Table 2 Radiographic indicators and baseline disease characteristics

	RRR-achieved (N=33)	RRR-failed (N=16)	p (probability $>\chi^2$)
Baseline			
Disease duration (years)	4.7 (0.5–14.0)	8.6 (0.5–25.0)	*0.0280*
DAS28 (ESR) score	5.5 (1.9–7.6)	5.7 (4.2–6.8)	0.6976
HAQ-DI	1.0 (0.0–2.3)	1.1 (0.0–1.8)	0.6271
mTSS	46.9 (1.0–216.5)	97.2 (6.0–314.0)	*0.0207*
Bone erosion score	23.7 (0.0–127.5)	55.5 (1.5–192.5)	*0.0119*
Joint space narrowing score	23.2 (1.0–89.0)	41.6 (4.5–121.5)	*0.0621*
Yearly progression of mTSS	13.1 (0.8–51.3)	15.0 (1.0–47.8)	0.5794
RRR-entry			
Yearly progression of mTSS	1.0 (−2.9 to 10.5)	0.7 (−2.0 to 6.7)	0.5788
Primary end point			
Yearly progression of mTSS	0.3 (−3.6 to 8.5)	1.6 (−3.6 to 7.0)	0.1087
Median of yearly progression of mTSS	0.0	1.5	–
Yearly progression of mTSS <0.5 (%)	67	44	0.2161

Data are number of patients (%) for categorical data and the means for continuous data. Statistical difference was assessed by non-parametric Wilcoxon t test and p (probability $>\chi^2$) values were shown. Values in italic indicate a significant difference ($p<0.05$). DAS28, Disease Activity Score based on assessments of 28 tender and 28 swollen joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; mTSS, modified total Sharp score; RRR, remission induction by Remicade in rheumatoid arthritis.

RRR than in those for whom RRR failed. These results imply that remission free from biological agents can be more easily obtained in patients with shorter disease duration than in those with more established disease, but discontinuation of infliximab is still possible even in patients with long-established RA, because eight patients whose disease duration was >10 years successfully remained without infliximab for 1 year.

Among 102 evaluated patients, disease in 29 patients flared within 1 year, 17 patients had DAS28≥3.2 at year 1 after discontinuing infliximab and 32 patients had already been re-treated with infliximab. One of the major concerns of restarting infliximab is the possibility of an infusion reaction after the long-term discontinuation, partly owing to human anti-chimeric antibodies.[22] However, minimal adverse reactions at infusion of the agent were seen only in five patients at the first or second infusion. Another concern is the progress of joint damage after discontinuation of infliximab. However, although the yearly progression of mTSS at RRR-study entry was also comparable between two groups, means (0.3 vs 1.6) and medians (0.0 vs 1.5) of ΔmTSS were shorter in the RRR-achieved group than in the RRR-failed group. Furthermore, at year 1 after the discontinuation of infliximab, more patients in the RRR-achieved group (67%) tended to satisfy ΔmTSS<0.5—that is, structural remission, than those in the RRR-failed group (44%) and HAQ-DI in patients who achieved RRR was significantly lower than that in patients for whom RRR failed (0.174 vs 0.614). These results indicate that both structural remission and functional remission were maintained for 1 year in patients with LDA even after discontinuing infliximab.

This study also shows the significance of DAS-guided tight control of RA in order to maintain remission free from biological agents. There was a significant correlation between DAS28 (ESR) or DAS28 (CRP) at RRR entry and DAS28 (ESR) at year 1 after the discontinuation of infliximab by univariate analysis of multiple variables and a logistic regression analysis. Thus, DAS28 at RRR-study entry had the greatest correlation with maintenance of LDA for 1 year after discontinuation. Also, DAS28 at study entry was mainly influenced by PaGA and ESR among the composite measures. By reciprocal statistics, the estimated DAS28 (ESR) at RRR-study entry was 2.22 (1.85–2.70), to attain DAS28<3.2 at the primary end point in 50% of the 102 patients studied. Also, 71.4% of patients whose DAS28 at study entry was <2.225, a cut-off point calculated from ROC curve, remained DAS28<3.2 for 1 year, whereas only 32.6% of patients whose DAS28 at RRR-entry was 2.225–3.2 remained DAS28<3.2. These results indicate that 'deep remission' appears to be required to maintain lower disease activity for 1 year after discontinuation of infliximab.

About 55% of the 102 patients, who were in an LDA state for >24 weeks with infliximab and MTX treatment, could discontinue infliximab for >1 year without progression of radiological articular destruction or functional disturbance. These data may have significant implications for the optimal use of expensive biological treatments: (*a*) re-treatment with infliximab is efficient and tolerable in the patients for whom RRR failed; (*b*) DAS-guided monitoring is valuable to keep tight control; (*c*) 'deep

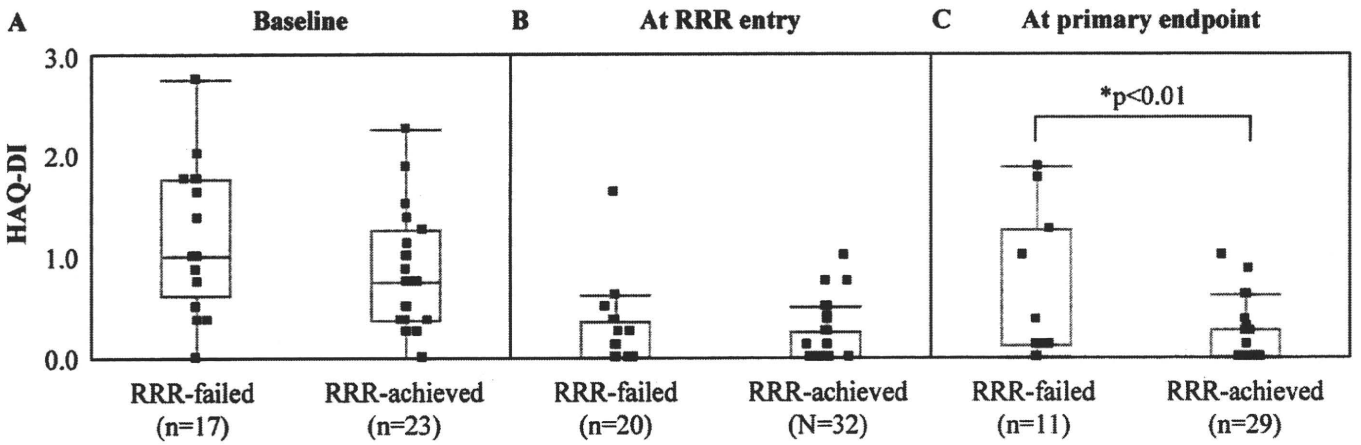

Figure 4 Health Assessment Questionnaire-Disability Index (HAQ-DI) in patients for whom remission induction by Remicade in rheumatoid arthritis failed (RRR-failed)' and in patients for whom 'RRR was achieved (RRR-achieved)' at (A) baseline, (B) RRR entry and (C) the primary end point. The line in the box represents the median value and the upper and lower ends of the box indicate the 25th and 75th centiles of the population. Statistical difference was assessed by non-parametric Wilcoxon t test.

remission' by tight control is required to maintain discontinuation of infliximab; (*d*) remission free from biological agents may be easier to attain in patients with early RA, but is possible for patients with long-established disease; (*e*) treatment aimed at reaching a target of LDA is pivotal to the approach to remission free from biological agents. Finally, TNFα is not a cause of RA, but if appropriate treatment with infliximab can lead to drug-free remission, TNF inhibitors may shut down pathological processes and may change or modify the disease course in RA. Thus, a clinical and basic research approach to the 'process-driven disease' of RA is warranted.

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Competing interests YT has received consultant fees from Mitsubishi-Tanabe Pharma, Pfizer Inc; lecture fees from Mitsubishi-Tanabe Pharma, Takeda Pharmaceutical Co Ltd, Abbott, Eisai Pharma, Chugai Pharma. TT has received consultant fees from Mitsubishi-Tanabe Pharma, Wyeth Japan, Abbott, Eisai Pharma, Janssen Pharma, Chugai Pharma, Bristol-Myers-Squibb, Novartis; lecture fees from Mitsubishi-Tanabe Pharma, Takeda Pharmaceutical Co Ltd, Abbott, Eisai Pharma, Chugai Pharma. HK has received lecture fees from Mitsubishi-Tanabe Pharma, Centocor, Wyeth Japan, Takeda Pharmaceutical Co Ltd, Abbott, Eisai Pharma, Chugai Pharma. NM has received consultant fees from Mitsubishi-Tanabe Pharma; Abbott, Eisai Pharma, Janssen Pharma, Chugai Pharma, Bristol-Myers-Squibb; lecture fees from Mitsubishi-Tanabe Pharma, Takeda Pharmaceutical Co Ltd, Wyeth Japan, Abbott, Eisai Pharma, Chugai Pharma. TK has received consultant fees from Bristol-Myers-Squibb, Abbott; lecture fees from Mitsubishi-Tanabe Pharma, Takeda Pharmaceutical Co Ltd, Wyeth Japan, Abbott, Eisai Pharma, Chugai Pharma.

Patient consent Obtained.

Ethics approval This study is an observational study and is registered with the University Hospital Medical Information Network-Clinical trials Registry, number R000002571. Also, ethics committees of the participating centres approved the study protocol.

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ORIGINAL ARTICLE

Change of Synovial Vascularity in a Single Finger Joint Assessed by Power Doppler Sonography Correlated With Radiographic Change in Rheumatoid Arthritis: Comparative Study of a Novel Quantitative Score With a Semiquantitative Score

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Objective. To investigate the relationship between synovial vascularity assessed by quantitative power Doppler sonography (PDS) and progression of structural bone damage in a single finger joint in patients with rheumatoid arthritis (RA).
Methods. We studied 190 metacarpophalangeal (MCP) joints and 190 proximal interphalangeal (PIP) joints of 19 patients with active RA who had initial treatment with disease-modifying antirheumatic drugs (DMARDs). Patients were examined by clinical and laboratory assessments throughout the study. Hand and foot radiography was performed at baseline and the twentieth week. Magnetic resonance imaging (MRI) was performed at baseline. PDS was performed at baseline and the eighth week. Synovial vascularity was evaluated according to both quantitative and semiquantitative methods.
Results. Quantitative PDS was significantly correlated with the enhancement rate of MRI in each single finger joint. Comparing quantitative synovial vascularity and radiographic change in single MCP or PIP joints, the level of vascularity at baseline showed a significant positive correlation with radiographic progression at the twentieth week. The change of vascularity in response to DMARDs, defined as the percentage change in vascularity by the eighth week from baseline, was inversely correlated with radiographic progression in each MCP joint. The quantitative PDS method was more useful than the semiquantitative method for the evaluation of synovial vascularity in a single finger joint.
Conclusion. The change of synovial vascularity in a single finger joint determined by quantitative PDS could numerically predict its radiographic progression. Using vascularity as a guide to consider a therapeutic approach would have benefits for patients with active RA.

INTRODUCTION

In recent years, the therapeutic goal for rheumatoid arthritis (RA) has moved far beyond the traditional factors of clinical remission, defined by the American College of Rheumatology (ACR) core data set or the European League Against Rheumatism (EULAR) Disease Activity Score in 28 joints (DAS28) remission criteria (1,2). To halt the progression of bone destruction, there has been a great need for a reliable predictive indicator of radiographic progression. Modern imaging techniques such as power Doppler sonography (PDS) and magnetic resonance imaging (MRI) have the potential to predict bone destruction (3–6). However, the relationship between therapeutic efficacy and image responses of these techniques has not been established.

PDS has several advantages in terms of medical cost and safety compared with other modern imaging techniques; therefore, it is more practical to use it repeatedly for monitoring disease activity. PDS detects the abnormal synovial vascular flow related to inflammation and has the potential to evaluate the level to represent this as a measurable

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Table 1. Clinical and laboratory characteristics of patients at baseline and the eighth and twentieth weeks*

	Baseline	8th week	20th week
Age, mean (range) years	54 (24–87)		
Sex, female/male	17/2		
RF positive, yes/no	15/4		
Prior use of DMARDs, yes/no	3/16		
Duration of symptoms, months	5 (3–11)		
Swollen joint count	3 (2–7)	1 (0–2)	0 (0–2)
Tender joint count	6 (2.5–13)	2 (1–5)	1 (1–1.5)
Patient's global assessment by VAS	60 (45–60)	29 (20.5–43.5)	25 (15.5–30)
ESR, mm/hour	43 (27–80)	24 (16–58)	27 (16–35)
CRP level, mg/dl	0.5 (0.25–2.82)	0.12 (0.1–1.1)	0.1 (0.1–1.4)
DAS28-ESR, mean ± SD mm/hour	5.21 ± 1.39	4.08 ± 1.60	3.56 ± 1.31

* Values are the median (interquartile range) unless otherwise indicated. RF = rheumatoid factor; DMARDs = disease-modifying antirheumatic drugs; VAS = visual analog scale; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints.

parameter (7,8). With growing interest in the ability to define remission in RA, it has been reported that abnormal synovial vascular flow still remains in individual joints after achievement of clinical remission, and therefore bone destruction would progress at a high rate in such cases (3,9). In this sense, direct assessment of synovial vascular flow in a single joint would be of use. Semiquantitative scoring has been widely used to evaluate synovial vascularity (10,11). The scoring was divided into 4 steps that were judged subjectively by the observer, and represented, accordingly, as a semiquantitative approach. The relationship between synovial vascular changes and progression of structural bone damage in a single joint has been the focus of much investigation, but only a few studies have been successful despite the intensive attempts of many researchers (3,12–14). In our preliminary study, we established quantitative PDS for synovial vascularity in each finger joint (15,16). The measurement was able to assess vascularity as quantitative data, objectively determined by the ultrasonographic program, and to detect small changes in individual finger joints. We investigated the relationship between synovial vascular changes and progression of structural bone damage in a single finger joint using the quantitative PDS measurement. We further defined the vascularity in response to disease-modifying antirheumatic drugs (DMARDs) by imaging and investigated its clinical significance in patients with active RA.

PATIENTS AND METHODS

Patients. Nineteen new patients with RA were enrolled in the study. All of the patients satisfied the ACR (formerly the American Rheumatism Association) 1987 diagnostic criteria (17). All of the patients were diagnosed as having the active state of RA according to the DAS28–erythrocyte sedimentation rate (ESR; >2.7 mm/hour). Demographic, clinical, and laboratory characteristics of the patients are shown in Table 1. Three patients were already receiving DMARDs at the initial diagnosis, but they were having no therapeutic effect (1 patient with sulfasalazine [SSZ], 2 patients with auranofin). After baseline examinations, all of the patients were given one of the new DMARDs. Initial treatments were continued throughout the study, but additional treatment and escalating doses of DMARDs were permitted in cases with disease exacerbation after the eighth week. We performed clinical and imaging examinations as mentioned in each section.

The study was conducted in accordance with the Helsinki Declaration. Informed consent to the protocol approved by the ethics committee of the hospital was obtained from all of the patients.

Ultrasonography and assessment. Ultrasonography was performed at baseline and the eighth week by 1 of the 3 ultrasonographers (MH, FS, AN) specialized in musculoskeletal ultrasonography who were blinded to other clinical information. A 13-MHz linear array transducer was used (HITACHI EUP-L34P). Pulse Doppler settings were standardized for the detection of synovial blood flow by adjusting color gain, pulse repetition, and flow optimization parameters according to a previous study (15). Power Doppler settings (75 dB dynamic range, medium persistence, medium frame rate, low wall filter, 1,300 Hz pulse repetition frequency, flow optimization: medium vein, 1,300 Hz speed velocity) were identical throughout the examinations. Room temperature was kept at 25°C. The patients were positioned comfortably, and the examinations were then started after 10 minutes of stabilization of the pulse rate. The scanning technique on each finger joint was standardized and fixed as follows: scanning of the first through fifth metacarpophalangeal (MCP) joints and the first through fifth proximal interphalangeal (PIP) joints was performed in the longitudinal plane over the dorsal surface of the joint with light skin pressure. The basic scanning technique followed the EULAR guidelines (18). The synovial vascular area with the most pronounced power Doppler activity was identified from the cine-loop and stored. The PDS images were recorded in the hard disk of the ultrasonographic machine. All of the examinations were completed within 15 minutes. Semiquantitative scoring has been described in previous studies (0 = absence of signal, 1 = single vessel dots, 2 = vessel dots over less than

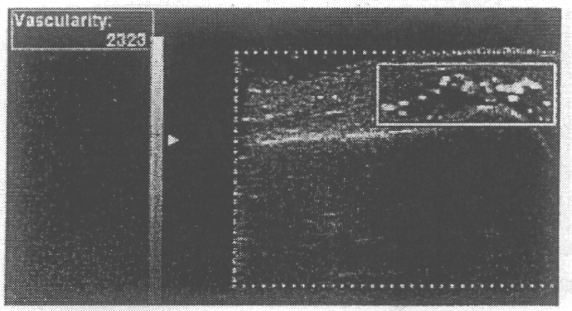

Figure 1. An image of finger joint ultrasonography (right 5th metacarpophalangeal joint). Each joint was scanned as described in the Patients and Methods section. The white line box indicates the region of interest (ROI) that was located at synovial vascular flow. Pixels of vascular flow inside the ROI were measured by the ultrasonographic program and displayed at the upper left corner of the monitor.

half of the synovium area, 3 = vessel dots over greater than half of the synovium area) (10,11,19). A synovial vascularity value, measured by quantitative PDS, was defined as P-vasc, which is the number of vascular flow pixels in the region of interest (ROI). The ROI was a standardized box type (5 mm × 10 mm) that was located to contain as many of the vascular flow pixels as possible. Vascular flow pixels in the ROI were measured automatically using the program's Vascularity mode in the ultrasonographic machine (HITACHI EUB-6500) (Figure 1).

Radiography and assessment. Plain radiographs of the hands, wrists, and feet were obtained at baseline and the twentieth week. Radiologic assessments were examined according to the Genant-modified Sharp score (GSS) by a rheumatologist (YK) who was blinded to other clinical information (20).

MRI and assessment. MRIs of both finger joints were taken at baseline using the 1.5T system (Signa Excite, version 12) with a cardiac coil. During the examination, patients were placed in the supine position with both hands on the abdomen, and these were covered by the anterior segment of the cardiac coil. Dynamic 3-dimensional forkhead activin signal transducer spoiled gradient-recalled acquisition in the steady state T1-weighted coronal images (time to recovery 500 msec, time to echo 11 msec, field of view 30 cm, matrix 256 × 160, 20 slices, slice thickness 3 mm, gap 0.4 mm, imaging time 10, 17 loops with an interval time of 5 seconds) were obtained for both hands in addition to the other images with different scan sequences. A bolus injection of gadopentate dimeglumine (Gd-DTPA; 0.1 mmole/kg body weight) was administered at 1 ml/second via a 21-gauge indwelling needle inserted into an antecubital fossa vein during acquisition of the baseline images (first loop) of the dynamic study. Data were transferred from the MRI console to a Digital Imaging and Communication in Medicine viewer and then a workstation (Advantage Windows workstation) for quantitative analysis. The severity of synovitis has been previously assessed by the rate of enhancement (E-rate) in a dynamic study by injection of Gd-DTPA (21). The E-rate indicates the index of enhancement by plotting the signal intensity against time in a selected ROI (~20–30 mm^2 in area) of the site of maximum enhancement in the above-mentioned 20 joints. Image analysis was carried out by an experienced radiologist (TK) who was blinded to other clinical information.

Statistical analysis. Statistical analyses were calculated with the use of the Excel program and the MedCalc program, version 10.4.5.0. Differences between the 2 groups were examined using either Student's *t*-test or a nonparametric test (Wilcoxon's signed rank test, Mann-Whitney U test), as applicable. A correlation between 2 variables was examined using either a parametric test (Pearson's correlation test) or a nonparametric test (Spearman's rank correlation test) according to the distribution of values. Intra-and interobserver reliability of the semiquantitative PDS score was estimated using calculations of weighted kappa statistics and overall agreement. Intra-and interobserver reliability of P-vasc was estimated using calculations of intraclass correlation coefficients (ICCs). The smallest detectable change for the radiographic score change was calculated according to a previous study (22).

RESULTS

Clinical disease activity. The mean ± SD DAS28-ESR at baseline was 5.21 ± 1.39 mm/hour. The mean ± SD DAS28-ESR at the eighth week was 4.08 ± 1.60 mm/hour, which was significantly decreased from baseline (P = 0.0001). There was no significant difference in the DAS28-ESR between the eighth week and the twentieth week (P = 0.0741). At the twentieth week, 13 patients were receiving monotherapy (9 with methotrexate [MTX], 2 with SSZ, and 2 with bucillamine) and 6 patients were receiving combination therapy of DMARDs (3 with MTX plus bucillamine, 1 with MTX plus SSZ, 1 with SSZ plus bucillamine, and 1 with SSZ plus tacrolimus). Thirteen patients were receiving oral prednisolone (3–10 mg/day) at the twentieth week.

Intra-and interobserver reliability for PDS. All PDS images for MCP joints and PIP joints were blindly evaluated twice according to the semiquantitative score for each joint by 2 ultrasonographers (MH, AN). The obtained intraobserver kappa values of the semiquantitative score were 0.944 for MCP joints and 0.930 for PIP joints. The intraobserver overall agreement for these joints was 96% and 95.4%, respectively. The obtained interobserver kappa values of the semiquantitative score were 0.950 for MCP joints and 0.923 for PIP joints. The interobserver overall agreement for these joints was 95.7% and 97.1%, respectively.

Representative images for 20 MCP joints and 20 PIP joints were randomly chosen, and P-vasc was measured 3 times each by 3 ultrasonographers (MH, FS, AN). The obtained intraobserver ICC values were 0.990 for MCP joints and 0.990 for PIP joints. The interobserver ICC values were 0.990 for MCP joints and 0.990 for PIP joints.

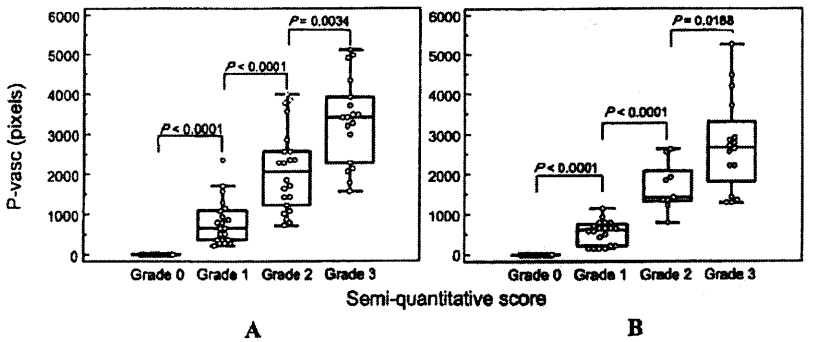

Figure 2. Relation between quantitative measurement and semi-quantitative scoring for synovial vascularity. The levels of synovial vascularity value (P-vasc) were plotted against semi-quantitative scores in MCP joints (A) and PIP joints (B).

Relationship of quantitative PDS measurement (P-vasc) to semiquantitative scoring for synovial vascularity and to the E-rate of MRI. The PDS images for 190 MCP joints and 190 PIP joints at baseline were evaluated using both the semiquantitative score and the P-vasc. The P-vasc significantly increased as the semiquantitative score increased in both MCP joints and PIP joints (Figure 2).

One patient was unable to undergo MRI because of claustrophobia. One hundred eighty MCP joints and 180 PIP joints of 18 patients were evaluated using both the P-vasc and E-rate. The P-vasc had a significant positive correlation with the E-rate of MRI in both MCP and PIP joints (Pearson's r = 0.739, $P < 0.0001$ and Pearson's r = 0.537, $P < 0.0001$, respectively) (Figure 3).

Association between vascularity and radiographic progression in a single joint. The median local GSS at baseline for MCP and PIP joints were 0 (interquartile range [IQR] 0–1) and 0.5 (IQR 0–1.5), respectively. The median local GSS at the twentieth week for MCP and PIP joints were 0.5 (IQR 0–1.5) and 0.75 (IQR 0–1.5), respectively. The median total GSS was 16.5 (IQR 11.3–37.3) at baseline. The median total GSS at the twentieth week was 30.0, which was significantly higher than the baseline score ($P = 0.001$).

We next focused on changes of single-joint P-vasc and local GSS. We investigated the association between the level of vascularity at baseline and radiographic progression at the twentieth week in each single finger joint. One hundred ninety MCP joints and 190 PIP joints at baseline were evaluated. The level of P-vasc at baseline significantly correlated with progression of the local GSS in both MCP and PIP joints (Spearman's $\rho = 0.466$, $P < 0.0001$ and Spearman's $\rho = 0.362$, $P < 0.0001$, respectively) (Figures 4A and B). The association between the semiquantitative score and the progression of the local GSS had the same tendency (data not shown). We took note of the positive PDS joints at baseline and calculated their improvement rate (IR), defined as the percentage change in P-vasc by the eighth week from baseline. The IR was calculated as follows: (P-vasc value at baseline − P-vasc value at eighth week)/P-vasc value at baseline × 100 (%). At baseline, 61 MCP joints and 44 PIP joints had positive PDS signals. The IR of P-vasc had a significant inverse correlation with local GSS progression in each single MCP joint (Spearman's $\rho = -0.340$, $P = 0.00386$) (Figure 5A). There was no significant correlation between the IR of P-vasc and local GSS progression in each single PIP joint (Spearman's $\rho = -0.223$, $P = 0.1430$) (Figure 5B). In the case of assessment by semiquantitative score, there was no significant correla-

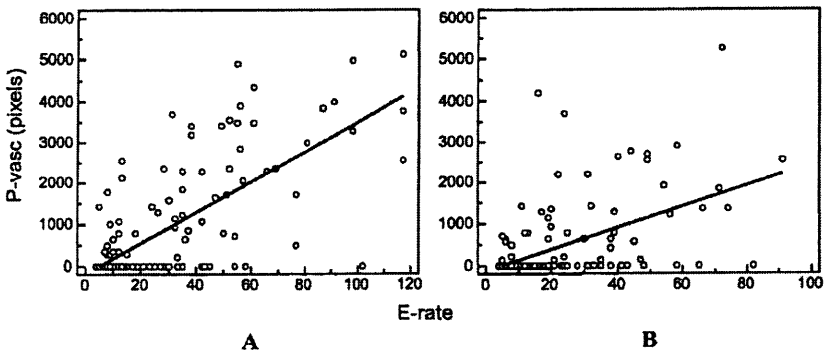

Figure 3. Relationship between quantitative measurement of synovial vascularity with power Doppler sonography and the index of synovial enhancement of magnetic resonance imaging (MRI). Scatter diagrams and regression lines of synovial vascularity value (P-vasc) against the enhancement rate (E-rate) of MRI in metacarpophalangeal joints (A) or proximal interphalangeal joints (B) are shown.

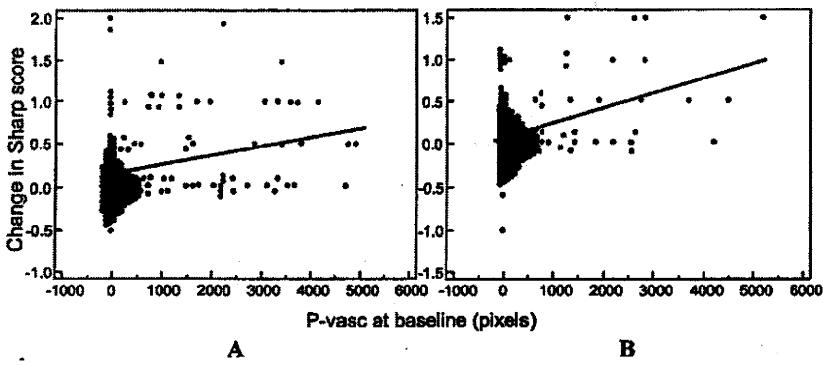

Figure 4. Relationship between the level of synovial vascularity and radiographic progression in each single finger joint. Scatter diagrams and regression lines of the synovial vascularity value (P-vasc) at baseline against progression of the local Genant-modified Sharp score from baseline to the twentieth week in metacarpophalangeal joints (A) or proximal interphalangeal joints (B) are shown.

tion to MCP or PIP joints (Spearman's $\rho = -0.256$, $P = 0.0579$ and Spearman's $\rho = -0.105$, $P = 0.5179$, respectively) (data not shown). The smallest detectable change values were calculated for the radiographic erosion score, joint space narrowing score, and combined score for single MCP and PIP joints (0.21–0.48). All of the calculated smallest detectable changes did not exceed the smallest unit of the scoring (0.5).

DISCUSSION

In this study, we quantitatively evaluated synovial vascularity in a single finger joint. In each finger joint, we found that a level of vascularity at baseline correlated with the radiographic progression. We also demonstrated that the change of vascularity in response to DMARD therapy could numerically predict the radiographic progression in each single finger joint.

We defined a standardized box type ROI and quantitatively evaluated synovial vascularity, as mentioned in the Patients and Methods section. All of the kappa values and ICCs calculated for intra-and interobserver reliability during the PDS measurements were acceptable in this study.

To demonstrate the validity of our quantitative PDS method, we first examined a relationship between the P-vasc and semiquantitative scoring. The P-vasc significantly increased in parallel with semiquantitative scoring. The E-rate of MRI is an index of Gd-DTPA enhancement indicating the inflammatory level (21,23,24), and was used for comparing with quantitative ^{99m}Tc-labeled nanocolloid scintigraphy for assessing RA (25). We next examined the relationship between the E-rate and P-vasc. Although the P-vasc was not detected in some joints with a high E-rate, a positive significant correlation was shown between the E-rate and P-vasc, suggesting that synovial vascularity determined by our quantitative PDS reflects, in part, the inflammatory level. The main reason of discrepancy between a joint with a high E-rate and negative PDS should be explained by the fact that MRI covered inflammation from all sites of synovial tissue, whereas PDS detected only from the dorsal side of synovial tissue. In addition, the difference of sensitivity of PDS and that of the E-rate might be a problem. Because the PDS is one of the advancing modalities for imaging rheumatic joints, there would be many more points to be improved in the

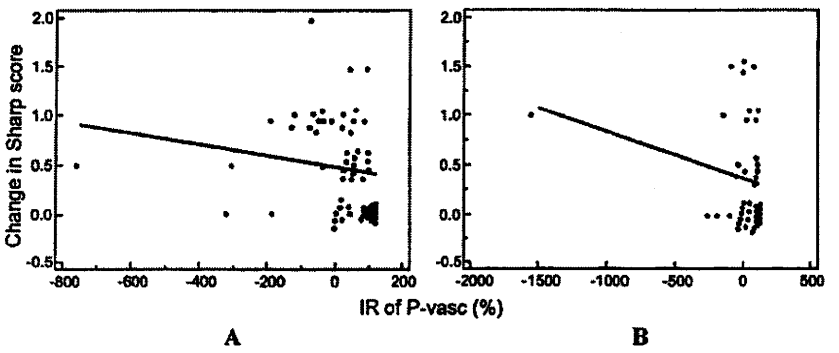

Figure 5. Relationship between improvement of synovial vascularity and radiographic progression in each single finger joint. Scatter diagrams and regression lines of the improvement rate (IR) for synovial vascularity value (P-vasc) between baseline and the eighth week against progression of the local Genant-modified Sharp score from baseline to the twentieth week in metacarpophalangeal joints (A) or proximal interphalangeal joints (B) are shown.

technological aspects, and such a process will promise to overcome the current problems in the future.

We used the P-vasc for investigating the relationship between the change of synovial vascularity and radiographic progression in a single finger joint. We found that, for each single finger joint, the baseline P-vasc significantly correlated with progression of the local GSS over 20 weeks. Our study, for the first time, has quantitatively confirmed the recent reports of Brown et al and Naredo et al that the presence of vascularity using PDS in a qualitative way correlated with the bone destruction in each single joint (3,13).

We next focused on PDS-positive finger joints at baseline and calculated each IR from baseline to the eighth week. The IR of P-vasc had a significant inverse correlation with radiographic progression in each single MCP joint. It was a novel finding that improvement in the rate of vascularity resulted in the suppression of radiographic progression. The semiquantitative score failed to demonstrate the same tendency due to its low sensitivity at detecting small changes in vascularity. On the other hand, the IR of P-vasc in PIP joints was not significantly correlated with radiographic progression, presumably due to either the sample size or the ROI setting. Further refinement of ROIs specific to PIP joints may improve the accuracy of the technique.

According to the 2002 ACR guidelines for the treatment of RA, therapeutic evaluation of first-line DMARDs was assessed at 8–12 weeks using clinical indices (26). Naredo et al reported that the time-integrated value of the PDS parameters correlated with the radiographic progression over 1 year (13), suggesting that rapid reduction in the PDS signal could predict a better radiologic prognosis. The IR of P-vasc, a change rate of 2 points, could be a useful index for preventing bone destruction. A quantitative PDS method was more useful than a semiquantitative method to detect change of synovial vascularity in each single finger joint.

Although this is a preliminary study with a small number of patients, it is noteworthy that the clinical implications of our results include the potential of synovial vascularity to numerically predict an outcome of bone destruction in each single finger joint. Furthermore, we found that the change of vascularity influenced radiographic progression. The IR of synovial vascularity should be an index of therapeutic efficacy, and therefore be of value in making judgments about additional treatment with DMARDs or to change to early biologic agent therapy. Using vascularity as guide to make therapeutic decisions at early stages would have benefits for patients with active RA. Larger and longitudinal studies would indicate the efficacy of PDS for the better management of affected patients.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Fukae had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Fukae, Kon, Tanimura, Kamishima, Atsumi, Koike.

Acquisition of data. Fukae, Kon, Henmi, Sakamoto, Narita, Shimizu, Tanimura, Matsuhashi, Kamishima.

Analysis and interpretation of data. Fukae, Kon, Henmi, Sakamoto, Narita, Shimizu, Tanimura, Matsuhashi, Kamishima, Atsumi, Koike.

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ORIGINAL ARTICLE

Screening for rheumatoid arthritis with finger joint power Doppler ultrasonography: quantification of conventional power Doppler ultrasonographic scoring

Jun Fukae · Masato Shimizu · Yujiro Kon · Kazuhide Tanimura · Megumi Matsuhashi · Tamotsu Kamishima · Takao Koike

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Abstract Power Doppler ultrasonography (PD-US) has proved to be a useful technique to measure synovial vascularity due to its capability to provide data that can be used to evaluate the level of joint inflammation and assess rheumatoid arthritis (RA). We have developed a novel PD-US finger joint scoring method that introduces quantitative measurements into the conventional PD-US assessment method. A comparison of the two methods revealed that our novel PD-US method strongly correlates with the conventional method in terms of RA assessment. We performed finger joint PD-US on 69 patients with RA and 70 patients who had multiple joint pain but showed no evidence of inflammatory diseases (non-inflammatory disease, NI) and measured the synovial vascularity of the metacarpophalangeal joints 1–5 and proximal interphalangeal (PIP) joints 1–5 for each patient. We analyzed the data with receiver operating characteristic analysis and, based on the results for the total vascularity of 20 finger joints, defined a cut-off value of 36% as discriminating between RA and NI. This cut-off value was found to be a valuable tool in screening for RA. We conclude that our finger joint PD-US scoring system is both useful and applicable for diagnosing RA.

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Keywords Diagnosis · Power Doppler ultrasonography · Quantitative scoring method · Rheumatoid arthritis · Synovial vascularity

Introduction

Biological agents that neutralize pro-inflammatory cytokines strongly inhibit rheumatoid arthritis (RA) activity and thus improve the prognosis of joint function [1–5]. Despite therapeutic innovations in rheumatology, there has been little progress in diagnostic criteria and the assessment of therapeutic efficacy. The classical explanation of inflammation consists of five components: redness, heat, swelling, pain and loss of function. Upon diagnosis, the severity of the arthritis is evaluated by assessing joint swelling and tenderness by palpation and patient interview [6, 7]. Since these procedures are highly dependent on subjective assessments by both the patients and rheumatologists, the potential for inaccuracies in the evaluation is always present. Power Doppler ultrasonography (PD-US) is a useful tool for imaging abnormal synovial vascular flow resulting from inflammation [8–10]. However, the conventional finger joint PD-US scoring method used for measuring vascularity consists of semi-quantitative scoring that is determined on only four steps [11, 12], which are insensitive to small changes. In addition, there is no distinct and well-defined cut-off value that distinguishes abnormal from normal. We have introduced a 100% quantitative measurement into the current finger joint PD-US scoring method. In the study reported here, we evaluated whether the scoring of our newly developed method is useful for the initial screening of RA patients.

Materials and methods

Patients

We studied and performed PD-US on metacarpophalangeal (MCP) joints 1–5 and proximal interphalangeal (PIP) joints 1–5 in 69 patients with RA (56 females, 13 males) and in 70 patients who had multiple joint pains but showed no evidence of inflammatory diseases (non-inflammatory disease; NI) (60 females, 10 males). Patients with RA were diagnosed according to the American College of Rheumatology (ACR) 1987 diagnostic criteria [6]. The mean ages of RA and NI patients were 59.2 and 54.5, respectively.

Power Doppler ultrasonography examination

Examinations were performed by three ultrasonographers specialized in musculoskeletal PD-US who were blinded to clinical information. A 13-MHz linear array transducer (model EUB-6500; Hitachi, Tokyo, Japan) was used. The machine settings (dynamic range 75 dB; medium persistence; medium frame rate; low wall filter; pulse repetition frequency 1300 Hz; flow optimization: medium vein; speed velocity 1300 Hz) were identical throughout all examinations. Room temperature was kept at 25°C. The patients were positioned comfortably, then examinations were started after a delay of 5–10 min to allow for the stabilization of pulse rate. Each finger joint scanning technique was standardized and fixed as follows: scanning of the MCP and PIP joints was performed in the longitudinal plane over the dorsal surface of the joint with light skin pressure. The joint space was defined as a hypo-echoic tissue space surrounded by the hyper-echoic extensor tendon and the cortical line of the cartilage. The area with the most pronounced power Doppler activity was identified from the cine-loop and stored. All examinations were completed within 15 min.

Power Doppler ultrasonography intraobserver reliability

Intraobserver reliability was assessed by examining four patients with active RA. The PD-US examinations were repeated ten times for each joint by a single ultrasonographer. Intraobserver reliability was estimated using calculations of intraclass correlation coefficients (ICC).

Power Doppler ultrasonography interobserver reliability

Interobserver reliability was assessed by 31 recording images of the randomly chosen 30 patients with active RA. Image evaluations were repeated three times, each time by a different observer. Interobserver reliability was estimated using calculations of ICC.

Ultrasonographic assessment

To measure finger joint synovial vascularity, we defined a joint synovial vascularity index (JSVI). The JSVI is the number of vascular flow pixels divided by the total number of pixels in the region of interest (ROI). We defined ROI as the synovium surrounded by the hyperechoic extensor tendon and the cortical line of the cartilage. Each ROI was drawn by free-hand (Fig. 1), and then each ROI and the vascular flow pixels inside it were measured automatically using the program in the PD-US machine (model Hitachi EUB-6500). The conventional scoring system for scoring for finger joint synovial vascularity has been described in previous studies (0 = absence of signal, 1 = single vessel dots, 2 = vessel dots over less than half area of the synovium, 3 = vessel dots over more than half the area of the synovium) [11, 12].

Statistical analysis

Statistical analyses were calculated with the use of the Excel program (Microsoft, Redmond, WA). Receiver operating characteristic (ROC) analyses were calculated with the use of the MedCalc program (MedCalc Software, Mariakerke, Belgium).

Results

Correlation between the JSVI and the conventional score

We first examined the correlation between the JSVI and conventional scoring in preliminary analyses. Three ultrasonographers examined 100 finger joint images using both the conventional score and the JSVI. The numerical relation between these two scoring systems are shown in Table 1. Regression analysis revealed that the two scoring techniques were strongly correlated with each other ($R^2 = 0.8629$, $y = 0.02927x + 0.6450$) (Fig. 2).

Intra- and interobserver reliability

The ICC values were 0.97 and 0.99 for intra- and interobserver reliability, respectively. An ICC value of >0.9 is considered to be very good.

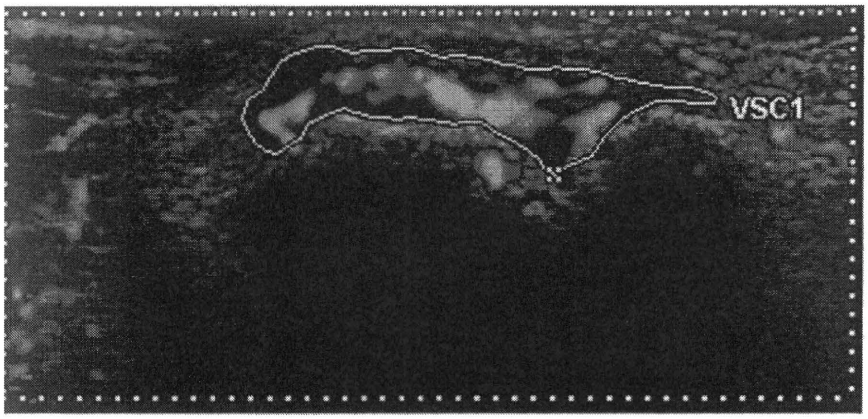

Fig. 1 An actual image of joint ultrasonography (metacarpophalangeal joint of left second finger). Each joint was scanned as described in the "Materials and methods". The area of the synovium was encircled by a *white line* drawn in free-hand line, then measured as 5323. The area of abnormal vascularity was shown as *red flow signals*, then measured as 3961. The joint synovial vascularity index (*JSVI*)—74.4% in the image shown here—was calculated automatically by the operating software

Table 1 The numerical relation between conventional scoring system and joint synovial vascularity index

Conventional score	0 (absence)	1 (mild)	2 (moderate)	3 (severe)
JSVI (mean ± SD) ($n = 100$)	2.6 ± 2.6 ($n = 3$)	13.5 ± 6.42 ($n = 51$)	44.3 ± 12.57 ($n = 29$)	75.5 ± 9.03 ($n = 17$)

JSVI joint synovial vascularity index

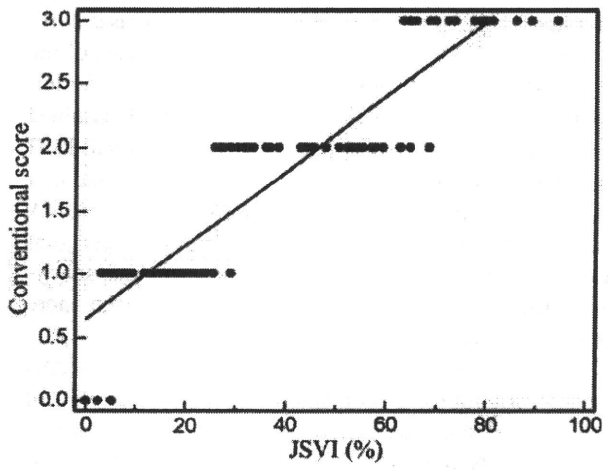

Fig. 2 Correlation between the JSVI and the conventional scoring system. A scatter diagram and regression line are shown. Regression analysis revealed that these two scoring methods are strongly correlated ($R^2 = 0.8629$, $y = 0.02927x + 0.6450$)

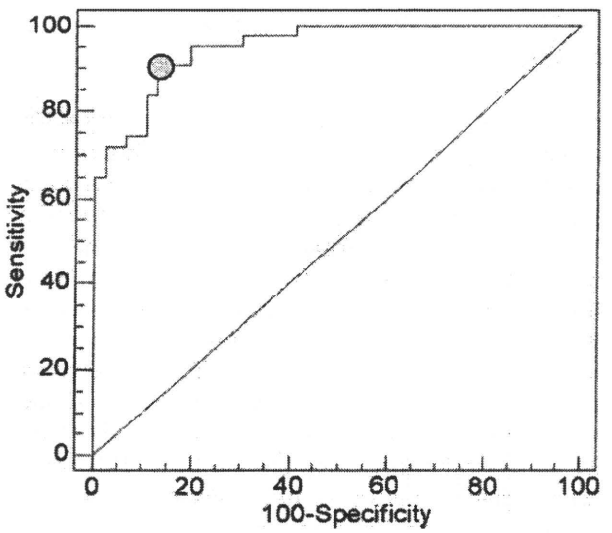

Fig. 3 The receiver operating characteristic (ROC) curve analysis. The ROC *curve* shows the ideal JSVI cut-off value that discriminates between joints of patients with rheumatoid arthritis and those without [ROC–area under the curve (AUC) 0.952 ± 0.024 vs. ROC–AUC 0.5, $P < 0.001$]. The *circle* marks the inflection point, indicating the ideal cut-off value (sensitivity 87%, specificity 90.7%)

Defining an ideal cut-off value for the 20-joint total JSVI with ROC analysis

One of the aims of this study was to define an ideal cut-off value for the 20-joint (sum of MCP joints 1–5 and PIP joints 1–5, for left and right) total JSVI that would distinguish between RA and NI. We examined and diagnosed 89 patients with multiple joint pains; of these, 43 were diagnosed with active RA. Subsequent analysis of the data with ROC analysis (Fig. 3) indicated that the ideal cut-off value was 36%, which agreed with the inflection point of the ROC curve.

Table 2 Screening rheumatoid arthritis in finger joints using the 20-joint total JSVI

Final diagnosis	Patients with a 20-joint total JSVI >36%	Patients with a 20-joint total JSVI <36%
Rheumatoid arthritis	24	2
Non-inflammatory disease	2	22

Sensitivity 92.3%, specificity 91.7%

Screening for RA using the 20-joint total JSVI with a cut-off value of 36%

We next examined whether the 20-joint total JSVI with a cut-off value of 36% was useful in screening for RA. Fifty patients with multiple joint pains who were referred to our hospital were examined. We performed finger joint PD-US on all patients as one of the initial medical examination criteria before making a definitive diagnosis. Twenty-six patients were ultimately diagnosed as having RA according to ACR 1987 diagnostic criteria [6]. The 20-joint total JVSI with a cut-off value of 36% detected RA with a sensitivity of 92.3%, specificity of 91.7% and a positive likelihood ratio of 11.077 (Table 2).

Discussion

Joint ultrasonography is technically classified as grey-scale ultrasonography (GS-US) and PD-US. The former is a useful tool for visualizing abnormal joint structure as it has a higher sensitivity than magnetic resonance imaging (MRI) [13]. In recent studies, PD-US has been able to visualize abnormal joint vascular flow resulting from inflammation and, consequently, enable the evaluation of inflammatory levels in joints [8, 9, 14–16]. The conventional scoring method of finger joint PD-US has been reported, mostly in Europe, to be a useful system for the evaluation of RA activity and to be strongly correlated with the disease activity score 28 (DAS28). This semi-quantitative scoring is useful for evaluating RA activity when used in combination with changes in multiple joints. However, because the conventional scoring method is graded in only four steps, it is not a useful method for evaluating individual joint changes. With growing interest in imaging the remission of sub-clinical joint inflammation [17], an evaluation system for detecting small changes in individual joints is needed. We therefore have improved the conventional scoring method by introducing quantitative measurements which enable small changes in individual joints to be detected. A comparison of our method with the conventional one revealed that they were strongly correlated (Fig. 2). One of our future research projects is to evaluate individual joint synovitis with our scoring method.

The conventional scoring method has some limitations in terms of reliability [18, 19]. When using the conventional scoring, observers must first assess images and then decide upon the score, both subjective judgments. Intra- and interobserver reliability are influenced by the step in the scoring process that is reliant upon subjective decisions alone. With our scoring method, the attachment program in the PD-US machine objectively and automatically measures pixels of the ROI and the vascular flow pixels contained within. Although observers are required to draw the ROI by free-hand in our method, we found the ICC values for intra- and interobserver reliability to be excellent. A recent study reported that the education of observers was important when using the conventional scoring method if reliable outcomes were to be obtained [20]. In contrast, in our scoring method, we switched from human subjective assessments to computer measurements as the observer proxy in order to obtain reliable outcomes.

With the ever-growing interest in the early and accurate diagnosis of RA, many research groups have reported methods for diagnosing early RA with joint imaging techniques [21, 22]. In the study reported here, we first determined whether finger joint PD-US was useful for screening of RA. To this end, we analyzed the data of the 20-joint (sum of MCP joints 1–5 and PIP joints 1–5, for left and right) total JSVI using ROC analysis and determined that a cut-off value of 36% for the 20-joint total JSVI discriminated between RA and NI (Fig. 3). We found that the cut-off value was valuable in screening for RA (Table 2). It is possible that a combination of finger joint PD-US and the analysis of autoantibodies, such as anticyclic citrullinated peptide antibody, would be even more useful for the early diagnosis of RA.

The European League Against Rheumatism (EULAR) response criteria have been widely used to assess clinical improvement of disease activity by comparing the change of DAS28. Its most recent report revealed that even if clinical remission is achieved, sub-clinical joint inflammation still remains locally and joint destruction continues to progress [17]. The MRI and PD-US methods have received attention as a potential tools for detecting sub-clinical joint inflammation. It would be interesting to determine the level of vascularity detected by our scoring method that would indicate the threshold of remission of sub-clinical joint inflammation. Joint MRI images, such as bone oedema, have been reported to be a strong predictor of radiographic progression [22]. Therefore, it would also be of interest to determine whether the individual joint abnormal vascularity detected by our scoring method is a predictor of individual joint destruction. A comparison

between our scoring system and MRI imaging should be undertaken in the future.

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Conflict of interest statement None.

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ORIGINAL ARTICLE

Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study

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Abstract This study is a prospective, randomized, double-blind study to compare the efficacy and safety of 10 mg/kg infliximab with those of 3 mg/kg infliximab treatment in methotrexate-refractory rheumatoid arthritis patients. After the patients received 3 mg/kg infliximab infusion at weeks 0, 2, and 6, they were randomly assigned to be administered 3, 6 or 10 mg/kg infliximab every 8 weeks from week 14 to 46. Mean American College of Rheumatology improvement (ACR-N) at week 54, the primary endpoint, was 51.3% and 58.3% for the 3 mg/kg and 10 mg/kg groups, respectively, with a statistically significant difference. Treatment with 10 mg/kg was found to be remarkably beneficial in patients who had not responded to three infusions with 3 mg/kg at week 10. The median changes in the modified Sharp score were 0.0 in the two groups. There were no significant differences in the incidences of adverse events between the groups. In patients who achieved better clinical response or greater inhibition of progression of joint damage, trough serum infliximab level was significantly higher than in patients who did not. The magnitudes of both efficacies were correlated with the trough serum infliximab level (ClinicalTrials.gov number: NCT00691028).

Keywords Clinical trial · Infliximab · Rheumatoid arthritis · Serum level · Tumor necrosis factor (TNF) antagonist

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Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory disease with the potential to cause substantial joint damage and disability [1]. Tumor necrosis factor-alpha (TNF-alpha) plays a central role in the pathogenesis of RA, as demonstrated by the clinical benefit of anti-TNF alpha therapy, and infliximab (anti-human TNF-alpha monoclonal antibody) therapy has been a great advance in the treatment of RA patients [2–7]. The pivotal multinational clinical study, the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT), showed that repeated treatment with 3 or 10 mg/kg infliximab was more effective than methotrexate (MTX) alone in reducing the clinical symptoms of RA, inhibiting the progression of joint damage, and improving physical function [3, 8]. However, the main purpose of the ATTRACT study was to evaluate the usefulness of the concomitant treatment of infliximab and MTX in comparison with MTX monotherapy, and there was not enough evidence to show an

advantage for therapy with 10 mg/kg over 3 mg/kg. In this prospective, randomized, double-blind study (the RISING study: impact on radiographic and clinical response to infliximab therapy concomitant with methotrexate in patients with rheumatoid arthritis by trough serum level in a dose-escalating study), we examined the usefulness of infliximab at the maximum dose (10 mg/kg) compared with the minimum dose (3 mg/kg) as a control. In addition, we investigated the association between the trough serum infliximab level and the magnitude of clinical response or inhibition of progression of joint damage.

Patients and methods

Patients

Eligible patients were those aged between 18 and 75 years who met the 1987 revised criteria of the American College of Rheumatology (ACR) for the classification of RA [9]. Patients were eligible if they had active RA despite treatment with MTX for more than 12 weeks. Active RA was defined in this study by the presence of six or more swollen joints, six or more tender joints, and an erythrocyte sedimentation rate (ESR) of at least 28 mm/h, or a serum C-reactive protein (CRP) concentration of at least 2.0 mg/dl.

Patients were excluded if they had: dysfunction with Steinbrocker functional class 4 [10]; other connective tissue disease with joint symptoms except Sjögren's syndrome; a history of infliximab therapy; experience of therapy with other biological agents within 4 months before registration; been treated with glucocorticoid injections or immunosuppressive agents such as lefulnomide and tacrolimus. Other exclusion criteria were: a history of serious or opportunistic infection within 6 months before registration; active tuberculosis; hepatitis B virus, hepatitis C virus or human immunodeficiency virus (HIV) carriers; and those with chronic infectious diseases.

Study protocol

The RISING study was a prospective, multicenter, double-blind, paralleled, comparative study conducted at 88 medical institutes in Japan. The study protocol was approved by the local institutional review board (IRB) of each study institution, and was carried out in accordance with the Helsinki Declaration and Good Clinical Practice. Patients gave their written informed consent prior to registration for this study. This study was registered with http://www.clinicaltrials.gov (NCT00691028).

In the open-label study from weeks 0 to 14, all patients enrolled in this study received 3 mg/kg infliximab at weeks 0, 2, and 6. At week 10, patients were randomly assigned to three treatment groups (3, 6 or 10 mg/kg) using a dynamic assignment conducted so that the clinical efficacy in ACR20 and ACR50 responses [11] at week 10 was similar among the three groups. Then, infliximab at doses of 3, 6 or 10 mg/kg was administered every 8 weeks from week 14 to 46 in a double-blind fashion, and the efficacies were evaluated at week 54. Adverse events were evaluated until week 54. In patients in whom administration was discontinued, adverse events were assessed until 12 weeks after final administration.

Over the entire study period, disease modifying antirheumatic drugs (other than leflunomide, tacrolimus, cyclosporine, and azathioprine), nonsteroidal anti-inflammatory drugs, oral glucocorticoids (prednisolone $\leq$10 mg/day), and folic acid preparations were permitted at the stable dose from at least 4 weeks before registration. The dose of MTX must have been stable (6 mg/week or more: the approved maximum dose of MTX for RA in Japan is 8 mg/week) for more than 4 weeks just before registration and over the entire study period.

Endpoints

The primary endpoint for clinical response was mean percentage American College of Rheumatology improvement (ACR-N) [4, 12, 13] in 3 and 10 mg/kg groups from baseline to week 54. ACR responses (ACR20, ACR50, and ACR70), disease activity score in 28 joints (DAS28) change [14], and European League against Rheumatism (EULAR) response [15] were also evaluated at week 54. We also subanalyzed the clinical response at week 54 in the patients with EULAR no response to three infusions (at week 0, 2 and 6) with 3 mg/kg at week 10.

Radiographic progression of joint damage was quantified as the change from baseline to week 54 in the total modified Sharp score (TSS) with a range of 0–390 [16, 17]. Two readers scored the radiographs independently without knowledge of treatment assignment, clinical response or the order of the radiographs. Radiographic progression of disease was defined as damage from baseline in TSS that was larger than the smallest detectable difference (SDD) [18]. The SDD in this study was 4.1. The progression of joint damage was categorized in TSS as follows: progressed (>4.1), no change (≥ -4.1 and $\leq$4.1), and improved (<-4.1).

Improving physical function at week 54 was evaluated by the change in the health assessment questionnaire (HAQ) score [19] and the percentage of patients who achieved an improvement of HAQ score exceeding 0.22 units, a value which may be clinically significant [20]. The trough serum infliximab level at week 54 was measured by enzyme-linked immunosorbent assay (ELISA), using a monoclonal

antibody against infliximab obtained from Centocor Ortho Biotech Inc., as previously described [2]. The lowest level of infliximab that could be reliably detected was 0.1 μg/ml. The serum trough level was measured in Mitsubishi Tanabe Pharma Corporation, Osaka, Japan, and the coefficient of variation or relative error values of intra- and interassay was within 20% or within ±25%, respectively.

The associations between the clinical response or the progression of joint damage and the trough serum infliximab level at week 54 were investigated in patients for whom the trough serum levels and DAS28 or TSS were obtained at week 54.

Statistical analysis

Since the aim of the RISING study is to compare the usefulness of the 10 mg/kg infliximab treatment with that of the 3 mg/kg in MTX-refractory RA patients, the sample size of the study was determined by the predicted values of ACR-N in 3 and 10 mg/kg groups in the ATTRACT study. A size of 100 patients per group gave 90% power to detect a difference in the primary endpoint (ACR-N) between the 3 and 10 mg/kg groups by use of the two-sided t test at $\alpha = 0.05$ with detection power of $1 - \beta = 0.90$.

Because the jumped dose escalation from 3 to 10 mg/kg was thought not to be realistic in clinical practice, we also investigated the efficacy and safety of 6 mg/kg treatment as an intermediate dose.

Efficacy was analyzed in the full analysis set. The efficacy other than the joint damage was assessed using the last observation carried forward approach.

Covariance analysis was performed, using the treatment groups as factors and ACR-N at week 10 as a covariant, to compare the parameters for evaluating differences in clinical responses between the 3 and 10 mg/kg groups. As a subanalysis, the results were compared between the 3 and 6 mg/kg groups, as well as between the 6 and 10 mg/kg groups. The HAQ scores were compared by covariance analysis using the treatment groups as factors and HAQ score at week 0 as a covariant. To compare the TSS changes among the treatment groups, we employed Van Elteren's test. Spearman's rank correlation coefficient was used in assessing the clinical response at week 54 in the patients with EULAR no response at week 10, and the association between the efficacy and the trough serum infliximab level. The incidences of adverse events were compared using the chi-squared test.

Results

Patient background

In the RISING study, 334 patients were enrolled. Of these, 327 received infliximab therapy at 3 mg/kg during the open-label period (Fig. 1). At week 10, 314 patients were randomized. The most common reason for discontinuation from week 0 to 14 was adverse events. A total of 307 patients were assigned to one of the 3, 6 or 10 mg/kg groups in the double-blind period starting from week 14. There were no significant differences in the backgrounds of

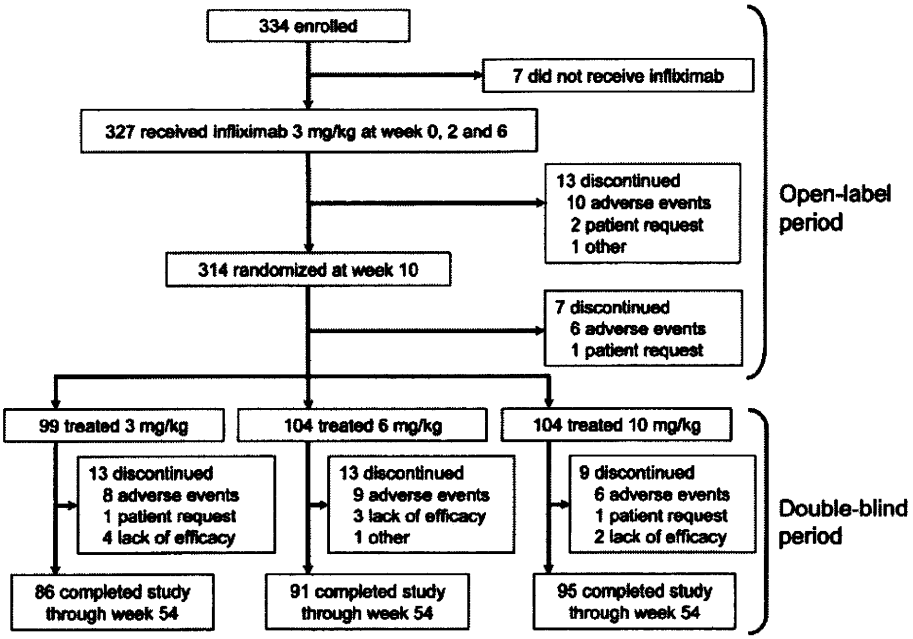

Fig. 1 Randomization, reason for discontinuing treatment, and number of patients completing the study. All patients received concomitant methotrexate

each group such as age, dose of MTX, disease activity, progression of joint damage or physical function (Table 1).

Two hundred seventy-two patients (88.6%) of the 307 patients completed this study. The main reason for discontinuation was adverse events, and there was no significant difference among all treatment groups.

Clinical response and improvement in physical function

ACR-N at week 54 in the 10 mg/kg group, the primary endpoint, was significantly higher ($p = 0.024$) than that in the 3 mg/kg group (Table 2). The ACR20, ACR50, and ACR70 responses at week 54 were 75.8%, 60.6%, and 37.4% in the 3 mg/kg group, 78.8%, 58.7%, and 42.3% in the 6 mg/kg group, and 82.7%, 66.3%, and 43.3% in the 10 mg/kg group, respectively, with no significant difference. There were significant differences in the reduction in DAS28 change and EULAR responses between the 3 and 10 mg/kg groups. No significant difference was observed in the proportions of patients achieving remission (DAS28 < 2.6) between the two groups.

Improvement in the HAQ score and the rate of patients with >0.22 units improvement were more marked in the 10 mg/kg groups than in the 3 mg/kg group, although there was no significant difference.

In the 6 mg/kg group, clinical responses and the improvement in physical function were intermediate between the 3 and 10 mg/kg groups.

Figure 2 showed the EULAR responses at week 54 in patients with EULAR no responses to three infusions with 3 mg/kg at week 10 ($n = 37$). The rate of responders

Table 1 Baseline demographics and clinical characteristics of patients enrolled in the double-blind study

	3 mg/kg ($n = 99$)	6 mg/kg ($n = 104$)	10 mg/kg ($n = 104$)
Age, mean (SD) (years)	49.7 (11.7)	48.8 (11.8)	50.4 (12.5)
Body weight, mean (SD) (kg)	57.3 (11.2)	54.1 (9.1)	54.7 (10.1)
Women, no. (%)	78 (78.8)	86 (82.7)	89 (85.6)
Comorbidity, no. (%)	81 (81.8)	80 (76.9)	78 (75.0)
Steinbrocker grade, no. (%)			
I	8 (8.1)	8 (7.7)	14 (13.5)
II	39 (39.4)	44 (42.3)	27 (26.0)
III	30 (30.3)	31 (29.8)	37 (35.6)
IV	22 (22.2)	21 (20.2)	26 (25.0)
Steinbrocker class, no. (%)			
1	15 (15.2)	26 (25.0)	15 (14.4)
2	77 (77.8)	68 (65.4)	80 (76.9)
3	7 (7.1)	10 (9.6)	9 (8.7)
Duration of disease, mean (SD), (years)	8.3 (7.8)	7.2 (7.1)	8.4 (7.7)
Duration of disease <3 years, no (%)	26 (26.3)	38 (36.5)	32 (30.8)
Weekly MTX dose, mean (SD) (mg/week)	7.8 (1.6)	7.9 (1.9)	7.7 (1.7)
Oral glucocorticoid, no. (%)	66 (66.7)	73 (70.2)	71 (68.3)
Tender joint count, mean (SD)	18.6 (11.3)	18.0 (10.5)	17.5 (10.9)
Swollen joint count, mean (SD)	14.2 (6.1)	13.1 (8.4)	13.7 (7.3)
CRP level, mean (SD) (mg/dl)	3.0 (2.4)	3.0 (2.7)	3.0 (2.3)
HAQ score, mean (SD)	1.18 (0.64)	1.18 (0.65)	1.21 (0.68)
DAS28, mean (SD)	6.2 (1.0)	6.2 (1.0)	6.2 (0.8)
Total Sharp score, median (IQR)	28.0 (9.0, 77.5)[a]	32.2 (12.0, 62.4)[b]	38.3 (11.0, 73.8)
Total Sharp score, mean (SD)	49.6 (53.7)[a]	47.4 (52.3)[b]	51.9 (47.1)

Tender joint count: sixty-eight joints were assessed. Swollen joint count: sixty-six joints were assessed. HAQ score: scores can range from 0 (no difficulty) to 3 (unable to perform this activity). Total Sharp score: scores can range from 0 to 390 (erosion score: 0–230, and joint space narrowing score: 0–160), with high scores indicating more joint damage

CRP C-reactive protein, *HAQ* Health Assessment Questionnaire; *DAS28* disease activity score in 28 joints; *IQR* interquartile range

[a] $n = 98$

[b] $n = 103$

Table 2 Clinical efficacy of high-dose infliximab therapy in RA patients from baseline to week 54

	3 mg/kg ($n = 99$)	6 mg/kg ($n = 104$)	10 mg/kg ($n = 104$)
Reducing signs and symptoms			
ACR-N, mean (SD), %	51.3 (32.1)	53.8 (34.4)	58.3 (31.3)*
Reduction in DAS28, mean (SD)	2.30 (1.56)	2.57 (1.69)	2.80 (1.58)**
EULAR response, no. (%)			
Moderate or good response	78 (78.8)	87 (83.7)	94 (90.4)**
Good response	37 (37.4)	52 (50.0)*	52 (50.0)*
DAS28 remission (DAS28 < 2.6), no. (%)	25 (25.3)	34 (32.7)	34 (32.7)
Improving physical function			
Improvement in HAQ score, mean (SD)	0.48 (0.70)	0.56 (0.64)	0.59 (0.63)
Rates of clinically meaningful improvement, no. (%)	69 (69.7)	75 (72.1)	76 (73.1)

Clinically meaningful improvement was defined as an improvement in HAQ score >0.22

ACR-N numeric ACR response

*$p < 0.05$ versus 3 mg/kg group, **$p < 0.01$ versus 3 mg/kg group

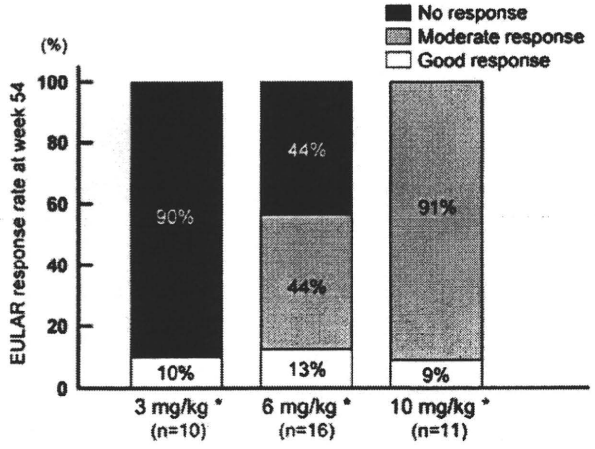

Fig. 2 Clinical response at week 54 in each group according to EULAR response criteria in nonresponders at week 10 to three infusions with 3 mg/kg. *$p < 0.001$, overall

(good or moderate response) at week 54 for 3 mg/kg was only 10%, while it was 56% and 100% for 6 and 10 mg/kg, respectively, with significant differences ($p < 0.001$, overall).

Radiographic progression

The median changes of TSS at week 54 were 0.0 in the 3 and 10 mg/kg groups (Fig. 3); the progression of joint damage was inhibited in most of the patients. There were no significant differences between the two groups. In the 6 mg/kg group, the median change in TSS was 0.5, significantly different to that at 10 mg/kg group. This was possibly associated with the finding that the most rapid yearly progression of joint damage was in the 6 mg/kg group. The percentages of patients with no progression of joint damage (improved or no change) in the 3, 6, and 10 mg/kg groups were 93.0%, 87.0%, and 94.7%, respectively. There was no significant difference among these groups.

Association between trough serum infliximab level and clinical response or radiographic progression

To explore the usefulness of higher doses of infliximab, the relationship between trough serum infliximab level and the magnitude of response was evaluated. The median (interquartile range, IQR) trough serum levels at week 54 in the 3, 6, and 10 mg/kg groups were 0.4 (<0.1, 1.5), 2.3 (0.3, 4.7), and 5.5 (1.5, 9.0) μg/ml, respectively, showing dose dependency.

As shown in Table 3, a significant association was observed between clinical response and trough serum infliximab levels at week 54. Better EULAR response was obtained in patients with higher trough serum infliximab levels ($p < 0.0001$). Furthermore, patients achieving remission also had significantly higher trough serum levels than patients without remission ($p < 0.0001$).

Significant differences were observed among trough serum infliximab levels at week 54 in patients classified as progressed, no change or improved in joint damage ($p = 0.0022$). Overall, the proportion of patients showing a good response increased with increasing trough serum infliximab level.

On the other hand, we classified the patients into four groups based on the trough serum level at week 54 (<0.1, ≥0.1 and <1.0, ≥1.0 and <10, and ≥10.0 μg/ml), and examined the EULAR response and the TSS change in each group (Table 4). Median (IQR) estimated yearly

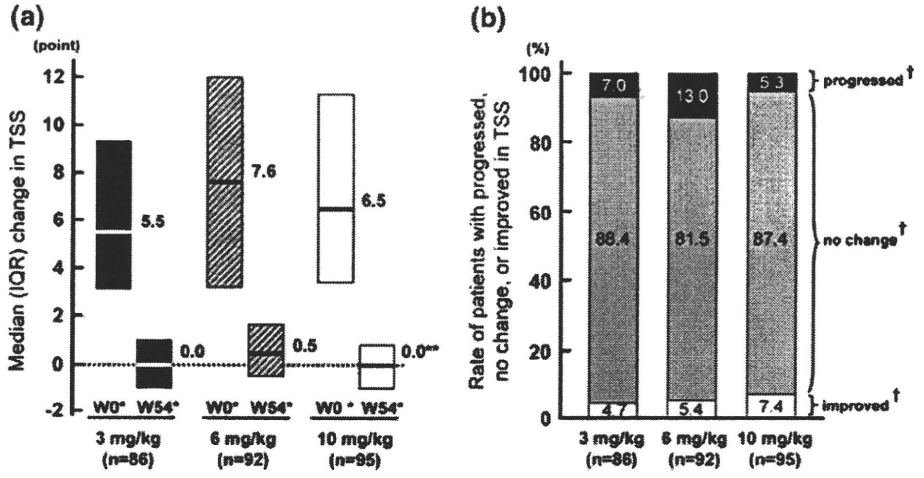

Fig. 3 Progression of joint damage in each group according to total modified Sharp score (TSS) at week 54: median (IQR) change score in TSS (**a**), and the rate of patients with progression, no change or improved in TSS (**b**). †Radiographic progression was categorized in TSS as follows: progressed (>4.1), no change (≥−4.1 and ≤4.1), and improved (<−4.1). W0*: Estimated yearly progression of TSS before infliximab therapy. W54*: Progression of TSS from baseline to week 54. **$p = 0.022$ versus 6 mg/kg group

Table 3 Serum trough level of infliximab in patients who showed efficacy of infliximab

Blood samples were obtained at week 54. Serum infliximab level were quantified by ELISA

Radiographic progression was categorized by total modified Sharp score as follows: progressed (>4.1), no change (≥−4.1 and ≤4.1), and improved (<−4.1)

	Trough serum infliximab level, median (IQR), μg/ml	*p* value (overall)
EULAR response		
No response ($n = 31$)	<0.1 (<0.1, 0.3)	
Moderate response ($n = 106$)	1.1 (<0.1, 3.6)	<0.0001
Good response ($n = 134$)	3.0 (1.5, 7.2)	
DAS28 remission (DAS28 < 2.6)		
No remission ($n = 182$)	1.0 (<0.1, 3.7)	<0.0001
Remission ($n = 89$)	3.1 (1.5, 7.1)	
Radiographic progression		
Progressed ($n = 23$)	0.5 (<0.1, 2.1)	
No change ($n = 231$)	2.0 (0.1, 5.4)	0.0022
Improved ($n = 16$)	3.8 (1.6, 6.7)	

progression of TSS before infliximab therapy in each group (<0.1, ≥0.1 and <1.0, ≥0.1 and <1.0, and ≥10.0 μg/ml) was 5.7 (3.6, 10.0), 6.7 (2.1, 13.0), 7.2 (3.4, 12.0), and 4.8 (2.6, 7.9), and there was no significant difference among these groups. The proportion of patients assessed as having no EULAR response decreased with increasing trough serum level, and there were no patients who showed no response when the trough serum level was 10.0 μg/ml or more. Overall, the proportion of patients showing good response increased with increasing trough serum level. There was a significant correlation between trough serum level and DAS28 remission as well as EULAR response ($p < 0.0001$).

Progression of joint damage was most frequently observed in patients with <0.1 μg/ml trough serum level, and none of these patients showed improvement. In contrast, there was no case with progression of joint damage in patients with >10.0 μg/ml trough serum level. There was also a negative correlation between progression of joint damage and trough serum level ($p = 0.0043$). The change of TSS as a cumulative probability plot showed that inhibition of progression of joint damage was more accurately predicted by an increase in trough serum level (Fig. 4a). This tendency was more remarkable in early RA patients whose duration of disease was less than 3 years (Fig. 4b) [4, 13, 21]. In patients with early RA and with <0.1 μg/ml trough serum level, the percentage of the progressed category was 35.0%.

Safety profile

There was no significant difference in the incidence of adverse events or serious adverse events among the groups (Table 5). The incidences of adverse events leading to