0 ± 11.3a                                  | 0.012*  |
| DAS28-CRP                 | 1.59 ± 0.52b                               | 1.66 ± 0.34b                                  | 0.76    |
| DAS28-ESR                 | 1.97 ± 0.59b                               | 2.23 ± 0.50b                                  | 0.38    |
| Boolean remission         | 10 (63%)                                   | 1 (17%)                                       | 0.15    |
| SIC                       | 0.38 ± 0.60a                               | 1.33 ± 1.11a                                  | 0.060   |
| TJC                       | 0.25 ± 0.43a                               | 0.33 ± 0.47a                                  | 1.00    |
| PGA (mm)                  | 10.6 ± 9.45a                               | 10.2 ± 4.74a                                  | 0.87    |
| CRP (mg/dl)               | 0.13 ± 0.16a                               | 0.04 ± 0.01a                                  | 0.17    |
| ESR (mm/h)                | 11.6 ± 6.65a                               | 16.3 ± 17.7a                                  | 0.39    |
| MMP-3 (ng/ml)             | 98.5 ± 105a                                | 51.8 ± 12.1a                                  | 0.32    |
| RF (U/ml)                 | 85.6 ± 90.7b                               | 54.1 ± 52.5a                                  | 0.49    |

*a The data are shown as mean ± SD.
b Measured in 15 patients in Boolean remission group and 5 patients in non-Boolean remission group.

**Association of low score of US parameters at baseline with achievement of Boolean remission**

As shown in Table 1, both US parameters, total GS and total PD scores, at baseline were significantly lower in patients with Boolean remission than without Boolean remission at 2 years (7.75 ± 6.02 vs 16.0 ± 11.3, p = 0.012, and 1.06 ± 1.14 vs 6.33 ± 6.99, p = 0.020). The similar results were observed when we included the cases with DAS28-based clinical relapse during 2 years in the non-Boolean remission group (Supplementary Table 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2013.857800). Additionally, we compared the baseline US parameters between the clinical relapse group and the Boolean remission group. Although there was no significant difference in total GS score (9.40 ± 2.58 vs 7.75 ± 6.02, p = 0.23), total PD score was significantly higher in the clinical relapse group as compared with the Boolean remission group (4.60 ± 3.01 vs 1.06 ± 1.14, p = 0.015).

As shown in Figure 2a, distribution of total GS score revealed a clear difference between the Boolean remission group and the non-Boolean remission group. The cutoff values for total GS score calculated from the ROC curve was total GS scores ≥ 8, and the area under the ROC curve was 0.82 (95% CI = 0.60 to 0.95, p = 0.0004;
Figure 2. US parameters at baseline and Boolean remission at 2 years. (a) Number of patients with or without Boolean remission at 2 years in each total GS score at baseline. (b) ROC curve for the total GS score. An open dot indicates the case that the cut-off value of total GS score is between 7 and 8. (c) Number of patients with or without Boolean remission at 2 years in each total PD score at baseline. (d) ROC curve for the total PD score. An open dot indicates the case that the cut-off value of total GS score is between 2 and 3. (e) Number of patients with or without Boolean remission at 2 years in each optimal US combination score at baseline. The optimal combination score is calculated as the sum of total GS score and three times total PD score. (f) ROC curve for the optimal US combination score. An open dot indicates the case that the cut-off value of combination score is between 16 and 17. In (a), (c) and (e), gray zones indicated under the cut-off values.

Figure 2b). Indeed, all 11 patients having a total GS score of \( \leq 7 \) at baseline US achieved Boolean remission 2 years later, whereas 6 of 11 patients having a total GS score of \( \geq 8 \) failed (Figure 2a). The cutoff condition provided 100% sensitivity (95% CI = 54.1 to 100) and 68.8% specificity (95% CI = 41.3 to 89.0) for Boolean remission at 2 years, with a positive predictive value of 54.5% and a negative predictive value of 100%.

Similar findings were also observed in total PD scores (Figure 2c). ROC analysis determined that the cutoff value for total PD score was total PD scores \( \geq 3 \) and that the AUC was 0.82 (95% CI = 0.60 to 0.95, \( p = 0.013 \); Figure 2d). The cut-off point provided 66.7% sensitivity (95% CI = 22.3 to 95.7) and 93.8% specificity (95% CI = 69.8 to 99.8) for Boolean remission at 2 years, with a positive predictive value of 80.0% and a negative predictive value of 88.2%. Thus, the data indicate that low total GS and PD scores are associated with achievement of Boolean remission in the near future.

Next, we investigated the optimal US combination score derived from total GS score and total PD score. Various combination scores were calculated by the following formula, with a different combination of coefficients \( a \) and \( b \), and the ROC analyses were performed.

\[
\text{US combination score} = a \times \text{total GS score} + b \times \text{total PD score}
\]

All conditions examined showed the higher levels of AUC than total GS score or total PD score alone (Table 2). Among them, the AUC showed the highest value when coefficients \( a \) and \( b \) were 1 and 3, respectively. Under that optimal condition, the cutoff value was \( \geq 17 \) and that the AUC was 0.87 (95% CI = 0.66 to 0.97, \( p < 0.0001 \); Figure 2f). The cutoff point provided 83.3% sensitivity (95% CI = 35.9 to 99.6) and 87.5% specificity (95% CI = 61.7 to 98.4) for Boolean remission at 2 years (Figure 2e).

Relationship between baseline total GS score and Boolean remission criteria

To characterize clinical features in patients who had low total GS scores, we divided 22 patients, who maintained DAS28-based clinical remission for 2 years, into two groups by using the cutoff score; 11 patients having the lower total GS score (total GS score \( \leq 7 \)) and 11 patients with higher total GS score (total GS score \( \geq 8 \)) (Table 3). At baseline, there was no significant difference in age, sex, disease duration, remission duration, DAS28-CRP, DAS28-ESR, rate of Boolean remission, SJC, TJC, and laboratory data between the two groups, except for advanced clinical stage and higher mTSS in the higher total GS score group.

DAS28-CRP at 2 years was significantly lower in the lower total GS score group at baseline, in concordance with a close association.
between low GS score and higher frequency of achieving Boolean remission 2 years later. In individual components in Boolean remission criteria at 2 years, SJC, TJC, PGA, but not CRP, were significantly lower in the lower total GS score group. Of them, no significant difference was found in the change of mTSS during 2 years between the lower total GS score group showed a PGA ≥ 1 (cm). All patients in the lower total GS score group showed a PGA ≥ 1, but 45% of the higher total GS score group failed to meet the criterion (p = 0.035; Figure 3a and b).

Consistent with the previous paper [16], no significant difference was found in the change of mTSS during 2 years between the higher and lower total GS score groups (1.91 ± 3.18 vs 0.55 ± 2.78, p = 0.63).

**Table 2. ROC curve analysis for various US combination scores.**

| Coefficient a | Coefficient b | AUC | 95% CI | p value | Youden index J |
|---------------|---------------|-----|--------|---------|---------------|
| 0 | 1 | 0.82 | 0.60–0.95 | 0.0004 | 0.69 |
| 1 | 1 | 0.85 | 0.63–0.96 | <0.0001 | 0.60 |
| 1 | 1.5 | 0.84 | 0.63–0.96 | 0.0001 | 0.65 |
| 1 | 2 | 0.85 | 0.63–0.96 | <0.0001 | 0.65 |
| 1 | 3 | 0.87 | 0.66–0.97 | 0.0007 | 0.71 |
| 1 | 4 | 0.86 | 0.65–0.97 | 0.0001 | 0.65 |
| 1 | 5 | 0.84 | 0.62–0.96 | 0.0001 | 0.65 |
| 1 | 6 | 0.84 | 0.62–0.96 | 0.0001 | 0.65 |
| 1 | 7 | 0.83 | 0.62–0.96 | 0.0002 | 0.65 |

Cutoff value: ≤ 7, ≤ 2, ≤ 12, ≤ 13, ≤ 14, ≤ 16, ≤ 18, ≤ 12.5, ≤ 16, ≤ 23, ≤ 30.

**Table 3. Relationship between baseline total GS score and variables.**

| Variable          | Total GS score ≤ 7 | Total GS score > 7 | p value |
|-------------------|--------------------|--------------------|---------|
| **Baseline**      |                    |                    |         |
| Age (year)        | 56.7 ± 10.2a       | 56.7 ± 12.7a       | 1.0     |
| Sex               | M: 3, F: 8         | M: 1, F: 10        | 0.59    |
| Duration of RA (month) | 87.3 ± 55.5a    | 78.9 ± 32.2a       | 0.71    |
| Duration of remission (month) | 24.2 ± 21.9a   | 16.8 ± 11.3a       | 0.86    |
| Stage             | I: 4, II: 6, III: 1, IV: 0 | I: 1, II: 5, III: 2, IV: 3 | 0.036* |
| mTSS              | 7.55 ± 6.56a       | 29.0 ± 26.9a       | 0.022*  |
| DAS28-CRP         | 1.54 ± 0.47a       | 1.68 ± 0.48a       | 0.54    |
| DAS28-ESR         | 1.96 ± 0.68a       | 2.13 ± 0.43a       | 0.51    |
| Boolean remission | 8 (73%)            | 3 (27%)            | 0.086   |
| SJC               | 0.36 ± 0.64a       | 0.91 ± 1.00a       | 0.23    |
| TJC               | 0.27 ± 0.45a       | 0.27 ± 0.45a       | 1.0     |
| PGA (mm)          | 9.09 ± 8.81a       | 11.8 ± 7.80a       | 0.41    |
| CRP (mg/dl)       | 0.11 ± 0.13a       | 0.10 ± 0.15a       | 0.90    |
| ESR (mm/h)        | 11.8 ± 7.16a       | 13.9 ± 13.8a       | 0.68    |
| MMP-3 (ng/ml)     | 74.1 ± 35.5a       | 97.4 ± 125a        | 0.58    |
| **2 years**       |                    |                    |         |
| mTSS              | 8.09 ± 8.55a       | 30.9 ± 28.2a       | 0.013a  |
| DAS28-CRP         | 1.26 ± 0.18a       | 1.83 ± 0.36a       | 0.00023** |
| DAS28-ESR         | 1.78 ± 0.78a       | 2.37 ± 0.61a       | 0.078   |
| Boolean remission | 11 (100%)          | 5 (45%)            | 0.012a  |
| SJC               | 0.09 ± 0.29a       | 0.73 ± 0.75a       | 0.046*  |
| TJC               | 0.00 ± 0.00a       | 0.45 ± 0.50a       | 0.035*  |
| PGA (mm)          | 5.55 ± 3.55a       | 15.7 ± 16.2a       | 0.029*  |
| CRP (mg/dl)       | 0.10 ± 0.11a       | 0.09 ± 0.07a       | 0.97    |
| ESR (mm/h)        | 16.8 ± 13.3a       | 16.0 ± 14.6a       | 0.90    |
| MMP-3 (ng/ml)     | 54.4 ± 33.4a       | 49.4 ± 24.6a       | 0.74    |

*Each combination score was calculated as the sum of a times total GS score and b times total PD score. LR, likelihood ratio.

**Relationship between baseline total PD score and factors for Boolean remission criteria**

We conducted similar analysis in relationship between total PD score and achievement of Boolean remission based on the cutoff points according to the ROC curve in 22 patients who maintained DAS28-based clinical remission for 2 years. Whereas 17 patients were categorized with lower total PD scores (total PD score ≤ 2), five patients were categorized with higher total PD scores (total PD score ≥ 3) (Table 4). There was no significant difference in demographic, clinical, and laboratory data at baseline between the two groups, except for SJC; only SJC was statistically higher in the higher total PD score group. At 2 years, Boolean remission was significantly related to the baseline total PD score (Table 4). Among the factors for Boolean remission criteria, only SJC was significantly higher in the higher total PD score group as compared with the lower group.

We compared fulfillment rates of individual components in Boolean remission criteria at 2 years between the two groups (Figure 3c). Patients who failed to satisfy SJC ≤ 1 at 2 years were more frequent in the higher total PD score group than the lower group (40 vs 0%, p = 0.043), but there was no significant difference in other components.

Finally, we assessed the relationship between total PD score and radiographic progression during 2 years. The interval change of mTSS was significantly higher in the higher total PD score
US predicts Boolean remission after DAS28 remission

Figure 3. US parameters at baseline and factors for Boolean remission criteria at 2 years. (a) Transition of PGA during 2 years in the lower total GS score group (total GS score ≤ 7; left) and the higher total GS score group (total GS score ≥ 8; right) at baseline. Gray zones indicate PGA levels which fulfill the condition of PGA for Boolean remission. (b) Comparison of each factor for Boolean remission criteria between the lower and higher total GS score groups. (c) Comparison of each factor for Boolean remission criteria between the lower total PD score (total PD score ≤ 2) and higher total PD score group (total PD score ≥ 3). *p < 0.05.

Discussion

This study demonstrates that maintaining DAS28-based clinical remission is not necessarily enough to achieve deeper remission such as Boolean remission and that US provides essential information to determine quality of remission in advance. First, our study shows that both total GS and PD scores at baseline are significantly related to achievement of Boolean remission at 2 years, indicating little or no positive US findings are associated with deep remission. Second, of individual components in Boolean remission criteria, PGA score and SJC were related to the baseline total GS and PD scores, respectively. The findings suggest that both parameters are necessary to determine imaging remission because they assess distinct aspects of synovitis in RA. Thus, the comprehensive assessment by US is essential for imaging remission which may theoretically correspond to true remission.

Because remission is currently recognized as an achievable goal, it is very important to reach consensus on how to define clinical remission. DAS28 has been widely used to monitor disease activity in daily practice and the DAS28-based remission criteria has been recommended by the ACR and EULAR [34]. Nonetheless, it is becoming evident that radiographic damage can progress in some patients even after achieving DAS28-based clinical remission [4,16,35]. In this context, ACR and EULAR have proposed two new definitions of remission recently; one is the Boolean-based definition and the other is the SDAI definition [5].

group at baseline as compared to the lower total PD score group (4.00 ± 3.03 vs 0.41 ± 2.55, p = 0.0075), which is consistent with our previous study [16]. Thus, the two US parameters, total GS and total PD scores, were related to the radiographic findings in different manners: the former were associated with accumulated joint damage, while the latter was accompanied by ongoing joint destruction.
Table 4. Relationship between baseline total PD score and variables.

| Variable            | Total PD score ≤ 2 | Total PD score ≥ 3 | p value |
|---------------------|--------------------|--------------------|---------|
| Baseline            |                    |                    |         |
| Age (year)          | 57.8 ± 11.8a       | 53.0 ± 9.21a       | 0.43    |
| Sex                 | M: 4, F: 13        | M: 0, F: 5         | 0.54    |
| Duration of RA (month) | 81.5 ± 42.5a     | 88.4 ± 54.5a      | 0.75    |
| Duration of remission (month) | 21.9 ± 19.7a   | 15.6 ± 6.89a      | 0.90    |
| Stage               | I: 5, II: 7, III: 2, IV: 3 | I: 0, II: 4, III: 1, IV: 0 | 0.31    |
| mTSS                | 16.6 ± 22.3a       | 24.0 ± 21.3a       | 0.27    |
| DAS28-CRP           | 1.61 ± 0.53a       | 1.62 ± 0.26a       | 0.95    |
| DAS28-ESR           | 1.95 ± 0.56a       | 2.36 ± 0.51a       | 0.18    |
| Boolean remission   | 10 (59%)           | 1 (20%)            |         |
| SJC                 | 0.41 ± 0.69a       | 1.40 ± 1.02a       | 0.030a  |
| TJC                 | 0.29 ± 0.46a       | 0.20 ± 0.40a       | 1       |
| PGA (mm)            | 10.4 ± 9.18a       | 10.6 ± 5.08a       | 0.71    |
| CRP (mg/dl)         | 0.13 ± 0.15a       | 0.04 ± 0.01a       | 0.22    |
| ESR (mm/h)          | 10.5 ± 5.54a       | 21.0 ± 18.7a       | 0.066   |
| MMP-3 (ng/ml)       | 96.0 ± 103a        | 50.8 ± 7.53a       | 0.36    |

2 years

| Variable            | Total PD score ≤ 2 | Total PD score ≥ 3 | p value |
|---------------------|--------------------|--------------------|---------|
| mTSS                | 17.0 ± 23.5a       | 28.0 ± 22.6a       | 0.19    |
| DAS28-CRP           | 1.51 ± 0.38a       | 1.67 ± 0.44a       | 0.44    |
| DAS28-ESR           | 1.93 ± 0.71a       | 2.58 ± 0.71a       | 0.10    |
| Boolean remission   | 15 (88%)           | 1 (20%)            | 0.009** |
| SJC                 | 0.24 ± 0.42a       | 1.00 ± 0.89a       | 0.041a  |
| TJC                 | 0.18 ± 0.38a       | 0.40 ± 0.49a       | 0.55    |
| PGA (mm)            | 10.1 ± 14.0a       | 12.6 ± 6.83a       | 0.25    |
| CRP (mg/dl)         | 0.11 ± 0.10a       | 0.03 ± 0.02a       | 0.10    |
| ESR (mm/h)          | 14.6 ± 11.7a       | 22.4 ± 18.7a       | 0.30    |
| MMP-3 (ng/ml)       | 54.9 ± 31.8a       | 42.4 ± 19.7a       | 0.49    |

*The data are shown as mean ± SD.
*p < 0.05, **p < 0.01.

Our finding that US parameters predict achievement of Boolean remission after DAS28 remission strongly encourages clinical application of US in targeting the new ACR/EULAR criteria. On the other hand, several reports have shown that any set of clinical remission criteria, including more stringent DAS28, SDAI, and Boolean criteria, are not always associated with no progression of joint damage [19,36]. This study showed that the cutoff value of total PD score for prediction of Boolean remission is 2 or less, indicating that PD signals are still observed in some patients achieving Boolean remission criteria. Because we previously found that the cutoff value for prediction of progressive joint damage is 1 or less [16], it still might be inadequate to target the Boolean remission for preventing joint damage. Actually, three patients (19%) in Boolean [16], it might be inadequate to target the Boolean remission for predicting joint damage. Therefore, it seems reasonable to target the Boolean remission for preventing joint damage. In conclusion, null or low-grade GS and PD findings in US are associated with the achievement of Boolean remission in advance, irrespective of therapeutic agents. US-based imaging remission is reasonable and applicable for daily practice as a realistic goal of RA treatment.

There were several limitations in this study. First, the backgrounds of patients, such as treatments and disease duration, were quite diverse. However, the aim of this study was to clarify the usefulness of US in predicting more stringent remission criteria after achieving DAS28 remission. In view of this, all of the enrolled patients were worthy of evaluation because they were quite homogeneous in that they fulfill the remission criteria of DAS28. Second, this study enrolled established RA, but not early RA patients. Whereas GS score, which mainly corresponds to synovial thickness, is hardly altered in long-standing RA, it reflects disease activity more strongly and can be reversible in response to treatment in early RA. The issue will be verified in a subsequent study. Third, evaluated joints are different among the assessment methods. DAS28 and Boolean criteria included the evaluation of shoulder, elbow, and knee joints while the US scoring system did not. There is some published evidence that reduced joint assessments in US are good enough for evaluating overall inflammatory activity [37–39]. However, the ideal joint count in patients during clinical remission is still unknown.

In conclusion, null or low-grade GS and PD findings in US are associated with the achievement of Boolean remission in advance, irrespective of therapeutic agents. US-based imaging remission is reasonable and applicable for daily practice as a realistic goal of RA treatment.

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Conflict of interest

None.

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Supplementary material available online
Supplementary Table 1 and Figure 1.

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