Three-dimensional Volumetric Ultrasound: A Valid Method for Blinded Assessment of Response to Therapy in Rheumatoid Arthritis

ESPERANZA NAREDO, CARLOS ACEBES, ELIA BRITO, JUAN JOSÉ de AGUSTÍN, EUGENIO de MIGUEL, LUCÍA MAYORDOMO, INGRID MÖLLER, CARMEN MORAGUES, EDUARDO REJÓN, ANA RODRIGUEZ, JACQUELINE USON, JESÚS GARRIDO, DAVID MARTÍNEZ-HERNÁNDEZ, and the Ultrasound School of the Spanish Society of Rheumatology

ABSTRACT. ***Objective.*** To assess the responsiveness and repeatability of volumetric power Doppler ultrasound (PDUS) evaluation of synovitis and bone erosions in rheumatoid arthritis (RA).

Methods. Twenty-three patients with RA (19 women, mean age 52.7 ± 12.6 yrs, mean disease duration 10.1 ± 8.6 yrs) were prospectively enrolled. All patients were beginning therapy with rituximab because of disease activity despite therapy with synthetic disease-modifying antirheumatic drugs and tumor necrosis factor-blocking agents. Patients underwent clinical, laboratory, and volumetric PDUS examination at baseline, 6 months, and 12 months. Ten centers participated in the study. Four centers recruited the patients and performed the volumetric acquisitions of PDUS images, while the remaining 6 centers assessed the PDUS volumes, blinded to the identity of patients and date of the visits. The most symptomatic hand and foot were scored for B-mode synovitis, synovial PD signal, and bone erosions. The repeatability of the volumetric PDUS assessment was investigated.

Results. An overall improvement in clinical and PDUS measurements was found at the followup assessments. The mean indexes for synovial PD signal and bone erosions and the number of sites with abnormalities decreased significantly throughout the followup ($p < 0.05$). The intraacquisition, intrareader reliability was excellent for all PDUS measurements (intraclass correlation coefficients > 0.9).

Conclusion. The results of our pilot study suggest that volumetric PDUS can be responsive and repeatable in multicenter cohort studies of RA. This technique may minimize assessment biases and reduce acquisition variability in open-label and observational studies. (J Rheumatol First Release Jan 15 2013; doi:10.3899/jrheum.121103)

Key Indexing Terms:

VOLUMETRIC ULTRASOUND	SYNOVITIS	EROSIONS
POWER DOPPLER	RHEUMATOID ARTHRITIS	RESPONSIVENESS

Rheumatoid arthritis (RA) is characterized by synovial inflammation (i.e., synovial proliferation, effusion, and angiogenesis) that can damage the joint cartilage, bones, capsule, and ligaments[1]. Accurate assessment of synovitis is essential in rheumatologic practice to make therapeutic decisions and to evaluate the response to treatment.

Within the last decade, technological improvements in ultrasound (US) B-mode image resolution of musculo-

From the Department of Rheumatology, Hospital General Universitario Gregorio Marañón and Complutense University; Department of Rheumatology, Fundación Jiménez Díaz; Department of Rheumatology, Hospital Ramón y Cajal; Department of Rheumatology, Hospital Universitario La Paz; Department of Rheumatology, Hospital Universitario de Móstoles; Department of Social Psychology and Methodology, Faculty of Psychology, Autonoma University; Department of Preventive Medicine and Public Health, Faculty of Medicine, Complutense University, Madrid; Department of Rheumatology, Hospital Vall d'Hebrón; Department of Rheumatology, Instituto Poal; Department of Rheumatology, Hospital de Bellvitge, Barcelona; and Hospital Universitario de Valme, Seville, Spain.

Supported by Roche Farma S.A.

E. Naredo, MD, Department of Rheumatology, Hospital General Universitario Gregorio Marañón and Complutense University; C. Acebes, MD, PhD, Department of Rheumatology, Fundación Jiménez Díaz; E. Brito, MD, Department of Rheumatology, Hospital Ramón y Cajal; J.J. de Agustín, MD, PhD, Department of Rheumatology, Hospital Vall d'Hebrón; E. de Miguel, MD, PhD, Department of Rheumatology, Hospital Universitario La Paz; L. Mayordomo, MD, Department of Rheumatology, Hospital Universitario de Valme; I. Möller, MD, PhD, Department of Rheumatology, Instituto Poal; C. Moragues, MD, Department of Rheumatology, Hospital de Bellvitge; E. Rejón, MD, Department of Rheumatology, Hospital Universitario de Valme; A. Rodriguez, MD, Department of Rheumatology, Hospital Ramón y Cajal; J. Uson, MD, Department of Rheumatology, Hospital Universitario de Móstoles; J. Garrido, MD, PhD, Department of Social Psychology and Methodology, Faculty of Psychology, Autonoma University; D. Martínez-Hernández, MD, PhD, Department of Preventive Medicine and Public Health, Faculty of Medicine, Complutense University.

Address correspondence to Dr. E. Naredo, Rheumatology Department, Hospital General Universitario Gregorio Marañón, Doctor Alvarez Sierra 4, 4A, 28033 Madrid, Spain. E-mail: enaredo@ser.es

Accepted for publication November 8, 2012.

skeletal (MS) structures have led to an increasingly important role for this imaging modality in daily rheumatology practice and research[2,3]. The added value of US in the evaluation and monitoring of patients with RA is based on the proven greater sensitivity of B-mode US compared to clinical examination for detecting synovitis in RA target joints[4,5,6]. US has also demonstrated accuracy for detecting bone erosions[7,8,9], with greater sensitivity than plain radiography in target RA joints in the hands and feet[4,10,11,12,13,14,15,16,17,18]. Color Doppler (CD) and power Doppler (PD) modes can detect pathological synovial blood flow, which reflects the joint inflammatory activity[19,20,21] and has predictive value in relation to radiographic progression of structural damage in patients with active RA and those in remission[18,22,23,24] and in relation to disease flares[25,26,27]. MSUS is a routinely available, noninvasive, and relatively inexpensive bedside technique with high patient acceptability that can be repeated as many times as required at the time of consultation.

Reports of several longitudinal studies have described significant reduction of joint inflammation in RA as evaluated by PDUS after a variety of treatment durations with synthetic or biologic disease-modifying antirheumatic drugs (DMARD)[22,23,28,29,30,31,32,33,34,35,36,37]. However, those cohort studies were open-label uncontrolled trials or observational studies conducted according to clinical practice, without a blinded control group. Thus, the PDUS assessors knew that patients with active RA were receiving treatment from baseline through the followup period. This could have influenced the baseline and followup US assessments by enhancing the US findings at baseline and reducing the US abnormalities at followup visits.

In addition, MSUS has long been viewed as the most operator-dependent imaging technique. Because of the intrinsic real-time nature of US image acquisition, MSUS results are strongly influenced by the examiner's skill and experience.

For the last few years, volumetric probes (VP) have been available in some high-end US machines. The acquisition of the US volume consists of an automatic sweeping scan movement of the piezoelectric crystals located inside the transducer. Both B-mode (i.e., greyscale) and CD or PD Doppler mode can be used in volumetric scanning. The US images generated can be examined on longitudinal, transverse, and coronal planes by navigating through the 3 planes and by producing a 3-dimensional (3-D) reconstruction of the anatomic area, in the US machine or in a computer equipped with appropriate software. Thus, the interpretation of the US images on the 3 planes can be carried out at any time after the volume acquisition, with or without the presence of the patient. In addition, volumetric US seems to reduce the operator dependence in assessing synovitis and bone erosions compared with conventional 2-D US, because of the automatic image acquisition[38,39].

Our prospective multicenter pilot study was undertaken to assess the responsiveness and repeatability (i.e., intra-acquisition, intrareader reliability) of volumetric PDUS evaluation of synovitis and bone erosions to blindly monitor response to rituximab (RTX), a chimeric anti-CD20 monoclonal antibody, in patients with active RA.

MATERIALS AND METHODS

Twenty-three patients with RA (19 women, 4 men) according to the American College of Rheumatology 1987 criteria[40] were prospectively enrolled in our observational longitudinal study. Patients were recruited from the outpatient rheumatology clinics at 4 centers from January 2009 to July 2010. All patients were beginning therapy with RTX because they had active RA [28-joint Disease Activity Score (DAS28) > 2.6]. In addition, at least 1 synthetic DMARD and at least 1 tumor necrosis factor (TNF)-blocking agent had failed, according to Spanish consensus on the use of biologic therapy for the treatment of RA[41] and the Spanish license for RTX (i.e., 15 patients, 1 anti-TNF agent; 6 patients, 2 anti-TNF agents; 2 patients, 3 anti-TNF agents). The mean age of the patients was 52.7 ± 12.6 SD years (range 30–76 yrs) and the mean disease duration was 10.1 ± 8.6 years (range 1.7–32 yrs). Nineteen patients (82.6%) were rheumatoid-factor positive and 16 (69.6%) were anticitrullinated peptide antibody-positive. The patients received two 1000-mg intravenous (IV) infusions of RTX separated by 2 weeks. Medications given prior to each infusion were methylprednisolone 100 mg IV, paracetamol 1000 mg, and diphenhydramine 50 mg. All patients were taking methotrexate (10–25 mg/week) at the time of enrollment. Twelve patients (52.2%) were taking prednisone (5–15 mg/day) and 13 (56.5%) were taking nonsteroidal anti-inflammatory drugs (NSAID). The study was conducted in accord with the Declaration of Helsinki and was approved by the local ethics committees of Andalucía and Cataluña. Informed consent was obtained from all patients.

Patients underwent clinical, laboratory, and volumetric PDUS examination at baseline (within 1 week before initiation of RTX therapy), 6 months, and 12 months. In addition, routine clinical and laboratory assessments were performed at 3 and 9 months. Treatment decisions throughout the followup period were based on the patient's clinical course, according to clinical practice, without knowledge of the PDUS findings.

Clinical and laboratory assessment. Patients were clinically evaluated at each visit by the same rheumatologist at each center, who was blinded to the PDUS findings. The following data were recorded for each patient at study enrollment: age, sex, symptom duration, and synthetic and biologic DMARD, corticosteroids and NSAID received for RA before study entry.

At each visit, 28 joints, including the left and right glenohumeral, elbow, and wrist joints, metacarpophalangeal (MCP) joints, proximal interphalangeal joints of the hands, and knee joints were assessed for tenderness and swelling. Patients rated their overall disease activity on a 100-mm visual analog scale at each visit. Functional ability was evaluated with a self-assessment Spanish version of the Health Assessment Questionnaire. Data on serum markers of inflammation [C-reactive protein (CRP; normal 0–10 mg/dl) and erythrocyte sedimentation rate (ESR; normal 10–20 mm/h)] were obtained from laboratory tests performed within 48 h of each clinical visit. Disease activity was estimated by calculating the DAS28 for each patient at each visit. Immunoglobulin levels and B cell subsets were obtained according to routine practice.

Volumetric PDUS investigation. Study design. Ten centers participated in the study. Four of them recruited the patients and performed the volumetric acquisitions of the PDUS images, while the remaining 6 centers assessed the PDUS volumes (blinded to the identity of patients, dates of visits, and hospital of origin). To keep the PDUS assessors blinded to the above data, the acquired PDUS volumes for each patient at each visit were recorded on individual digital versatile discs (DVD) and were identified exclusively by a random 3-digit code consecutively assigned by a statistician and sent to the coordinating central office. The central office collected the DVD from

the consecutive visits of the enrolled patients and randomly distributed them among the assessors. The DVD from the same patient were assigned to the same assessor. Two sets of DVD were sent, separated by 6 months, to each PDUS assessor with no other identification than the preassigned code. The PDUS assessors read the volumes and returned the DVD and their assessments in a database within a maximum period of 1 month after receiving them.

Joints and abnormalities assessed. The following joint areas of the most symptomatic hand and foot, established by the clinical investigator at baseline, were evaluated for greyscale synovitis and synovial PD signal: the dorsal aspect of the radiocarpal and midcarpal joints together, dorsal aspect of the MCP joints, and dorsal aspect of the metatarsophalangeal (MTP) joints (i.e., 11 areas). The following joint sites of the most symptomatic hand and foot at baseline were evaluated for bone erosions: dorsal, palmar, and radial aspect of the second MCP joint; dorsal, palmar, and ulnar aspect of the fifth MCP joint; dorsal, plantar, and medial aspect of the first MTP joint; and dorsal, plantar, and lateral aspect of the fifth MTP joint (i.e., 12 areas). The metacarpal head and the proximal phalanx base were evaluated for erosions at each joint site.

Greyscale synovitis was defined as the presence of abnormal hypoechoic (relative to subdermal fat) intraarticular material[33]. Synovial hypertrophy and effusion were evaluated together. We considered wrist synovitis or synovial PD signal positive if they were detected in either the radiocarpal or the midcarpal joints. Erosion was defined as an intraarticular discontinuity of the bone surface that is visible in 2 perpendicular planes[42].

Volumetric PDUS acquisition. PDUS volumetric acquisition was performed within 4 hours of each clinical evaluation by the same rheumatologist at each center, all experienced in MSUS. These rheumatologists were unaware of the clinical and laboratory findings and were not involved in the treatment decisions; the only patient information that they received from the clinical investigators was the identification of the most symptomatic hand and foot.

For each patient at each visit, the investigators acquired, in a consecutively preestablished fashion, 1 volume in B-mode per each investigated joint area for greyscale synovitis and/or erosions (i.e., 19 volumes) and 1 volume in PD mode per each investigated joint area for synovial PD signal (11 volumes) with the same real-time scanner in all centers (Logiq 9; GE Medical Systems Ultrasound and Primary Care Diagnostics LLC). The scanner was equipped with multifrequency electromechanical 3-D dedicated VP (8–15 MHz). A generous layer of gel was applied on the examined joints. The volumetric probe was placed over the central part of the investigated joint areas. A volumetric sweeping on the longitudinal plane was performed at each studied site.

PDUS volumetric acquisitions were carried out without entering the patient identity, hospital origin, and real date in the database of the US machine. An acronym of the study and the preassigned code were introduced into the required field without the patient or the hospital name. A fictitious standardized date (i.e., January 1, 2009) was established for all explorations involved in the study.

B-mode and PD machine settings were adjusted before the study and standardized among investigators for the whole study. These settings were as follows: dynamic range of 66 dB, greyscale frequency of 15 MHz, Doppler frequency of 7.5 MHz, greyscale gain of 66 dB, color gain of 39 dB, low-wall filters, pulse repetition frequency of 900 Hz, and volume angle of 14°. Each volumetric sweeping scan took 20 s. The total time spent on the US acquisition of the 30 volumes was 30 min. The 30 volumes acquired from each patient at each visit were recorded in a single DVD and sent to the central office with the corresponding preassigned code written in permanent marker on the DVD.

Volumetric PDUS assessment. PDUS volumes were assessed in personal computers equipped with the Logiq Works software (ViewPoint Bildverarbeitung GmbH), a tool that allows storage, review, and postprocessing of patient images, cineloops, and volumes obtained from an US system. The volumes were rescanned on longitudinal and transverse planes in the work station. The software allowed simultaneous visualization of the joints and the pathological findings (i.e., greyscale synovitis, synovial PD signal, and bone erosions) at the same point in both perpendicular planes. The 6 rheumatologists who assessed the PDUS volumes were experts in MSUS, had a similar background in MSUS, had conducted multiple consensus meetings and training sessions on RA PDUS findings, and had previously demonstrated reproducibility in the above abnormalities in multicenter studies[6,23,39].

The maximal greyscale and PD activity found during the longitudinal and transverse assessments were scored as in real-time 2-D scanning. Greyscale synovitis was scored semiquantitatively on a scale of 0–3 (0, absent; 1, mild; 2, moderate; 3, marked). Synovial PD signal was also scored on a semiquantitative scale of 0–3 [0, absent (no synovial flow); 1, mild (≤ 3 PD signals); 2, moderate (> 3 PD signals in less than half the synovial area); 3, marked (signals in more than half the synovial area)][23]. Erosions were scored in a dichotomous scale (presence/absence). A global index for B-mode synovitis (IBM; the sum of the greyscale synovitis scores obtained for each evaluated joint) and a global index for synovial PD signal (IPD; the sum of the PD signal scores obtained for each evaluated joint) were calculated for each visit of each patient. In addition, a global index for bone erosions (IER) was also calculated from the sum of the erosions found in all evaluated areas. The time spent on the assessment of the volumes from 1 DVD was about 30 min.

Volumetric PDUS repeatability assessment. To evaluate the intraacquisition, intrareader reliability of the PDUS investigation, the acquisition of the PDUS volumes at the first visit of the second and third patients enrolled at each center was repeated twice consecutively and recorded in 2 different DVD with different preassigned codes each. These DVD were sent to the assigned assessor as independent investigations, each included in 1 of the 2 sets of DVD that were sent 6 months apart.

Statistical analysis. Statistical analysis was performed using SPSS, version 15.0. Quantitative variables (clinical, laboratory, and PDUS) were presented as the mean ± SD and range. Qualitative variables were summarized as absolute and relative frequencies. To compare quantitative variables at the group level, Student t test for independent or paired samples or ANOVA for repeated measures was used when normality was assumed. Otherwise, nonparametric alternatives, Mann-Whitney U, Wilcoxon, or Friedman test were used. Because it was a goal of the study to determine the timepoint in which an improvement in each variable was detected, planned comparison of means between baseline and 6 months and 12 months was analyzed and 95% CI for difference was calculated. To compare qualitative variables for repeated measures, the Cochran test was used. Intraacquisition, intrareader reliability for the PDUS measurements was evaluated by calculating the intraclass correlation coefficient (ICC). ICC values < 0.40 were considered poor, 0.40–0.75 good to optimal, and > 0.75 excellent[43]. Responsiveness of the PDUS variables at the patient level was also estimated by calculating the smallest detectable difference (SDD) from the differences between the assessments of the baseline PDUS investigations repeated twice in 8 patients, which represents the minimum change that can be discriminated from the measurement error of the scoring method[44]. P values < 0.05 were considered significant.

RESULTS

Complete clinical, laboratory, and volumetric PDUS data were obtained on 20 patients (18 women, 2 men) who received RTX therapy for 12 months during the followup period. One patient was excluded after 3 months because of adverse events (sepsis), 1 patient missed the followup visits, and 1 patient was switched to an anti-TNF agent at 7 months because of inefficacy. Seven patients received RTX retreatment at 6 months and 2 patients at 12 months.

Clinical, laboratory, and PDUS course. Findings of the

clinical, laboratory, and PDUS measurements are shown in Table 1. All patients showed IBM > 0 at all visits. IPD was 0 in 6 patients (30%) at baseline and in 11 (55%) at 12 months. At baseline, bone erosions on volumetric US assessment were detected in 19 patients (95%), while this abnormality was detected in 18 patients at 12 months. An overall improvement in clinical, functional, and PDUS measures was found at the followup assessments. Differences in mean values throughout followup were significant for DAS28 ($p < 0.0005$), HAQ ($p < 0.0005$), ESR ($p = 0.002$), IPD ($p = 0.048$), and IER ($p = 0.019$). These differences were not significant for CRP ($p = 0.055$) and IBM ($p = 0.482$).

Table 2 displays changes in clinical, laboratory, and PDUS from baseline to 12 months, throughout the followup period. The mean DAS28 and HAQ decreased significantly from baseline to 6 and 12 months. The mean ESR decreased significantly from baseline to 6 and 12 months, while the mean CRP decreased significantly only from baseline to 12 months. The mean IBM did not show significant changes throughout the followup. However, the mean IPD decreased significantly from baseline to 12 months. The mean IER showed a significant decrease from baseline to 12 months.

Table 3 shows the total number and percentage of joint areas with B-mode synovitis, synovial PD signal, and bone erosions throughout the followup. All the above PDUS measures improved from baseline to 12 months. These numbers decreased significantly throughout the followup: the number of joints with B-mode synovitis, the number of joints with synovial PD signal, and the number of joint sites with bone erosions. The number of joints with erosions also decreased but not significantly.

Repeatability. Table 4 displays the intraacquisition, intrareader ICC, the CI, and the SDD for the IBM, IPD, and IER. The ICC were excellent, reflecting a high degree of repeatability.

Eight patients (40%) showed a decrease in the IBM greater than the SDD, 8 (40%) showed a decrease in the IPD greater than the SDD, and 4 (20%) showed an improvement in the IER greater than the SDD. Five patients (25%) had an increase in the IBM greater than the SDD, and only 1 patient had an increase in the IPD greater than the SDD. One patient had a worsening in the IER greater than the SDD.

Representative volumetric PDUS images are shown in Figures 1 and 2.

DISCUSSION

To our knowledge, apart from a single case report[45], our study is the first to assess the responsiveness of RA synovitis and bone erosions evaluated with volumetric PDUS in a multicenter cohort. The PDUS volumes allowed the readers to carefully rescan the target areas on longitu-

Table 1. Mean ± SD (range) values for clinical, laboratory, and power Doppler ultrasound measurements at the baseline and followup assessments.

Measurement	Baseline	6 Months	12 Months
DAS28	6.1 ± 1.2 (2.8–7.6)	4.6 ± 1.5 (2.3–7.3)	3.8 ± 1.3 (1.7–6.2)
HAQ	1.7 ± 0.7 (0–2.5)	1.1 ± 0.6 (0–2.4)	1.0 ± 0.7 (0–2.5)
ESR, mm/h	40 ± 30 (3–120)	26 ± 22 (4–93)	22 ± 17 (5–66)
CRP, mg/dl	20 ± 21 (2–75)	13 ± 18 (0.1–73)	10 ± 17 (0.5–95)
IBM	9.6 ± 3.4 (4–17)	9.5 ± 3.7 (1–16)	8.5 ± 3.6 (2–16)
IPD	2.4 ± 2.6 (0–10)	1.5 ± 2.4 (0–8)	1.4 ± 2.1 (0–8)
IER	7.7 ± 6.3 (0–22)	8.0 ± 5.0 (0–16)	5.4 ± 4.2 (0–14)

DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IBM: global index for B-mode synovitis; IPD: global index for synovial PD signal; IER: global index for bone erosions.

Table 2. Mean (95% CI) changes in clinical, laboratory, and PDUS measurements throughout the followup.

Measurement	Baseline–6 Months	Baseline–12 Months
DAS28	1.5 (1.0–2.1); p < 0.0005	2.3 (1.6–3.1); p < 0.0005
HAQ	0.6 (0.2–0.9); p = 0.001	0.7 (0.4–1.0); p < 0.0005
ESR, mm/h	11.5 (1.4–21.5); p = 0.014	17.9 (5.9–29.9); p = 0.006
CRP, mg/dl	6.1 (–0.5–14.8); p = 0.086	10.2 (2.7–23.2); p = 0.022
IBM	0.1 (–1.9–2.0); p = 0.882	1.2 (–0.8–3.1); p = 0.222
IPD	0.9 (0.0–1.8); p = 0.064	1.0 (0.2–1.8); p = 0.021
IER	–0.3 (–2.1–1.5); p = 0.747	2.3 (0.2–4.4); p = 0.035

PDUS: power Doppler ultrasound; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IBM: global index for B-mode synovitis; IPD: global index for synovial PD signal; IER: global index for bone erosions.

Table 3. Number (percentage) of joints/sites with power Doppler ultrasound findings throughout the followup.

Measurement	Baseline	6 Months	12 Months	p
Joints with B-mode synovitis	145 (65.9)	140 (63.6)	126 (57.3)	0.048
Joints with synovial PD signal	36 (16.4)	24 (10.9)	23 (10.5)	0.010
Joint sites with bone erosions	108 (45.0)	116 (48.3)	86 (35.8)	< 0.0005
Joints with bone erosions	58 (72.5)	56 (70.0)	49 (61.3)	0.054

Table 4. Intraacquisition, intrareader reliability, and SDD for the PDUS measurements.

PDUS Measurement	ICC (95% CI)	SDD
IBM	0.97 (0.87–0.99)	2.5
IPD	0.92 (0.58–0.98)	1.5
IER	0.99 (0.93–0.99)	3.4

PDUS: power Doppler ultrasound; ICC: intraclass correlation coefficient; SDD: smallest detectable difference; IBM: global index for B-mode synovitis; IPD: global index for synovial PD signal; IER: global index for bone erosions.

dinal and transverse planes. The technology allowed for blinding of the assessors regarding the chronological order of the PDUS investigations that had previously been acquired. This blinding can be greatly advantageous when PDUS metric properties are tested in open-label uncontrolled trials or observational studies in which knowledge of when all investigated patients have begun to receive effective therapy may introduce assessment biases. Indeed, all published studies on PDUS monitoring of RA synovitis, except 1 placebo-controlled, double-blind randomized trial[46], had the above design. In addition, volumetric PDUS may greatly reduce the interacquisition variability in multicenter studies because of its automatic sweeping of the scanned area[38,39]. Volumetric acquisition requires only knowledge of the anatomic landmarks, correct placement of the probe, use of an appropriate amount of gel, and avoidance of movement by the patient and the examiner to obtain US volumetric images with sufficient diagnostic

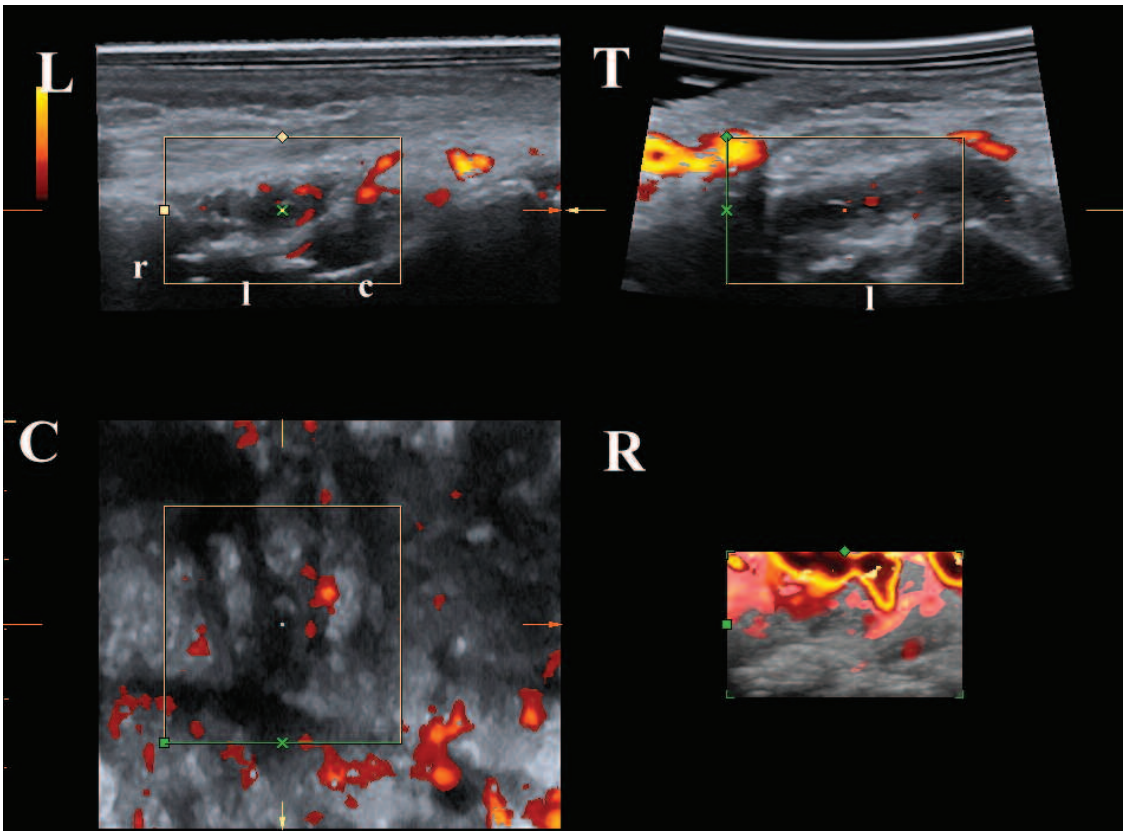

Figure 1. Volumetric power Doppler ultrasound image of the dorsal aspect of the radiocarpal and midcarpal joints. The longitudinal (L), transverse (T), and coronal (C) planes at the selected anatomic level of the joints and the reconstruction volume (R) are shown. Wrist was globally scored moderate on both B-mode and power Doppler mode. r: radius; l: lunate; c: capitate.

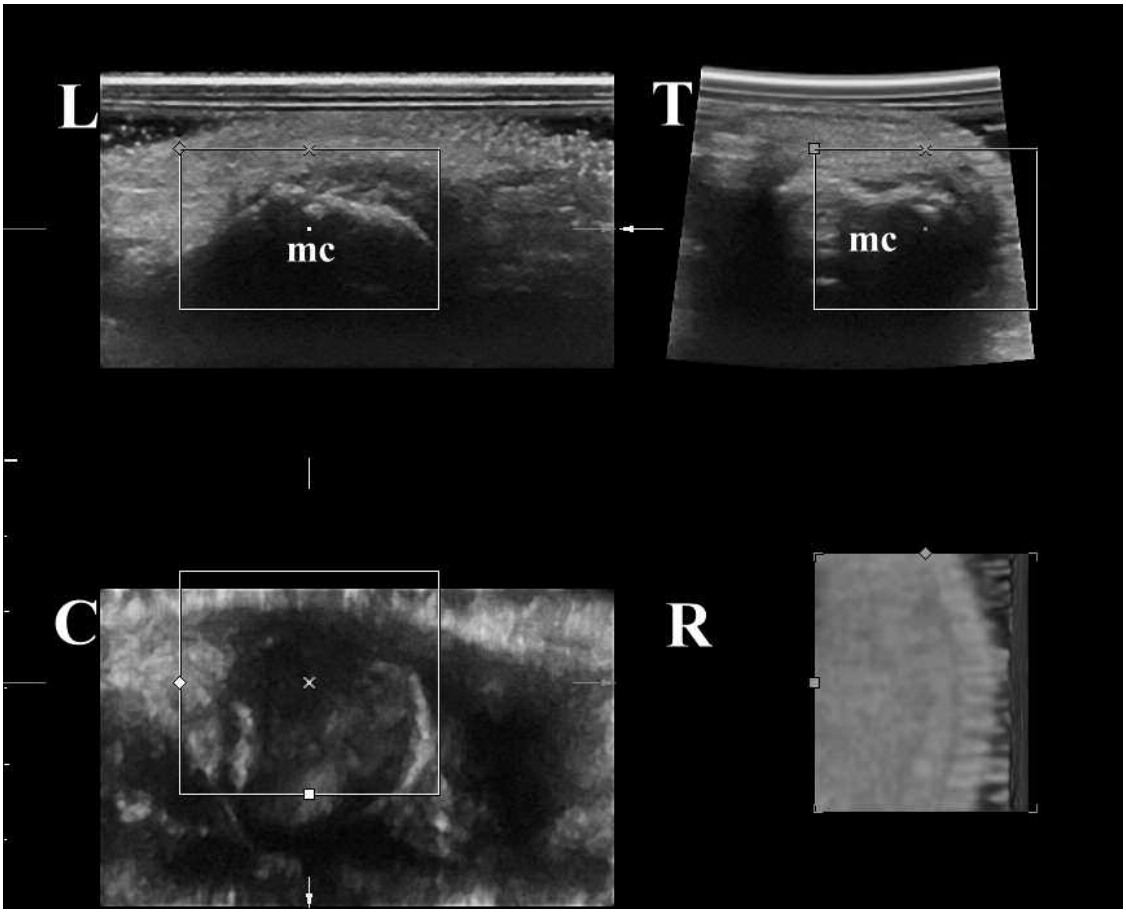

Figure 2. Volumetric B-mode image of the radial aspect of the second metacarpophalangeal joint. The longitudinal (L), transverse (T), and coronal (C) planes at the selected anatomic level of the joints and the reconstruction volume (R) are shown. A bone erosion is visualized at the metacarpal head in 2 perpendicular planes. mc: metacarpal bone.

quality. The coronal plane and the reconstruction volume were also available. However, their added value was beyond the scope of our study.

Overall, our results were in accord with those of previous longitudinal studies that have shown improvement of inflammatory B-mode and PD measures associated with clinical and laboratory response to biologic therapy in patients with RA[23,29,30,31,32,33,35,36]. However, as reported in previous studies on patients with RA treated with anti-TNF agents, persistent PDUS inflammation was detected in clinical responder patients[18,47]. In addition, changes in inflammatory PD measures in our populations were slower than those reported in patients with RA treated with anti-TNF agents[23,30,31,33,36]. This difference could be due to the drug (RTX), the characteristics of the population, or simply the blinded study design that could minimize assessment biases.

In our study, synovial PD signal (global index and number/percentage of joints) improved significantly throughout the followup. The number of joints with B-mode synovitis improved significantly, while the B-mode synovitis index improved, but not significantly. These findings were consistent with some studies that have shown a greater improvement in Doppler measures than in B-mode measures in patients receiving anti-TNF agents[47]. The probably long-sustained synovial hypertrophy that was unresponsive to previous treatments (such as synthetic DMARD and anti-TNF agents) in our RA population could have contributed to the lesser improvement in B-mode synovitis as compared to synovial PD signal.

Notably, we found a significant overall decrease in both the index for bone erosions and the number/percentage of joint areas with bone erosions. In 4 patients the improvement in the global index for bone erosions exceeded the SDD. Similar results have been reported in patients with RA who were treated with biologic therapy (adalimumab) and using computed tomography and US for assessing bone erosions[18]. In particular, it has been shown in randomized controlled trials that RTX treatment can improve clinical measures and reduced radiographic disease progression in patients with RA[48,49,50]. Although we did not measure the size of the erosions, the decrease in the global index for erosions was consistent with the decrease in the number of joint sites with erosions.

Our intraacquisition, intraobserver reliability was excellent for the assessment of B-mode and PD synovitis and bone erosions. Although we did not test interobserver reliability, the investigators had previously demonstrated good interreader reliability in RA abnormalities in multicenter PDUS studies[6,23,39].

The principal limitations in our study were the small population size and the heterogeneity of the patients' characteristics. However, this was a pilot study conducted in accord with daily clinical practice. In addition to RTX and methotrexate, the patients were treated with oral corticosteroids and NSAID at various dosage levels. These differences in treatment could introduce bias into the study. However, because RTX was indicated for RA that remained active despite treatment with synthetic DMARD and anti-TNF agents, it may be that changes in PDUS measures were due mainly to the RTX treatment.

The results of our pilot study suggest that volumetric PDUS can be used in multicenter open-label cohort studies on patients with RA. The added value of this technology over conventional US could be to minimize assessment biases and reduce acquisition variability.

ACKNOWLEDGMENT

We thank the rheumatologists from the centers that performed the clinical assessments.

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