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ORIGINAL ARTICLE

Prediction of Radiographic Damage in Early Arthritis by Sonographic Erosions and Power Doppler Signal: A Longitudinal Observational Study

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Objective. **To assess the ability of ultrasonography (US) to predict radiographic damage in early arthritis.**

Methods. **ESPOIR is a multicentric cohort of early arthritis (i.e., ≥2 swollen joints between 6 weeks and 6 months). US synovitis in B mode, power Doppler (PD) mode, and erosions were searched on the second through the fifth metacarpophalangeal and fifth metatarsophalangeal joints according to Outcome Measures in Rheumatology definitions. Structural radiographic progression was assessed using the modified Sharp/van der Heijde erosion score (SHS) at baseline and 1 and 2 years. Predictive factors of erosive arthritis at 2 years and rapid radiographic progression (RRP) at 1 year (defined by change of SHS ≥5) were searched.**

Results. **A total of 127 patients were included, with a mean ± SD Disease Activity Score in 28 joints of 5.1 ± 1.3; 37.6% were anti–citrullinated protein antibody positive and 27.6% had typical rheumatoid arthritis (RA) erosions on radiographs. At 2 years, 42 patients (39.2%) had typical RA erosions. US erosions predicted radiographic evidence of erosive arthritis (odds ratio [OR] 1.44, 95% confidence interval [95% CI] 1.04–1.98). PD synovitis score was predictive of RRP at 1 year (OR 1.22, 95% CI 1.04–1.42). US erosions and PD synovitis scores were associated with change of SHS on linear regression. Of the 1,184 analyzed joints, 105 (8.9%) had radiographic erosion at 1 year. At the joint level, baseline US erosions were predictive of the presence of radiographic erosions at 1 year ($P < 0.001$). The same trend was observed in the joints without radiographic erosions at baseline ($P = 0.052$).**

Conclusion. **US is useful to evaluate the potential severity of early arthritis: US erosions and PD-positive synovitis have prognostic value to predict future radiographic damage.**

INTRODUCTION

Evaluation of early arthritis is a complex issue in daily clinical practice: early diagnosis assessment and the search for prognostic factors to adapt treatment are essential. In rheumatoid arthritis (RA), the severity of the disease in terms of structural progression can be estimated during the first 2 years after the onset of symptoms, and a window of opportunity for remission occurs in the earliest

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Significance & Innovations

- Ultrasonography (US) performed at the first visit of patients with early arthritis predicts future radiographic joint damage.
- US erosions on the second and fifth metacarpophalangeal joints and fifth metatarsophalangeal joint have true prognostic value.

stages of the disease (1). Treatment should be introduced early to improve prognosis in terms of structural progression and the tendency for remission (2). New effective therapies create a need for early prognostic markers for RA diagnosis and severity to help the clinician choose the best treatment. Therefore, the clinical presence of synovitis or radiographic evidence of erosions affects both the diagnosis and prognosis in early arthritis.

New techniques such as magnetic resonance imaging and ultrasonography (US) have been sensitive in the earliest stages of arthritis in detecting both synovitis and erosions (3–8). However, only a few longitudinal studies have investigated the prognostic value of US for the evaluation of disease severity in the long-term outcome of patients with early and established RA (9–13). The ESPOIR cohort is a longitudinal observational study of patients with early arthritis designed to identify diagnostic and prognostic features (14). It provides clinical, biologic, and imaging data for patients with early arthritis, without restriction to RA. In a cross-sectional study of the ESPOIR data, US demonstrated high sensitivity for both synovitis and detection of erosions (5). The present study aimed to further evaluate the prognostic value of US in early arthritis. Baseline US findings were compared with radiographic evidence of erosive arthritis at 2 years, and US predictors of structural radiographic progression at 1 year were searched at the patient and joint levels.

PATIENTS AND METHODS

Patients. Patients were included in ESPOIR between December 2002 and March 2005. They were between ages 18 and 70 years, had ≥2 swollen joints between 6 weeks and 6 months, and were not receiving disease-modifying antirheumatic drugs (DMARDs) (14). Data collected at baseline and at 1 and 2 years consisted of age, number and site of swollen and tender joints, Disease Activity Score in 28 joints (DAS28), C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and positivity for IgM rheumatoid factor (IgM-RF) and anti–citrullinated protein antibody (ACPA). Treatment was reevaluated at each visit by the investigators and was not standardized. We used the 2010 data set of the ESPOIR cohort, in which 1 extra patient with a US evaluation was included, compared to the cross-sectional study (5).

The study was performed according to the principles of the Declaration of Helsinki. The protocols were approved by the local ethics committee. Informed consent for inclusion in the study was obtained from all patients.

Radiography. Patients underwent radiography of the anteroposterior view of the hands and the anteroposterior and oblique views of the feet at each visit. The modified Sharp/van der Heijde erosion score (SHS) was measured in the radiograph coordinating center by a single investigator (GJT) and was evaluated pairwise and blinded to clinical and US evaluation (15). At baseline and at 2 years, structural lesions seen on radiography were considered typical of RA or not, according to location and aspect. Structural damage progression was evaluated by change in the SHS ($\Delta SHS_{erosion}$) between baseline and 1 year. Rapid radiographic progression (RRP) was defined as $\Delta SHS_{erosion} \geq 5$ at 1 year (16).

Intraobserver analyses were performed on a set of 78 radiographs from the ESPOIR cohort at 1-year followup. Radiographs were read twice, 6 months apart. Global intrareader reliability was excellent, with an intraclass correlation coefficient of 0.99. The smallest detectable difference for radiographs was 0.96.

US. Of the 14 centers of the cohort, 4 (Paris, Brest, Montpellier, and Kremlin-Bicêtre) systematically performed the US evaluation. Each center had only 1 trained examiner who was a radiologist (n = 2) or a rheumatologist (n = 2; FE, CC, AM, SJ-J). US evaluation was performed with blinding to the clinical and radiographic evaluation. Two centers used the Aplio instrument (Toshiba), and the 2 other centers used the Technos MPX instrument (Esaote). US examination involved a 10–13-MHz linear array transducer. Power Doppler (PD) involved a frequency of 8.3 MHz and a pulse repetition frequency of 750 Hz. The dynamic range was 20–40 dB. Color gain was set just below the level at which color noise appeared underlying bone (no flow should be visualized at the bony surface). The examiners agreed on definitions of synovitis and bone erosions before the beginning of the study, as previously described (5). These definitions fulfilled the actual US Outcome Measures in Rheumatology criteria (17). Synovitis in B mode, PD mode, and erosions was assessed as present or not on each selected joint. Synovitis in PD mode and bone erosions was also noted according to semiquantitative scores. PD signal was graded as follows: 0 = no flow in the synovium, 1 = one-third or less of the synovium area (SA), 2 = two-thirds or less of the SA, and 3 = more than two-thirds of the SA (18). Erosions were graded as follows: 0 = no erosion, 1 = ≤1-mm erosion, 2 = 1–2-mm erosion, 3 = 2–4-mm erosion, and 4 = >4-mm erosion (19). A limited number of scanned joints was chosen on the basis of previous US studies that identified the most frequently affected joints in RA (7). For analysis of synovitis, the targeted joints were the bilateral second through the fifth metacarpophalangeal (MCP) joints and the fifth metatarsophalangeal (MTP) joint (i.e., 10 joints per patient). For erosion analysis, the targeted joints were limited to the bilateral MCP2 and 5 joints and the MTP5 joint (i.e., 6 joints per patient). Joints were examined on the palmar, dorsal, and lateral or medial sides. US erosion score was the sum of the grades of all erosions on the targeted joints. PD synovitis score was the sum of the grades of all PD synovitis on the targeted joints (see Sup-

Table 1. Patient characteristics at baseline*

	Patients undergoing US (n = 127)	Other ESPOIR patients (n = 686)
Age, years	50.3 ± 12.1†	47.7 ± 12.6
Women, %	77.2	76.7
Duration of symptoms, days	102.6 ± 53	103.2 ± 53
No. of swollen joints (of total 28)	7.8 ± 5.6	7.1 ± 5.3
No. of tender joints (of total 53)	7.44 ± 6.4	8.6 ± 7.1
DAS28	5.1 ± 1.3	5.1 ± 1.3
CRP level, mg/liter	22.6 ± 44.0	22.1 ± 31.4
ESR, mm/hour	31.2 ± 23.9	29.1 ± 24.7
IgM-RF positivity, %	42.2	42.0
ACPA positivity, %	37.6	41.1
Typical RA radiographic signs, %	26.8	23.7
ACR criteria fulfillment, %	77.2	70.1

* Values are the mean ± SD unless otherwise indicated. US = ultrasonography; DAS28 = Disease Activity Score in 28 joints; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IgM-RF = IgM rheumatoid factor; ACPA = anti–citrullinated protein antibody; RA = rheumatoid arthritis; ACR = American College of Rheumatology.
† $P = 0.03$.

plementary Figure 1, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.21912/abstract).

Statistical analysis. To investigate the prognostic value of US, we tested the ability of the US baseline findings to predict radiographic evidence of erosive arthritis at 2 years and structural damage progression at 1 year.

Wilcoxon's tests were used for quantitative variables and Fisher's exact tests were used for qualitative variables. At the patient level, the search for independent predictive factors of erosive arthritis and structural radiographic progression included univariate analyses and descending stepwise multivariate logistic regression. Explanatory variables tested were age, DAS28, CRP level, ESR, positivity for RF and ACPAs, corticosteroid therapy, DMARDs, biologic agents, center, US erosion score, US synovitis score in B mode, and US PD synovitis score. Explanatory variables were selected depending on univariate analysis, with a P value less than 0.3 for entering variables. A selection of the variables to be included in the model was performed in case of a strong correlation between them. Logistic regression involved stepwise selection. Variables with a P value less than 0.05 were included in the final model. Linear regression was also performed to assess the variables associated with $\Delta SHS_{erosion}$ between baseline and 1 year. At the joint level, associations between baseline US and radiographic findings at 1 year were analyzed using a mixed procedure, taking into account a patient effect. Statistical analyses involved use of SAS, version 9.1. P values less than 0.05 were considered statistically significant.

RESULTS

Of the 813 patients in the cohort, 127 were seen in the 4 centers performing US, and all underwent US evaluation at baseline. The patients' characteristics are shown in Table 1. At inclusion, the disease was active, with a mean ± SD swollen joint count of 7.8 ± 5.6, a mean ± SD DAS28 score of 5.1 ± 1.3, and a mean ± SD CRP level of 22.6 ± 44.0 mg/liter. In total, 37.6% and 42.2% of patients were positive for ACPA and RF, respectively, and 98 (77.2%) fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA (20). At baseline, a total of 34 patients (26.8%) showed typical RA erosions on radiographs and 45 (35.4%) had US erosions. Radiographs were missing for 8, 16, and 20 patients at baseline, 1 year, and 2 years, respectively. At 1 and 2 years, 73% and 65%, respectively, were receiving conventional DMARDs alone, and 3% and 9%, respectively, were receiving biologic agents.

Prediction of structural damage in patients with early arthritis by US. *Association of baseline US erosions with radiographic evidence of RA erosions at the patient level at 2 years.* At 2 years, radiographs for 42 patients (39.2%) showed typical RA erosions. On univariate analysis, swollen joint count and positivity for RF or ACPA were associated with typical RA erosions seen on radiographs at 2 years. The presence of US erosions and the erosion score were both significantly associated with radiographic evidence of typical RA at 2 years ($P < 0.001$). On multivariate analysis, after adjusting for age, DAS28, CRP level, ESR, positivity for RF and ACPA, and corticosteroids, US erosions at baseline were still predictive (odds ratio [OR] 1.44 [95% confidence interval (95% CI) 1.04–1.98], $P = 0.027$), as was serum RF (OR 4.99 [95% CI 1.77–14.04], $P = 0.002$).

In the subgroup of 93 patients (73.2%) without typical RA erosions on baseline radiographs, only 13 (14.0%) showed new erosions at 2 years. Baseline US evaluation revealed at least 1 erosion in 3 (23.1%) of these patients. However, only RF positivity remained significant on univariate and multivariate analysis.

Association of baseline US erosions with the presence of radiographic erosions at the joint level at 1 year. Radiographic erosions were found at baseline on 105 (8.9%) of the 1,184 joints scanned by US for synovitis detection (MCP2–5 and MTP5 joints) with full data. US evaluation at baseline found 381 joints (32.3%) with B-mode synovitis

Table 2. Prediction of radiographic joint erosions at 1 year in univariate analysis*

	Radiographic findings at 1 year (all joints)				Radiographic findings at 1 year (nonerosive joints at baseline)			
US findings at baseline	Eroded (n = 105)	Noneroded (n = 1,077)	OR (95% CI)	*P*	Eroded (n = 26)	Noneroded (n = 1,065)	OR (95% CI)	*P*
Synovitis (B mode)	43 (40.9)	338 (31.4)	1.51 (1.01–2.28)	0.048	13 (50.0)	334 (31.4)	2.18 (1.00–4.76)	0.05
Synovitis with Doppler	32 (30.4)	196 (18.2)	1.97 (1.26–3.07)	0.003	12 (46.1)	194 (18.2)	3.85 (1.17–8.45)	0.001
Erosion	21 (29.5)†	57 (9.0)‡	4.26 (2.39–7.59)	< 0.001	5 (27.8)§	56 (8.9)¶	3.93 (1.35–11.43)	0.01

* Values are the number (percentage) unless otherwise indicated. US = ultrasonography; OR = odds ratio; 95% CI = 95% confidence interval.
† N = 71.
‡ N = 635.
§ N = 18.
¶ N = 629.

and 228 (19.3%) with PD-positive signal. The presence of US erosions was found on 78 (11.0%) of the 706 joints scanned for erosion detection (MCP2 and 5 and MTP5 joints) with full data.

Predictors of radiographic erosions at 1 year were searched at the joint level. In the univariate analysis, the presence of B-mode synovitis, PD synovitis score, and US erosions was associated with the presence of erosions on radiographs at 1 year (OR 1.51 [95% CI 1.01–2.28], $P = 0.048$; OR 1.97 [95% CI 1.26–3.07], $P = 0.003$; and OR 4.26 [95% CI 2.39–7.59], $P < 0.001$, respectively) (Table 2). In the mixed procedure, after adjusting for age, DAS28, CRP level, ESR, positivity for RF and ACPA, US parameters, and treatments (corticosteroids, DMARDs, and biologic agents), baseline CRP level and the presence of RF were independent factors associated with the presence of erosions on joints at 1 year ($P < 0.001$) (Table 3). Moreover, the presence of US erosions at baseline was also an independent predictor of the presence of erosions on the same joint at 1 year ($P < 0.001$). When restricted to nonerosive joints at baseline, this association was still borderline significant ($P = 0.052$), showing that the presence of US erosions that are not yet visible on radiographs at baseline has a true predictive value.

Prognostic value of US in early arthritis: prediction of RRP at 1 year by baseline PD activity. Ten patients (9.0%) presented RRP ($\Delta SHS_{erosion} \geq 5$) at 1 year. PD signal was the most relevant predictor of RRP during the first year.

Table 3. Factors predicting radiographic erosion at 1 year at the joint level*

	All joints, *P*	Nonerosive joints at baseline, *P*
CRP level	0.0002	0.02
RF positive	< 0.001	0.004
US synovitis (B mode)	0.97	0.69
US synovitis with Doppler	0.56	0.91
US erosion	0.0003	0.052

* Results of the mixed procedure, after adjustment for age, Disease Activity Score in 28 joints, C-reactive protein (CRP) level, erythrocyte sedimentation rate, positivity for rheumatoid factor (RF) and anti–citrullinated protein antibody, ultrasonography (US) parameters, and treatments (corticosteroid therapy, disease-modifying antirheumatic drugs, and biologic agents).

Linear regression revealed that CRP level ($P < 0.01$), incidence of PD-positive synovitis ($P < 0.01$), PD score ($P < 0.001$), and incidence of US erosions ($P < 0.001$) at baseline were associated with structural disease progression during the first year of the disease (Table 4).

PD scores significantly differed between patients with and without evidence of RRP (mean ± SD 5.6 ± 4.8 versus 2.1 ± 3.2; $P = 0.004$) (Figure 1). The PD score was significantly associated with RRP ($\Delta SHS_{erosion} \geq 5$; OR 1.22 [95% CI 1.041–1.42], $P = 0.013$). Controlling for PD score, the number of cases of PD-positive synovitis was significantly associated with RRP (OR 1.33 [95% CI 1.041–1.691], $P = 0.02$). On multivariate analysis, RF positivity was also associated with RRP (OR 7.4 [95% CI 1.38–39.75], $P = 0.02$). The presence of at least 2 cases of PD-positive synovitis was associated with risk of RRP, with a sensitivity of 80% and a specificity of 62% (area under the receiver operating characteristic curve [AUC] 0.744). A PD score ≥2 at baseline was associated with risk of RRP, with a sensitivity of 80% and a specificity of 60% (AUC 0.766) (Figure 2).

DISCUSSION

This study was one of the largest early arthritis cohorts in which US evaluation was performed. We demonstrated that US has prognostic value in estimating the potential severity of early arthritis during the first year after diagnosis. PD score at baseline was associated with structural disease progression at 1 year. PD signals allowed for determination of the patients with early arthritis who were at

Table 4. Determinants of structural progression (change in the modified Sharp/van der Heijde erosion score) between baseline and 1 year, explored by multivariate linear regression*

	PE	SD	*P*
CRP level	0.02	0.008	0.002
PD-revealed synovitis	−0.94	0.31	0.003
PD score	0.84	0.22	0.0004
US-revealed erosion	0.78	0.20	0.0003

* PE = parameter estimate; CRP = C-reactive protein; PD = power Doppler; US = ultrasonography.

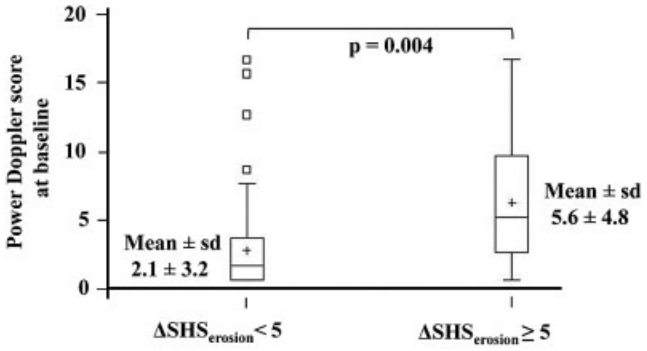

Figure 1. Association of power Doppler score at baseline and radiographic evidence of rapid disease progression at 1 year. $\Delta SHS_{erosion}$ = change in the modified Sharp/van der Heijde erosion score.

high risk of major structural damage within the first year because PD score was predictive of RRP ($\Delta SHS_{erosion} \geq 5$) during the first year of the disease. In our study, a PD score ≥2 or the presence of at least 2 cases of synovitis with PD signal at baseline was highly associated with the risk of RRP at 1 year, with a sensitivity of 80%. In assessed RA, the PD signal was previously found to be associated with structural damage (21) and with disease change on treatment with DMARDs or tumor necrosis factor blockers (22–24). PD signal was also predictive of radiographic evidence of disease progression or relapse within 6 months in RA patients in clinical remission (25,26). Our study showed PD signal as an independent risk factor of rapid disease progression during the first year of early arthritis. This marker can help the clinician determine the potential severity of RA and adjust RA management with tight control and, for example, introduce biologic agents early in patients with a high PD score at baseline.

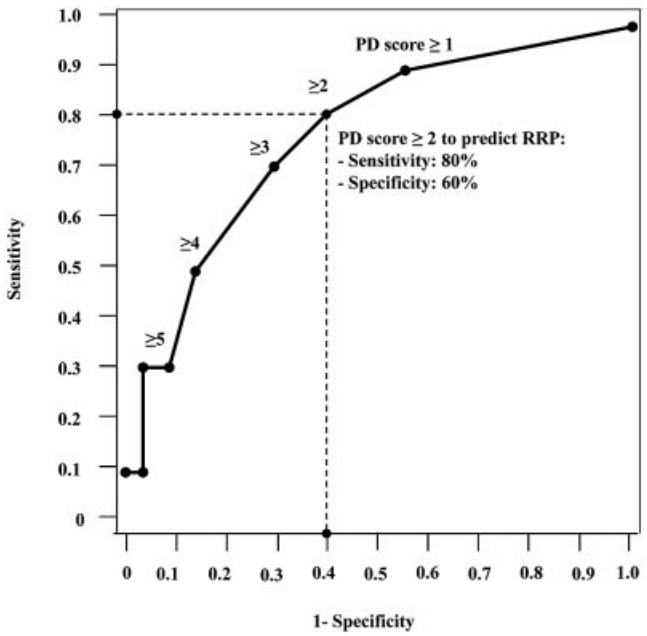

Figure 2. Association of power Doppler (PD) score at baseline and radiographic evidence of rapid structural progression at 1 year (area under the receiver operating characteristic curve 0.766). RRP = rapid radiographic progression.

In this cross-sectional study, as compared with radiography, US revealed erosions in 1.4-fold more patients at baseline, as evaluated by the SHS (5). Here, US erosions were also significantly associated with radiographic evidence of disease progression on linear regression. This is the first demonstration of the value of this US variable (evidence of erosion) in a longitudinal study of early arthritis. Moreover, US erosion findings were predictive of typical radiographic evidence of RA erosion at 2 years. This finding is of particular interest for the early diagnosis of RA according to the new 2010 ACR/European League Against Rheumatism classification (27). In addition, previous cross-sectional and longitudinal studies have demonstrated that US-revealed erosions are true erosions in patients with assessed RA (28,29). Our study demonstrates for the first time that baseline US erosions predict radiographic erosions on the same joint at 1 year.

However, our study failed to confirm the predictive value of US-demonstrated erosion at baseline for radiographic evidence of typical RA erosion at 2 years in the subgroup of patients without typical radiographic evidence of erosions at baseline. This situation may be due to a lack of power in our study, as well as the limited number of joints scanned by US. The choice to explore only 3 sites for US erosion detection was justified by scientific evidence on the one hand, and by feasibility reasons on the other hand. US was performed only on MCP joints, while radiography included wrist examination, where erosions more frequently occur. In the patients with a new appearance of typical erosions at 2 years, nearly one-quarter had US-revealed erosions on the targeted joints at baseline. Moreover, the erosion score we used showed good interexaminer reproducibility and was feasible.

US examination allows for determination of the potential severity of early arthritis and may help physicians manage RA optimally in patients at high risk of erosive and rapidly progressing disease. US findings, both erosions and PD signal, may have a role in the identification of patients at risk of erosive joint disease. Further prospective studies are needed to confirm the role of US in the management of patients with early RA.

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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 published. Dr. Gandjbakhch 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. Funck-Brentano, Gandjbakhch, Etchepare, Jousse-Joulin, Saraux, Boumier, Bourgeois, Fautrel.
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Analysis and interpretation of data. Gandjbakhch, Etchepare, Boumier, Goupille, Bourgeois, Fautrel.

ROLE OF THE STUDY SPONSOR

Merck Sharp & Dohme, Abbott, Wyeth, and Amgen had no role in the study design, data collection, data analysis, and writing of the manuscript, as well as approval of the content of the submitted manuscript. Publication of this article was not contingent on the approval of Merck Sharp & Dohme, Abbott, Wyeth, and Amgen.

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