ARTHRITIS & RHEUMATISM
Vol. 65, No. 8, August 2013, pp 2005–2014
DOI 10.1002/art.38016

Sonographic Joint Assessment in Rheumatoid Arthritis

Associations With Clinical Joint Assessment During a State of Remission

Miriam Gärtner,[1] Peter Mandl,[2] Helga Radner,[1] Gabriela Supp,[1] Klaus P. Machold,[1] Daniel Aletaha,[1] and Josef S. Smolen[1]

Objective. **Sonography, as compared with clinical assessment, is a sensitive tool for evaluating synovitis in rheumatoid arthritis (RA). However, differences between these assessment tools may depend on how joint activity (i.e., an active joint) is defined. The present study was undertaken to compare clinically active joints with sonographically active joints in patients with RA, applying different sonographic definitions of an active joint.**

Methods. **Sonographic assessment of the finger and wrist joints (total of 11 joints) of each hand was performed in RA patients whose disease was in remission (Clinical Disease Activity Index ≤2.8; n = 60). Gray-scale (GS) and power Doppler (PD) ultrasound signals for synovitis were evaluated on a 4-point scale (grade 0 = none, grade 3 = severe). The sensitivity and specificity of swollen joint counts were investigated using, as reference, increasingly stringent sonographic definitions of an active joint. Sonographic findings were also assessed for correlations with other clinical variables, including the Health Assessment Questionnaire (HAQ) disability index (DI). Followup analyses were performed after 6–12 months.**

Results. **GS ultrasound signals yielded positive findings for synovitis in 67.2% of the 1,320 joints assessed, and PD ultrasound signals indicated signs of synovitis in 20.4% of the joints assessed. Clinical identification of joint swelling was 100% specific for sonographic joint activity, independent of the stringency of the sonographic definition used; maximum sensitivity of the swollen joint counts was 25% for the most stringent definition (i.e., GS grade 3 and PD grade 3). Furthermore, patients with a higher-grade PD signal (grade 3) showed a higher HAQ DI score compared to patients with lower-grade PD signals (mean ± SD HAQ DI 0.45 ± 0.62 versus 0.20 ± 0.35). A higher grade of PD signal at baseline was found in joints that were assessed as clinically swollen at the consecutive followup visit.**

Conclusion. **Low-grade PD and GS ultrasound signals may not necessarily reflect the presence of active synovitis in RA joints. High-grade PD signals correlate well with the presence of clinical joint swelling and clinical disease activity, and a higher grade of PD signal is associated with higher degrees of functional impairment.**

Joint damage and functional impairment are highly important adverse outcomes of rheumatoid arthritis (RA). They have been repeatedly shown to be associated with clinical disease activity, in particular with swollen joint counts and acute-phase reactant levels, as well as composite measures of disease activity in which these variables are included as components (1–3). Moreover, in states of very low disease activity, progression of joint damage is related to residual joint swelling rather than acute-phase reactant levels (2), and the association between radiographic progression and joint swelling has been observed at the level of individual joints (3). Interestingly, grading the extent of clinical joint swelling

This is a publication of the Joint and Bone Center for Diagnosis, Research, and Therapy of Musculoskeletal Disorders of the Medical University of Vienna.

Supported in part by Pfizer, the European Union Seventh Framework Programme (Coordination Theme 1 [Health], project Masterswitch; HEALTH-F2-2008-223404), and the Innovative Medicines Initiative Joint Undertaking (BTCure grant 115142).

[1]Miriam Gärtner, MD, Helga Radner, MD, Gabriela Supp, MS, Klaus P. Machold, MD, Daniel Aletaha, MD, Josef S. Smolen, MD: Medical University of Vienna, Vienna, Austria; [2]Peter Mandl, MD, PhD: National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, and Medical University of Vienna, Vienna, Austria.

Dr. Mandl has received consulting fees, speaking fees, and/or honoraria from Pfizer, Abbott, and AbbVie (less than $10,000 each).

Address correspondence to Josef S. Smolen, MD, Department of Rheumatology, Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria. E-mail: Josef.smolen@meduniwien.ac.at.

Submitted for publication December 22, 2012; accepted in revised form May 7, 2013.

has not withstood sensitivity analyses over time (4), and therefore it is recommended that evaluation of joint swelling be performed in an ungraded manner (5). Thus, any clinical swelling is deemed indicative of progression of destruction, while "more swelling" in an individual joint is not considered to result in more damage. However, in clinical practice, a joint should only be classified as clinically swollen if the swelling is beyond doubt (6).

Today's therapeutic targets in patients with RA are achievement of disease remission or low disease activity, whereby the term remission comprises lack of clinical disease activity, halt of joint damage progression, and normalization or maximal improvement of physical function (7). Nevertheless, it has been suggested that some patients may experience radiographic progression of joint disease despite being in clinical remission (8), although this presumably is a carry-over effect of past disease activity (9). Nevertheless, if clinical assessment of joint swelling is not a sufficiently reliable method to assess patients with RA in a state of remission, more sensitive methods for assessment of disease activity might be needed.

Sonography is a useful and highly sensitive tool for the evaluation of joint involvement in RA (10). Signs of synovitis, i.e., synovial effusion and synovial hypertrophy, are evaluated on gray-scale (GS) ultrasound. Color Doppler and power Doppler (PD) ultrasound techniques allow the sensitive characterization of blood flow in small joints, with PD especially suited for detecting superficial, slow-velocity flow due to either the vasodilation of normally existing vessels, neoangiogenesis, or a combination of both, as is typically seen in inflamed joints (11–14). PD imaging, in particular, was shown to be as sensitive as magnetic resonance imaging in detecting inflammation (15), and both GS and PD ultrasound techniques have been demonstrated to be reliable and sensitive to change (16–20).

Ultrasound also appears to detect subclinical synovitis in patients who are in clinical remission, i.e., without clinically swollen joints (11,21–24). The weak correlation of sonographic findings with clinical findings may be explained by the high sensitivity of sonography. Indeed, several studies have indicated that there may be no difference in the number of active joints measured by sonography between patients who are in clinical remission and those who are not in remission (22–24).

Furthermore, ultrasound-detected synovitis has demonstrated predictive validity with regard to radiographic progression (25–27). A recent study demonstrated that ultrasound, and specifically PD ultrasound, may predict radiographic progression of joint disease even in patients with RA whose disease is in clinical remission (28), but the results were dependent on the grade of PD signal detected.

To fully appreciate the potential added value of sonography over clinical joint assessment, we compared these 2 examination methods in the present study, taking into account the differences in quantification method (graded assessment by sonography and binary approach for clinical evaluation) and the impact of the findings on various aspects of the disease, especially physical function.

PATIENTS AND METHODS

Patients. Participants in the study were consecutive RA patients (age ≥18 years) who regularly visited our outpatient clinic and whose diagnosis met the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria for RA (29). The patients were divided into 2 groups: a remission cohort (with remission defined as a Clinical Disease Activity Index [CDAI] ≤2.8 [30]) and a convenience sample of patients with higher levels of disease activity (CDAI >2.8). There were no restrictions regarding treatment, disease duration, or comorbidities.

The study was approved by the local ethics committee and conducted according to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Clinical assessment. Tender and swollen joint counts (31) were performed on 28 joints in all patients. Swelling and tenderness were defined in accordance with the standardized assessment recommendations from EULAR, whereby, in the presence of any doubt, a joint was considered "not swollen" (6). For the evaluation of pain and global assessments of disease activity (both patient's and evaluator's), 100-mm visual analog scales (VAS) were used. Patients were also asked about the duration of morning stiffness (in minutes). In addition, the Health Assessment Questionnaire (HAQ) disability index (DI) (32) was used to determine the extent of the patients' physical function. Demographic and clinical data, as well as laboratory results, including the C-reactive protein level, erythrocyte sedimentation rate, presence of rheumatoid factor, and presence of anti–citrullinated protein antibodies, were collected from the patients' charts. For the evaluation of disease activity, the CDAI, Simplified Disease Activity Index (SDAI), and Disease Activity Score in 28 joints (DAS28) were used (5).

Sonographic assessment. All sonographic assessments were performed using high-sensitivity ultrasound equipment (Logiq E9; General Electric), with an ML 6-15 transducer. Sonographic assessments were performed using a frequency range from 9 MHz to 15 MHz. When performing PD ultrasound evaluation, the pulse repetition frequency was set between 500 Hz and 800 Hz, and receiver gain settings were controlled to eliminate the appearance of artifacts. Synovitis was defined according to the published Outcome Measures in Rheumatoid Arthritis Clinical Trials definitions (14).

An experienced sonographer (GS) who had no access to the clinical and laboratory data and was unaware of the results of the clinical joint examination evaluated 11 joints of each hand (including the proximal interphalangeal [PIP] joints,

the metacarpophalangeal [MCP] joints, and the wrists), using the method proposed by Filer et al (33) for both GS and intraarticular PD ultrasound signals. All included joints were scanned for GS and PD signals in the dorsal aspect, using longitudinal midline planes as well as transversal planes. The wrists were additionally examined using longitudinal dorsoradial and dorso-ulnar scans. GS and PD signals for signs of synovitis were graded using a 4-grade semiquantitative scoring system, on a scale of 0–3 (grade 0 = none, grade 1 = mild, grade 2 = moderate, and grade 3 = severe), according to the method developed by Szkudlarek et al (34). The highest GS and PD grade detected during the different scans was adopted as representative for each respective joint.

The intraobserver reliability of sonographic examinations (assessed by performing the evaluation twice in 10 patients on the same day) revealed a good intraclass correlation coefficient (ICC) of 0.978 (0.972 for GS ultrasound and 0.665 for PD ultrasound). The interobserver reliability (using sonographic examinations of identical joints in 10 patients performed by 2 experienced sonographers [GS and PM] independently on the same day) likewise revealed good agreement (ICC of 0.856 for all sonographic assessments, 0.837 for GS ultrasound, and 0.762 for PD ultrasound). These levels of reliability were very similar to those observed in recent evaluations of the metrologic properties of joint sonography (19,20). In all analyses, the sonographic grades were stratified according to the level of "stringency" for defining an active joint; in this context, stringent was taken to indicate a GS and/or PD signal grade of ≥1, more stringent as a GS and/or PD signal grade of ≥2, and most stringent as a GS and/or PD grade of 3.

Statistical analysis. For statistical analyses, SPSS software (version 20.0; IBM) was used. Normally distributed data are presented as the mean ± SD, and *t*-tests were performed for statistical comparisons. Analysis of variance was performed for group comparisons, and the chi-square test was conducted to analyze categorical variables. Cohen's kappa was calculated to determine agreement between clinical and sonographic findings. Spearman's correlation coefficients were calculated to determine correlations between clinical and sonographic findings.

We investigated the sensitivity and specificity of the clinical assessments of swollen and tender joint counts for the

Table 1. Baseline demographic and clinical characteristics and sonographic signal grades in each study cohort*

	Patients with RA in clinical remission (n = 60)	Patients with RA not in clinical remission (n = 30)	*P*
Age, years	60.1 ± 10.8	60.1 ± 11.3	0.9946
Female, no. (%)	47 (78.3)	23 (76.7)	0.8597
Disease duration, years	9.4 ± 8.9	10.3 ± 7.7	0.6725
CDAI	1.0 ± 0.9	11.2 ± 8.1	<0.0001
SDAI	1.4 ± 0.9	11.8 ± 8.1	<0.0001
DAS28	2.2 ± 0.5	3.8 ± 1.1	<0.0001
SJC28	0.3 ± 0.5	3.2 ± 3.3	<0.0001
TJC28	0.1 ± 0.4	3.0 ± 4.0	<0.0001
VAS pain, mm	4.0 ± 6.5	32.4 ± 25.4	<0.0001
Global assessment of disease activity, mm			
Evaluator's	1.6 ± 2.2	16.0 ± 13.5	<0.0001
Patient's	4.4 ± 6.7	34.1 ± 24.9	<0.0001
CRP, mg/dl	0.4 ± 0.4	0.6 ± 0.5	0.0306
ESR, mm/hour	22.9 ± 16.1	30.5 ± 25.4	0.0993
RF, % positive	63.3	50.0	0.3203
ACPAs, % positive	61.6	60.0	0.9907
Duration of morning stiffness, minutes	5.1 ± 31.1	22.9 ± 36.9	0.0187
HAQ DI	0.2 ± 0.3	0.8 ± 0.7	0.0015
Sonographic findings			
GS grade of synovitis	20.75 ± 8.8	24.7 ± 12.8	0.0908
PD grade of synovitis	7 ± 5.8	9.3 ± 7.8	0.160
GS grade, no. (%)			0.1630
Grade 0	1 (1.6)	0	
Grade 1	9 (15.0)	3 (10.0)	
Grade 2	34 (56.7)	12 (40.0)	
Grade 3	16 (26.7)	15 (50.0)	
PD grade, no. (%)			0.1384
Grade 0	4 (6.7)	6 (20.0)	
Grade 1	33 (55.0)	10 (33.3)	
Grade 2	18 (30.0)	11 (36.7)	
Grade 3	5 (8.3)	3 (10.0)	

* Except where indicated otherwise, values are the mean ± SD. RA = rheumatoid arthritis; CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index; DAS28 = Disease Activity Score in 28 joints; SJC28 = swollen joint count in 28 joints; TJC28 = tender joint count in 28 joints; VAS = visual analog scale; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; ACPAs = anti–citrullinated protein antibodies; HAQ DI = Health Assessment Questionnaire disability index; GS = gray-scale (ultrasound); PD = power Doppler (ultrasound).

presence of any sonographically detected changes in disease activity. We then tested the association of the clinical findings with both the GS signal and the PD signal in different combinations of sonographic features with different cutoff points, as follows: GS grade ≥1 and PD grade ≥1; GS grade ≥1 and PD grade ≥2; GS grade ≥1 and PD grade 3; GS grade ≥2 and PD grade ≥1; GS grade ≥2 and PD grade ≥2; GS grade ≥2 and PD grade 3; GS grade 3 and PD grade ≥1; GS grade 3 and PD grade ≥2; and GS grade 3 and PD grade 3.

To determine the value of sonographic assessment for evaluation of a state of remission, we calculated a sonography-based CDAI (sCDAI), in a multimodal way similar to that done in a recent study (20,35). In this index, we replaced the clinical swollen joint count with the 22 joints that were assessed by ultrasound, again using the various combinations of sonographic activity criteria described above. However, for the remaining 6 joints from the 28-joint count (elbows, shoulders, and knees), the result of the clinical examination was utilized for both the clinical and the sonographic joint count. Thus, the sCDAI was calculated as follows: sCDAI = number of active joints by sonography (wrists, PIPs, MCPs; range 0–22 joints) + clinical swollen joint count on remaining joints (elbows, shoulders, knees; range 0–6 joints) + clinical tender joint count in 28 joints + patient's global assessment of disease activity + evaluator's global assessment of disease activity.

RESULTS

Demographic and clinical data. In total, 90 RA patients were assessed. The demographic and clinical characteristics of the 60 patients with RA whose disease was in clinical remission (CDAI ≤2.8) and the control cohort of 30 patients with active RA (CDAI >2.8) are listed in Table 1.

Sonographic findings in patients with RA during a state of clinical remission. The numbers of patients with RA in clinical remission and those with active RA who exhibited at least 1 joint with different grades of GS and PD signals are shown in Table 1. Among the patients with RA in clinical remission, a total of 1,320 joints were assessed. As shown in Table 2, one-third of these 1,320 joints showed no indication of synovitis by both criteria (GS signal grade 0 and PD signal grade 0), while 1 in 5 joints (269 [20.4%] of 1,320 assessed) showed PD signals and two-thirds (887 [67.2%]) showed GS signals indicative of synovitis (Table 2). All joints with PD signals also showed GS signals, both in patients with RA in remission and in controls with active RA.

Interestingly, the majority (703 [79.3%]) of the 887 GS-positive joints exhibited only the lowest grade of synovitis (GS grade 1), while 150 joints (16.9%) had GS grade 2 and only 34 joints (3.8%) had GS grade 3. Quite similar results were observed in the distribution of the PD signals. Among the 269 PD-positive joints, 213 (79.2%) had PD grade 1, 49 (18.2%) had PD grade 2, and only 7 (2.6%) exhibited a PD grade 3 signal. Of note, among the GS-positive joints of patients with RA in remission, 69.7% had no PD signals and only 6.3% had a PD grade ≥2. Most patients had at least 1 sonographically involved joint; only a single patient lacked positivity for both GS and PD signals in all joints, and 3 additional patients lacked a PD signal in all examined joints.

Even though the overall percentage of PD- and GS-positive joints did not vary between patients with active RA and patients with RA in remission (66.1% versus 67.2% showing GS signals; 20.9% versus 20.4% showing PD signals), significantly more joints in the group not in clinical remission had higher GS signal grades (GS grade ≥2) compared to patients whose disease was in remission (23.2% versus 14% of joints; $P < 0.0001$ by chi-square test). A similar trend was seen for joints with a PD signal grade ≥2 (6.8% of joints in the active RA group versus 4.2% of joints in the clinical remission group; $P = 0.0629$).

Table 2. Frequencies of the different GS and PD ultrasound grades of synovitis among 1,320 evaluated joints in 60 patients with RA in clinical remission and 660 evaluated joints in 30 control patients with active RA*

	PD grade							
	Clinical remission				Active RA			
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3
GS grade								
Grade 0	433 (32.8)	0	0	0	224 (34.0)	0	0	0
Grade 1	531 (40.2)	152 (11.5)	20 (1.5)	0	233 (35.3)	45 (6.8)	5 (0.7)	0
Grade 2	72 (5.5)	52 (3.9)	23 (1.7)	3 (0.2)	56 (8.5)	28 (4.2)	16 (2.4)	1 (0.2)
Grade 3	15 (1.2)	9 (0.7)	6 (0.5)	4 (0.3)	9 (1.4)	20 (3.0)	20 (3.0)	3 (0.5)

* Values are the number (%) of joints with the indicated gray-scale (GS) and/or power Doppler (PD) sonographic grade of synovitis among the total number of joints evaluated. Among the patients with rheumatoid arthritis (RA) in clinical remission, the distribution of joints with GS and PD grades 0–3 was as follows: for GS, grade 0 n = 433, grade 1 n = 703, grade 2 n = 150, grade 3 n = 34; for PD, grade 0 n = 1,051, grade 1 n = 213, grade 2 n = 49, grade 3 n = 7. Among the patients with active RA, the distribution of joints with GS and PD ultrasound grades 0–3 was as follows: for GS, grade 0 n = 224, grade 1 n = 283, grade 2 n = 101, grade 3 n = 52; for PD, grade 0 n = 522, grade 1 n = 93, grade 2 n = 41, grade 3 n = 4.

Comparative analysis of sonographic and clinical joint assessment. Only 15 joints (1.2% of all assessed) were clinically swollen in patients in remission, while 97 joints (14.7%) exhibited clinical swelling in the active disease controls. To evaluate agreement between sonographic and clinical assessment on the basis of individual joints, Cohen's kappa was calculated for the agreement in the swollen joint count for each joint and for the total swollen joint count of the hand. As shown in Figure 1, there was higher agreement between sonography and the clinical swollen joint count when more stringent definitions of sonographic activity (i.e., higher GS and PD signal grades) were applied. Overall, there was agreement only as expected by chance ($\kappa = 0.011$), but this improved when more stringent sonographic criteria for synovitis (GS grade ≥2 and PD grade ≥2) were used ($\kappa = 0.22$).

The sensitivity and specificity of clinical assessment of joint swelling, considering sonography as the gold standard, was calculated using different combinations and cutoff points of sonographic signal grades. The specificity of clinically assessed swollen joint counts for sonographically active joints was consistently 99–100%, independent of the sonographic definition used; in other words, almost all joints that were clinically swollen exhibited abnormalities by sonography. Nevertheless, increasing the stringency of the sonographic criteria led to an increase in sensitivity for the clinical joint assessment; thus, sonographically active joints as defined by more stringent criteria were increasingly more strongly related to clinical swelling. When the least stringent sonographic criteria (requiring either a GS grade ≥1 or PD grade ≥1) were used, the sensitivity of clinical assessment of swollen joints was ~2%. In contrast, when the most stringent criteria for sonographic joint activity (requiring both a GS grade 3 and PD grade 3) were applied as the reference standard, the sensitivity of clinical swollen joint assessment rose to 25%; when applying the criteria requiring either a GS grade 3 or PD grade 3, the sensitivity of clinical swollen joint assessment amounted to 16%.

We further assessed changes in a composite measure of disease activity, the CDAI, in patients with RA in clinical remission, by replacing the clinical swollen joint count with sonographic signs of synovitis as seen by PD and/or GS activity (sCDAI), as has been previously done (20,35) but with use of different cutoffs based on the sonographic grading. When all joints demonstrating any signs of synovitis on ultrasound (GS grade ≥1 or PD grade ≥1) were included, the sCDAI values were substantially higher, at a mean sCDAI of 15.7, compared to the cutoff point for clinical remission (defined as a mean clinical CDAI of 2.8). When joints showing both GS grade ≥1 signals and PD grade ≥1 signals were included in the calculation, the mean sCDAI was 5.4. However, the mean sCDAI approached the mean clinical CDAI values when more stringent cutoffs for sonographic activity were applied. Indeed, when only joints with a PD grade 3 were included, there was nearly no difference, on the total group level, between the clinical CDAI and the sCDAI (mean 1.0 versus 1.1), regardless of the GS grade (Figure 2). When only the 3 patients whose joints exhibited both a PD grade 3 and a GS grade 3 were assessed, the differences were also small. In these 3 patients, the mean ± SD CDAI was 1.4 ± 0.15 and the sCDAI was 2.4 ± 0.96 ($P = 0.15$), both of which are values that were below the cutoff point for clinical remission (CDAI of 2.8).

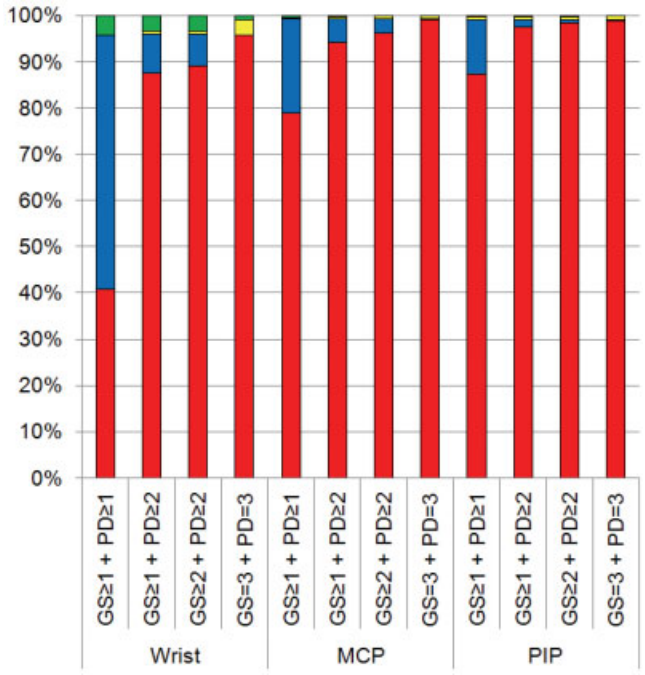

Figure 1. Percentage of agreement on disease activity (green) or inactivity (red) evaluated clinically and sonographically in the joints of patients with rheumatoid arthritis, as well as the percentage of joints positive on clinical examination only (yellow) or on sonography only (blue), applying the various sonographic definitions of joint disease activity (based on different combinations of gray-scale [GS] and power Doppler [PD] ultrasound grades) in the wrists, the metacarpophalangeal (MCP) joints, and the proximal interphalangeal (PIP) joints. The highest percentage of agreement was found when using the most stringent sonographic criteria (GS grade 3 and PD grade 3).

Sonographic findings in relation to physical function and other outcomes. Significant correlations between sonographic findings and other clinical measures, such as laboratory results, VAS score for pain,

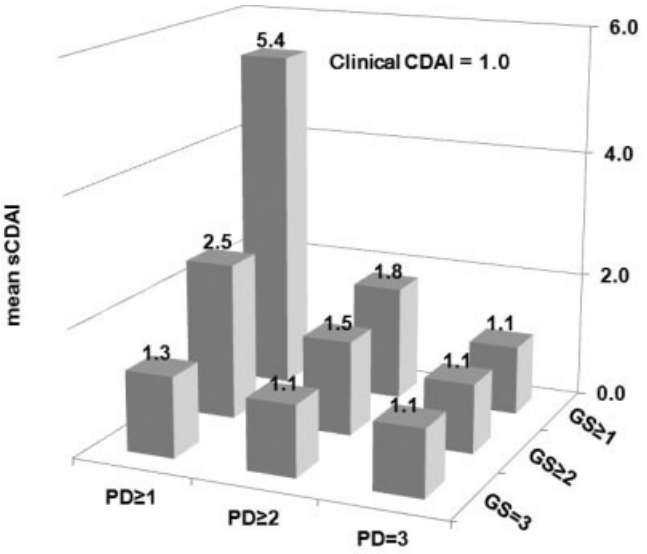

Figure 2. Comparison of the sonographic Clinical Disease Activity Index (sCDAI) with the clinical CDAI (set at 1.0) according to different combinations of sonographic criteria among patients with rheumatoid arthritis in clinical remission (n = 60). Values above the bars are the mean sCDAI values. Application of the most stringent criteria for joint disease activity (gray-scale [GS] ultrasound grade 3 and power Doppler [PD] ultrasound grade 3 for synovitis) revealed similarities between the sCDAI and clinical CDAI.

patient's global assessment of disease activity, evaluator's global assessment of disease activity, or duration of morning stiffness, were only seen when more stringent sonographic criteria (PD grade ≥2 and GS grade ≥2) were applied. Importantly, when we assessed HAQ DI scores in relation to sonographic results (Table 3), we found that patients having a high-grade PD signal (PD grade 3) showed a doubling of the HAQ DI values (mean ± SD HAQ DI score 0.45 ± 0.62) compared to patients whose PD grades were lower (mean ± SD HAQ DI score 0.24 ± 0.41 in those with PD grade ≥2 and 0.20 ± 0.35 in those with any PD grade; both $P = 0.057$ versus those with PD grade 3), indicating that only high-grade PD signals on ultrasound (which were more strongly related to the clinical findings, as discussed above) had functional consequences. Indeed, when the SDAI and CDAI were assessed for correlation with the HAQ DI among patients with RA in clinical remission, we found a significant correlation (r = 0.273, $P = 0.037$ for SDAI, and r = 0.355, $P = 0.009$ for CDAI).

Table 3. HAQ DI scores in patients with different PD ultrasound grades of synovitis*

	HAQ DI, mean ± SD
PD grade 0 (n = 4)	0.16 ± 0.19
PD grade ≥1 (n = 56)	0.20 ± 0.35
PD grade 1 (n = 33)	0.19 ± 0.33
PD grade 2 (n = 18)	0.17 ± 0.29
PD grade ≥2 (n = 23)	0.24 ± 0.41
PD grade 3 (n = 5)	0.45 ± 0.62

* HAQ DI = Health Assessment Questionnaire disability index; PD = power Doppler.

Table 4. Sonographic and clinical values at baseline and at followup in the 12 patients who were in clinical remission at baseline but not at followup*

	Baseline	Followup	*P*
PD grade	6.6 ± 6.8	6.3 ± 4.6	NS
GS grade	19.1 ± 10	20.4 ± 8.2	NS
CDAI	1.7 ± 0.9	5.5 ± 1.9	<0.001
SDAI	2.1 ± 0.8	5.9 ± 2	<0.001
SJC	0.6 ± 0.7	1.6 ± 1.4	0.032
TJC	0.25 ± 0.45	1.42 ± 1.61	0.015
HAQ DI	0.33 ± 0.4	0.5 ± 0.4	0.019
DAS28	2.3 ± 0.6	2.9 ± 0.7	NS

* Values are the mean ± SD. PD = power Doppler (ultrasound); NS = not significant; GS = gray-scale (ultrasound); CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index; SJC = swollen joint count; TJC = tender joint count; HAQ DI = Health Assessment Questionnaire disability index; DAS28 = Disease Activity Score in 28 joints.

Followup analysis. A total of 71 patients had one followup visit (52 patients in the remission cohort and 19 in the control group). Of the 52 patients whose disease was in clinical remission at baseline, 12 patients showed CDAI values of >2.8 at the second visit. There was no difference in the mean PD and GS grades between these patients (n = 12) and those who sustained the state of remission (n = 40), neither at baseline nor at followup. Of the patients in sustained remission at followup, 25% (n = 10) had a PD grade 2 at baseline and 7.5% (n = 3) had a PD grade 3 at baseline, compared to 50% (n = 6) with a PD grade 2 at baseline and 8.3% (n = 1) with a PD grade 3 at baseline among those who had lost their state of clinical remission over the followup ($P = 0.1152$).

Furthermore, we found no significant difference between the baseline and followup PD and GS values within the 12 patients who lost their state of remission (mean ± SD PD grade 6.6 ± 6.8 at baseline versus 6.3 ± 4.6 at followup; GS grade 19.1 ± 10.0 at baseline versus 20.4 ± 8.2 at followup). In contrast, we saw a small, but significant, increase in the number of clinically assessed swollen and tender joints and, importantly, also a significant increase in the HAQ DI among the 12 patients who lost their state of remission during followup (Table 4), which is consistent with our findings indicating that clinical disease activity has an impact on functional impairment, while sonographic activity has an impact only when marked signal findings are present.

Interestingly, however, those patients whose individual joints became clinically swollen at followup exhibited significantly higher PD values at baseline (13 joints [59.1%] showing no PD signs, 5 [22.7%] showing PD grade 1, and 4 [18.2%] showing PD grade ≥2 at baseline) as compared to patients whose joints remained unswollen at followup (898 joints [80%] showing no PD signs, 177 [15.8%] showing PD grade 1, and 47 [4.2%] showing PD grade ≥2 at baseline) ($P = 0.0036$ by chi-square test).

Among patients whose disease remained in sustained remission and who had 3 consecutive visits from baseline to followup after 1 year (n = 21), we saw a numerical decrease in the PD grade (mean ± SD PD grade 5.3 ± 4.1 at baseline decreasing to 3.1 ± 2.1 at the third visit; $P = 0.08$). This is in line with clinical observations indicating that sustained remission is a state in which composite measures of disease activity and physical function frequently continue to improve (36).

DISCUSSION

Several studies addressing sonographic assessment of RA patients in clinical remission (with remission defined by the DAS28) have indicated that signs of inflammation on ultrasound, including signs of synovitis on GS ultrasound as well as positive signals on PD ultrasound, can be demonstrated in the joints of such patients (23,24,27,37,38). Consistent with these findings, we saw many joints with PD and/or GS signals indicating the presence of synovitis in patients with RA in clinical remission (according to the stringent CDAI definition of remission) (7). However, the majority of these patients (~80%) had PD or GS signals at the lowest grade levels, and we also saw a significant difference in GS and PD signals between patients with RA in remission and those with active disease.

When we compared clinically assessed joint swelling with sonographically assessed synovitis, we observed much better agreement with ultrasounds that displayed high PD signals, although it has to be borne in mind that in obese patients, for instance, swelling due to synovitis may be difficult to distinguish from fat deposition on clinical examination. Nevertheless, while the specificity of clinically assessed swollen joint counts in relation to sonographic results was nearly 100%, irrespective of the grading, sensitivity amounted to a maximum of 25% when the most stringent ultrasound criteria were used, namely grade 3 on both GS and PD ultrasound. Thus, while essentially all clinically swollen joints also display sonographic abnormalities, the majority of joints with maximal sonographic activity are not captured by clinical examination, indicating that significant subclinical synovitis may be present in joints with clinically inactive disease in a state of stringently defined remission.

To prove or disprove that sonographic signals truly reflect the presence of synovitis, histologic analyses of joints exhibiting different grades of GS and PD signals would be needed, but these are currently not available. However, a study in which PD and histopathologic findings were compared failed to show a correlation between the amount of PD signal and the histopathologic score (12), while in another recent study, histopathologic findings were more closely correlated with PD signals than with GS signals or with the magnetic resonance imaging synovitis score (13). Interestingly, only 0.3% of the joints of patients with RA in clinical remission exhibited both a PD and GS grade of 3, and only ~3% of the joints of patients with RA in clinical remission had a PD and GS grade of ≥2. This low frequency of significant subclinical ultrasound activity should be considered when more rigorous ultrasound screening of joints with clinically unapparent disease is performed. Consistent with this conclusion, a recent study by Sakellariou et al demonstrated that, in contrast to patients with DAS28-defined remission, patients who met the stringent ACR/EULAR definition of remission (7) had only a very low frequency of joints with PD signals positive for signs of synovitis (39), and similar findings have been made previously in another cohort (21).

Synovitis that is demonstrated by GS ultrasound has been repeatedly suggested to be a remnant of earlier synovitis, and thus GS ultrasound is not necessarily a reliable tool to diagnose active synovitis (38,40,41). It has further been revealed that 11% of the joints of healthy volunteers showed PD signals for joint activity (42), likely corresponding to the presence of physiologic vessels, which are increasingly being visualized because of the recent advances in high-sensitivity ultrasound machines. Distinction between a "normal" and "abnormal" level of PD signal was also suggested to constitute a limitation of global ultrasound scores in a recent systematic literature review (18). Thus, in light of our data and given that several investigators regard GS ultrasound as nonspecific (38), and given that in a further recent study, PD signals were also only utilized as a predictive variable if the PD grade was >1 (28), the number of joints in patients with clinical remission that show signs of "meaningful" sonographic synovitis may indeed be very small.

When considering findings of subclinical synovitis in more detail, it has to be borne in mind that remission at a single point in time or during the short term may

not be identical to sustained remission, the actual therapeutic goal (43). Indeed, only sustained clinical remission (remission of >18 months) has been shown to be associated with a total halt of damage progression, while some progression of damage was seen in patients with a shorter time of remission (9), indicating that some subclinical inflammatory, or at least destructive, activity must still be ongoing in some patients at the initiation of remission. Indeed, in a recent analysis, we could show that patients with sustained remission experienced a significant decrease in their disease activity scores and their residual functional impairment over time (36). All of these observations are supported by the present findings, showing that PD signals improved significantly in a state of sustained remission and that individual joints destined to develop clinical swelling exhibited higher baseline PD values than did joints that remained unswollen.

An important observation of our study, however, was the association of physical disability with the clinical, rather than the sonographic, findings, both cross-sectionally and longitudinally. Moreover, given that we observed that higher PD and GS signals are more closely related to the clinical finding of joint swelling, indicating that the relationship between sonographic and clinical assessment is not random, these findings, taken together, would be compatible with the assumption that detection of any PD or GS signal may be oversensitive, and that, in particular, low grades of PD or GS signals may not necessarily reflect ongoing inflammation during a state of clinical remission. Consistent with this conclusion, it has been shown that a GS and PD grade of 1 is of much lower reproducibility than are grades of 2 or higher (44). The fear of structural progression in the presence of subclinical synovitis in a state of clinical remission may have to be balanced against these insights, and against the very small number of joints showing signs of sonographically active synovitis in patients with RA in clinical remission, although observation periods longer than 12 months may be needed to fully appreciate the effects of sonographic synovitis on joint damage.

One of the limitations of our study relates to the lack of radiographic data, and this will have to be tested in future analyses. However, a recent publication revealed that joint involvement, irrespective of the method of assessment, i.e., clinical or sonographic, is associated with progression of damage, indicating that both methods are important, but also that sonography had no particular advantage in this regard (45). Furthermore, we evaluated all included joints from a single, dorsal aspect. Ideally, each joint should be scanned from every possible aspect (including radial and ulnar, where feasible), as this provides the most complete information with regard to synovitis. However, we assessed the dorsal aspect in order to maintain feasibility; although this might have reduced the sensitivity of ultrasound in the detection of synovitis in the PIP joints, where the volar side has been shown to be somewhat more sensitive (46,47), there exists a number of publications validating global sonographic joint counts for synovitis focusing on the dorsal aspect (26,48–50).

In addition, we evaluated 11 joints rather than a larger number of joints, but there is currently no universally accepted combination to be included in a global ultrasound score for synovitis (18), and we followed the recent suggestions of Filer et al (33). Nevertheless, evaluation of additional joints might provide added value in the assessment of clinical remission.

Finally, we used a very high–end machine with a very sensitive Doppler for ultrasound analysis. Although this may weaken the applicability of our results in studies and settings that utilize lower-end machines, this limitation in fact applies not only to this particular study, but also to essentially almost all recent studies on sonographic evaluation of synovitis, where similar high-end machines have been used.

In conclusion, the results of the present study indicate that sonography as a tool to detect synovitis may only have sufficient value when the signals are high, and that low signals may not necessarily represent inflammation and, in contrast to the clinical findings, are not related to disability. Indeed, the differences between sonographic and clinical assessment are considerably lower when using higher cutoff points for defining an active joint in sonography. Still, sonography has been shown to be a more reliable measure of joint activity—in particular, high-grade PD signals appear to be a harbinger of joint damage—and sonographic findings may be a stronger measure than clinical findings. Moreover, our data do not exclude the possibility that clinical assessment may be undersensitive and that sonography may, importantly, complement clinical evaluation. Thus, the present findings reveal that more detailed assessment of sonographic data is needed to fully appreciate the value of ultrasound in the followup of patients with RA.

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 published. Dr. Smolen 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. Gärtner, Smolen.

Acquisition of data. Gärtner, Mandl, Radner, Supp.

Analysis and interpretation of data. Gärtner, Machold, Aletaha, Smolen.

ROLE OF THE STUDY SPONSOR

Pfizer had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Pfizer.

REFERENCES

1. Aletaha D, Smolen JS. Joint damage in rheumatoid arthritis progresses in remission according to the Disease Activity Score in 28 joints and is driven by residual swollen joints. Arthritis Rheum 2011;63:3702–11.
2. Aletaha D, Alasti F, Smolen JS. Rheumatoid arthritis near remission: clinical rather than laboratory inflammation is associated with radiographic progression. Ann Rheum Dis 2011;70:1975–80.
3. Landewe RB, Strand V, Conaghan PG, van der Heijde D. Damage and progression on radiographs in individual joints: data from pivotal randomized controlled trials. J Rheumatol 2011;38: 2018–22.
4. Prevoo ML, van Riel PL, van 't Hof MA, van Rijswijk MH, van Leeuwen MA, Kuper HH, et al. Validity and reliability of joint indices: a longitudinal study in patients with recent onset rheumatoid arthritis. Br J Rheumatol 1993;32:589–94.
5. Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. Rheum Dis Clin North Am 2006;32:9–44, vii.
6. Scott D, van Riel PL, van der Heijde DM, Studnicka-Benke A. Assessing disease activity in rheumatoid arthritis: the EULAR handbook of standard methods. Zürich: EULAR; 1993.
7. Felson D. Defining remission in rheumatoid arthritis. Ann Rheum Dis 2012;71 Suppl 2:ii86–8.
8. Molenaar ET, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BA. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum 2004; 50:36–42.
9. Aletaha D, Funovits J, Breedveld FC, Sharp J, Segurado O, Smolen JS. Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment. Arthritis Rheum 2009;60: 1242–9.
10. Szkudlarek M, Klarlund M, Narvestad E, Court-Payen M, Strandberg C, Jensen KE, et al. Ultrasonography of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis: a comparison with magnetic resonance imaging, conventional radiography and clinical examination. Arthritis Res Ther 2006;8:R52.
11. Brown AK, Quinn MA, Karim Z, Conaghan PG, Peterfy CG, Hensor E, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug–induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum 2006;54:3761–73.
12. Koski JM, Saarakkala S, Helle M, Hakulinen U, Heikkinen JO, Hermunen H. Power Doppler ultrasonography and synovitis: correlating ultrasound imaging with histopathological findings and evaluating the performance of ultrasound equipments. Ann Rheum Dis 2006;65:1590–5.
13. Takase K, Ohno S, Takeno M, Hama M, Kirino Y, Ihata A, et al. Simultaneous evaluation of long-lasting knee synovitis in patients undergoing arthroplasty by power Doppler ultrasonography and contrast-enhanced MRI in comparison with histopathology. Clin Exp Rheumatol 2012;30:85–92.
14. Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol 2005;32: 2485–7.
15. Backhaus M, Kamradt T, Sandrock D, Loreck D, Fritz J, Wolf KJ, et al. Arthritis of the finger joints: a comprehensive approach comparing conventional radiography, scintigraphy, ultrasound, and contrast-enhanced magnetic resonance imaging. Arthritis Rheum 1999;42:1232–45.
16. Dougados M, Jousse-Joulin S, Mistretta F, D'Agostino MA, Backhaus M, Bentin J, et al. Evaluation of several ultrasonography scoring systems for synovitis and comparison to clinical examination: results from a prospective multicentre study of rheumatoid arthritis. Ann Rheum Dis 2010;69:828–33.
17. Larche MJ, Seymour M, Lim A, Eckersley RJ, Petavy F, Chiesa F, et al. Quantitative power Doppler ultrasonography is a sensitive measure of metacarpophalangeal joint synovial vascularity in rheumatoid arthritis and declines significantly following a 2-week course of oral low-dose corticosteroids. J Rheumatol 2010;37: 2493–501.
18. Mandl P, Naredo E, Wakefield RJ, Conaghan PG, D'Agostino MA. A systematic literature review analysis of ultrasound joint count and scoring systems to assess synovitis in rheumatoid arthritis according to the OMERACT filter. J Rheumatol 2011; 38:2055–62.
19. Mandl P, Balint PV, Brault Y, Backhaus M, D'Agostino MA, Grassi W, et al. Metrologic properties of ultrasound versus clinical evaluation of synovitis in rheumatoid arthritis: results of a multicenter, randomized study. Arthritis Rheum 2012;64:1272–82.
20. Mandl P, Balint P, Brault Y, Backhaus M, D'Agostino M, Grassi W, et al. Clinical and ultrasound-based composite disease activity indices in rheumatoid arthritis: results from a randomized, multicentre study. Arthritis Care Res (Hoboken) 2012. E-pub ahead of print.
21. Balsa A, de Miguel E, Castillo C, Peiteado D, Martin-Mola E. Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. Rheumatology (Oxford) 2010;49:683–90.
22. Dejaco C, Duftner C, Wipfler-Freissmuth E, Weiss H, Graninger WB, Schirmer M. Similar performance of DAS-28, CDAI, and SDAI in rheumatoid arthritis patients with and without sonographic signs of active inflammation in routine clinical practice. Scand J Rheumatol 2011;40:234–6.
23. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Wakefield R, et al. Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. Ann Rheum Dis 2011;70:792–8.
24. Wakefield RJ, Freeston JE, Hensor EM, Bryer D, Quinn MA, Emery P. Delay in imaging versus clinical response: a rationale for prolonged treatment with anti–tumor necrosis factor medication in early rheumatoid arthritis. Arthritis Rheum 2007;57:1564–7.
25. Foltz V, Gandjbakhch F, Etchepare F, Rosenberg C, Tanguy ML, Rozenberg S, et al. Power Doppler ultrasound, but not low-field magnetic resonance imaging, predicts relapse and radiographic disease progression in rheumatoid arthritis patients with low levels of disease activity. Arthritis Rheum 2012;64:67–76.
26. Naredo E, Collado P, Cruz A, Palop MJ, Cabero F, Richi P, et al. Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. Arthritis Rheum 2007;57:116–24.
27. Scire CA, Montecucco C, Codullo V, Epis O, Todoerti M, Caporali R. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology (Oxford) 2009; 48:1092–7.
28. Yoshimi R, Hama M, Takase K, Ihata A, Kishimoto D, Terauchi K, et al. Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis. Mod Rheumatol 2012. E-pub ahead of print.
29. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an

American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62: 2569–81.
30. Aletaha D, Smolen JS. The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) to monitor patients in standard clinical care. Best Pract Res Clin Rheumatol 2007;21:663–75.
31. Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, et al. Validity and reliability of the twenty-eight–joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum 1995;38:38–43.
32. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. J Rheumatol 1982;9:789–93.
33. Filer A, de Pablo P, Allen G, Nightingale P, Jordan A, Jobanputra P, et al. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. Ann Rheum Dis 2011;70:500–7.
34. Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, Ostergaard M. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum 2003;48:955–62.
35. Damjanov N, Radunovic G, Prodanovic S, Vukovic V, Milic V, Simic PK, et al. Construct validity and reliability of ultrasound disease activity score in assessing joint inflammation in RA: comparison with DAS-28. Rheumatology (Oxford) 2012;51:120–8.
36. Radner H, Alasti F, Smolen JS, Aletaha D. Time in remission is important for improvement of physical function in patients with rheumatoid arthritis (RA) [abstract]. Arthritis Rheum 2012;64 Suppl:S1104–5.
37. Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Ann Rheum Dis 2011;70:172–5.
38. Wakefield RJ, D'Agostino MA, Naredo E, Buch MH, Iagnocco A, Terslev L, et al. After treat-to-target: can a targeted ultrasound initiative improve RA outcomes? Ann Rheum Dis 2012;71:799–803.
39. Sakellariou G, Scire CA, Verstappen SM, Montecucco C, Caporali R. In patients with early rheumatoid arthritis, the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis. Ann Rheum Dis 2013;72:245–9.
40. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008;58:2958–67.
41. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Karim Z, et al. Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: a clinical and imaging comparative study. Arthritis Rheum 2009;60:1915–22.
42. Terslev L, Torp-Pedersen S, Qvistgaard E, von der Recke P, Bliddal H. Doppler ultrasound findings in healthy wrists and finger joints. Ann Rheum Dis 2004;63:644–8.
43. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631–7.
44. Jousse-Joulin S, D'Agostino MA, Marhadour T, Albert JD, Bentin J, Chary Valckenaere I, et al. Reproducibility of joint swelling assessment by sonography in patients with long-lasting rheumatoid arthritis (SEA-Repro study part II). J Rheumatol 2010;37:938–45.
45. Dougados M, Devauchelle-Pensec V, Ferlet JF, Jousse-Joulin S, D'Agostino MA, Backhaus M, et al. The ability of synovitis to predict structural damage in rheumatoid arthritis: a comparative study between clinical examination and ultrasound. Ann Rheum Dis 2013;72:665–71.
46. Backhaus M, Ohrndorf S, Kellner H, Strunk J, Backhaus TM, Hartung W, et al. Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: a pilot project. Arthritis Rheum 2009;61:1194–201.
47. Vlad V, Berghea F, Libianu S, Balanescu A, Bojinca V, Constantinescu C, et al. Ultrasound in rheumatoid arthritis: volar versus dorsal synovitis evaluation and scoring. BMC Musculoskelet Disord 2011;12:124.
48. Gutierrez M, Filippucci E, Salaffi F, Di Geso L, Grassi W. Differential diagnosis between rheumatoid arthritis and psoriatic arthritis: the value of ultrasound findings at metacarpophalangeal joints level. Ann Rheum Dis 2011;70:1111–4.
49. Naredo E, Bonilla G, Gamero F, Uson J, Carmona L, Laffon A. Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. Ann Rheum Dis 2005;64:375–81.
50. Salaffi F, Filippucci E, Carotti M, Naredo E, Meenagh G, Ciapetti A, et al. Inter-observer agreement of standard joint counts in early rheumatoid arthritis: a comparison with grey scale ultrasonography—a preliminary study. Rheumatology (Oxford) 2008;47: 54–8.