Benefits of ultrasonography in the management of early arthritis: a cross-sectional study of baseline data from the ESPOIR cohort

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Objective. To assess ultrasonography's (US) performance to detect the structural damage in the initial evaluation of early arthritis (EA) using the Etude et Suivides Polyarthrites Indifférenciées Récentes (ESPOIR) cohort.

Methods. ESPOIR is a French, multi-centric EA cohort. Four centres assessed the structural damage by both X-ray and US examination at baseline. X-rays of hands and feet were read first by the centre's local investigator (usual reading), then in the X-ray coordinating centre (central reading). Four trained examiners performed US blindly from clinical data to detect erosions on the second and fifth MCP (MCP2 and 5) and the fifth MTP (MTP5) joints bilaterally.

Results. Patients' characteristics ($n = 126$) were: female 78%; mean age 50.3 years; disease duration 103 days; disease activity score on 28 joints 5; CRP level 22.7 mg/l; and 79.4% of the patients fulfilling RA ACR criteria. Twelve patients had missing data for X-rays. US revealed 42 (36.8%) patients with erosive disease, whereas radiography revealed only 30 (26%) with central reading and only 11% with usual reading. US missed erosive disease present in X-rays in 10 (8.8%) patients. Combined technique of both revealed 52 (45.6%) patients with erosive diseases. On the targeted joints, US detected erosion on 75 (11%) joints *vs* X-rays on only 11 (1.5%). Only three joints with erosion(s) detected on X-rays were missed on US. At baseline, the presence of PD activity was not associated with joint erosions.

Conclusions. US on six joints detected 1.4-fold more patients with erosions (3.3-fold more with the usual reading). In clinical practice, US combined with X-rays is of helpful diagnostic value in EA.

KEY WORDS: Rheumatoid arthritis, Rheumatoid diagnosis, Ultrasonography, Radiography, Etude et Suivides Polyarthrites Indifférenciées Récentes cohort.

Introduction

Evaluation of synovial inflammation and detection of bone erosion is key to the management of early arthritis (EA). Identifying persistent and erosive arthritis appears to be a medical emergency. In fact, numerous studies have shown that in RA, joint damage occurs within the first 2 years after symptoms appear [1]. Others have demonstrated early *vs* delayed treatment associated with better clinical and structural outcomes after 2 years, which emphasizes the precocity of structural damage in RA [2, 3]. These points were outlined in recent European recommendations and models for management of EA, and prognostic markers for persistent arthritis have been established [4–6]. However, standards for markers such as number of swollen joints and presence of erosions can vary depending on the detection method used [7].

In daily clinical practice and actual studies, structural damage in RA is assessed by the presence of bone erosions on standard radiography. Joint space narrowing is another structural damage that is observed in RA, but erosions are more likely to appear at the first stage of the disease. However, routine radiography has only fair detection power for erosions at the earliest stage, which can lead to an underestimation of the disease severity at the onset of arthritis. Improving the assessment and monitoring of persistent and/or erosive arthritis therefore appears important [8].

A body of evidence suggests that the ability to detect erosion is higher with other imaging techniques such as ultrasonography (US) and MRI than with routine techniques [9, 10]. Szkudlarek *et al.* [11], comparing conventional radiography and US with MRI, showed that the US is more sensitive than X-rays or clinical examination for the detection of both joint erosion and synovitis [11]. This technique is becoming commonly used in European rheumatologists' practices and therefore needs more precise evaluation.

We aimed to assess the capacity of US as compared with standard radiography for the early detection of erosive diseases in EA. A secondary objective was to compare characteristics at the joint level seen on clinical examination and X-rays with that seen on US.

Methods

Patients

Etude et Suivides Polyarthrites Indifférenciées Récentes (ESPOIR) is a French, multi-centric cohort of adults with EA, who had at least two swollen joints for at least 6 weeks and <6 months, and were not under treatment with DMARDs [12]. All clinical, biological and radiographic data were collected by the investigators and compiled in the ESPOIR cohort baseline database. Available (or collected) data were age, number and site of swollen and tender joints, calculated disease activity score on 28 joints (DAS28) and the HAQ score, CRP level, ESR and positivity for IgM RF and anti-cyclic citrullinated peptide (anti-CCP) antibodies. Fulfilment of RA by the ACR criteria was noted. The ESPOIR cohort study was performed according to the principles of the Declaration of Helsinki. The protocol of the ESPOIR cohort study was approved in July 2002 by the ethical committee of Montpellier. All the patients signed an informed consent form before inclusion. We obtained approval from the scientific committee of the ESPOIR cohort to use these data for the statistical analysis.

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Standard radiography (X-rays)

Radiography of the hands was performed in the anteroposterior view and of feet in the anteroposterior and oblique views. X-ray images were read at two levels: (i) in the centre by the ESPOIR investigator (usual reading) who assessed the presence or not of typical RA lesions (erosive disease) in the images; and (ii) X-ray images were then collected in the coordinating centre (central reading). Two trained rheumatologists read the images, blinded from each other and assessed the van der Heijde-modified Sharp score, thereby giving information on each joint. In case of disagreement, a third trained reader assessed the images.

US

Of the 813 patients from the ESPOIR cohort, 126 underwent baseline US examination in four evaluation centres (Brest, Le Kremlin Bicêtre, Montpellier and Paris). Each centre had only one examiner who was either a radiologist or a rheumatologist experienced in US. The patients underwent US examination randomly depending on the examiner availability. Two centres used the Aplio® (Toshiba, Tokyo, Japan); the two others the Technos MPX® (Esaote, Genova, Italy). US examination involved a 10–13 MHz linear array transducer. Power Doppler (PD) involved a frequency of 8.3 MHz and pulse repetition frequency of 750 Hz. The dynamic range was 20–40 dB. Colour gain was set just below the level at which colour noise appeared underlying bone (no flow should be visualized at the bony surface). The targeted joints were the second and fifth MCP (MCP2 and -5) and the fifth MTP (MTP5) joints for the detection of bone erosion (six joints per patient); the MCP2 and -5 and MTP5 joints for the detection of synovitis (10 joints per patient). Joints were examined on palmar, dorsal and lateral or medial sides. Consensus definitions of synovitis and bone erosions were assessed among the examiners before the beginning of the study. These definitions fulfilled the actual US outcome measures in rheumatoid arthritis clinical trials (OMERACT) criteria [13]. Synovitis in B mode, PD mode and erosions were assessed as present or not on each selected joint. Synovitis in PD mode and bone erosions were also noted according to semi-quantitative scores. Erosions were scored as follows: Grade 0, no erosion; Grade 1, erosion ≤ 1 mm; Grade 2, erosion 1–2 mm; Grade 3, erosion 2–4 mm; and Grade 4, erosion > 4 mm [14]; and for synovitis in PD mode: Grade 0, no flow in the synovium; Grade 1, flow ≤ 1/3; Grade 2, flow ≤ 2/3; and Grade 3, flow > 2/3 [15]. The inter-examiner reliability was assessed on selected images, blindly from clinical data and other examiner results: 20 images in B mode and 30 images of synovitis in PD mode were sent to each examiner. Examiners had to assess the presence or absence of synovitis in B mode and score synovitis in PD mode according to the semiquantitative score previously defined.

Statistical analysis

At the patient's level, erosive disease was defined by the presence of one or more erosion(s) by US on the six selected joints, or by the presence of one or more erosion(s) or joint space narrowing on X-rays. Mc Nemar chi-square tests were used to compare the capacity of US and X-rays to detect erosive disease (at the level of the patient) or an erosive joint (at the level of the joint) on the six selected joints and to compare the capacity of US and clinical examination to detect a synovitis on the 10 previously described joints. The intra-class correlation coefficient (ICC) was calculated to analyse interobserver reliability. A *P*-value of < 0.05 was considered as statistically significant. All statistical analysis involved use of STATA® software (StataCorp LP, TX, USA).

Results

Clinical, biological and US data were available for 126 patients, although X-ray data were missing for 12 (Fig. 1). Patient's
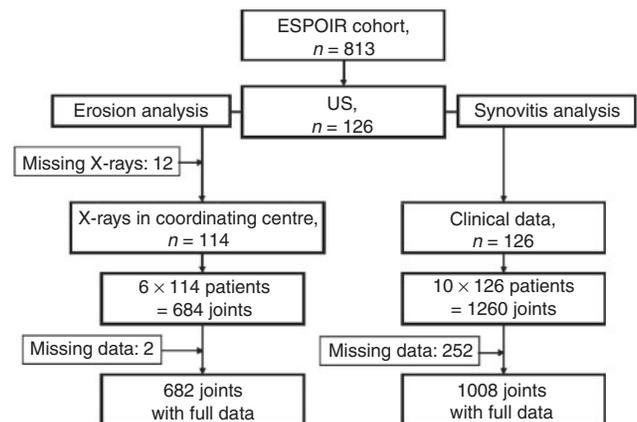

Fig. 1. US information was compared to X-rays for the erosion analysis on 6 joints per patient and to clinical examination for the synovitis analysis on 10 joints.

TABLE 1. Patients' characteristics at baseline

Baseline characteristics	Patients with US $n = 126$	Other ESPOIR patients $n = 687$
Age, years	50.3 ± 1.1*	47.9 ± 0.5
Female, %	78.6	76.4
Duration of symptoms, days	102.6	103.2 ± 53
No. of swollen joints, $n = 28$	7.74 ± 5.6	7.1 ± 5.3
No. of tender joints, $n = 53$	7.44 ± 6.4	8.6 ± 7.1
DAS28 score	5.04 ± 1.3	5.2 ± 1.5
HAQ score	0.85 ± 0.64*	1 ± 0.7
CRP, mg/l	22.7 ± 44.1	22.2 ± 32
ESR, mm in first hour	31 ± 24.2	29.1 ± 24
IgM RF positivity, %	42.9	48.2
Anti-CCP antibodies positivity, %	35.7	39.5
Typical RA radiographic signs, %	26.3	22.2
ACR criteria fulfilment, %	79.4	83.4

Values are given as mean ± S.D. unless otherwise indicated. *$P = 0.02$.

characteristics are summarized in Table 1. Patients who underwent US did not significantly differ from the rest of the cohort in data, except for having a higher HAQ score and being slightly older. At inclusion, the disease was active (50.8% of the patients had a DAS28 score > 5.1, and 41.3% had a score between 3.2 and 5.1). A total of 35.7% of the patients showed positivity for anti-CCP antibodies, and 42.9% showed positivity for IgM RF. Nearly 80% of the patients fulfilled the ACR criteria at the inclusion visit.

Inter-examiner reliability study

The reliability among the four examiners was excellent with very good agreement on the ICC (0.82 for synovitis in B mode and 0.92 for synovitis in PD mode).

Capacity of US and X-rays to detect erosive disease (patient's level)

Table 2 shows the capacity of US and X-rays to detect erosive disease at the level of the patient. In 114 patients with both X-rays and US data, erosive EA was detected in 42 (36.8%) by US *vs* 30 (26.3%) by X-rays in central reading (ratio = 1.4; $P = 0.05$) and in only 14 (11.2%) by X-rays read by the local investigator (ratio = 3.3; $P \leqslant 0.001$). US detected erosive disease in 22 (19.3%) patients not detected by X-rays. Nevertheless, US of the six targeted joints failed to detect erosive disease in 10 (8.8%) patients who were so detected on X-rays [only three (2.4%) patients in usual reading]. Of these patients, eight had erosions located on other joints (third and fourth MCP joints and

TABLE 2. Detection of erosive disease by US and radiography

Patients, n = 114	X-ray non-erosive disease, n (%)	X-ray erosive disease, n (%)
US non-erosive disease, n = 72	62 (54.4)	10 (8.8)
US erosive disease, n = 42	22 (19.3)	20 (17.5)

US detects 1.4-fold more patients with erosive disease than X-rays. Exact McNemar significance $P = 0.05$. Ratio = 1.4 (1.02 : 1.9).

TABLE 3. Detection of bone erosion on targeted joints by US and radiography

Joints, n = 682	X-ray non-erosive joints, n (%)	X-ray erosive joints, n (%)
US non-erosive joints, n = 607	604 (88.6)	3 (0.4)
US erosive joints, n = 75	67 (9.8)	8 (1.1)

On the six selected joints (MCP2 and -5, MTP5) US detects 6.8-fold more joints with erosion than X-rays. Exact McNemar significance $P \leqslant 0.001$. Ratio = 6.8 (3.8 : 12).
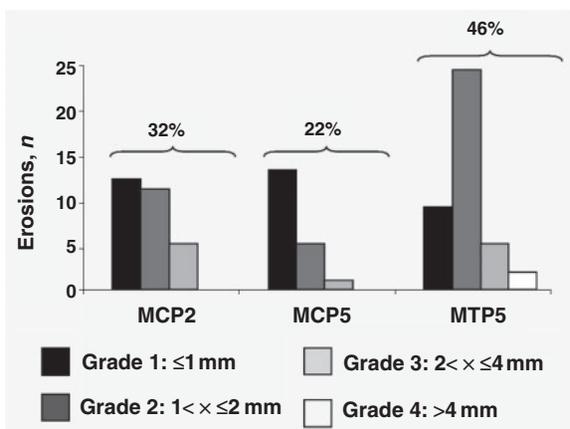

FIG. 2. Site of erosions by US. The preferential site for erosion detected by US was MTP5 (46%) followed by MCP2 (32%) and MCP5 (22%). Most of the erosions were of Grade 2 (46%); only two erosions of Grade 4 were found on MTP5 at baseline.

the carpe), and only two had erosions on the joints targeted by US. Combining both techniques, 52 cases of EA (45.6%) were detected early, as soon as the first assessment by the rheumatologist.

A subgroup analysis focused on patients with positive anti-CCP antibodies, US and X-ray central reading displayed similar capacity to detect erosive diseases. However, US still detected erosive disease significantly more frequently than X-ray read by the local investigator with a ratio of 2.3 (1.3 : 4.1) (Exact McNemar significance $P = 0.004$).

Comparison between US and X-rays to detect erosive joints (joint level)

Both X-rays and US data were available on the 682 joints (i.e. six joints in 114 patients). US detected 75 (11%) erosive joints, whereas X-rays on the selected joints found only 11 (1.6%) [ratio = 6.8 (3.8 : 12); Exact McNemar significance $P \leqslant 0.001$; Table 3]. US missed only three joints that were considered erosive on X-rays. The most frequent site for erosions was the MTP5 joint (42% of the US-detected erosions; Fig. 2). Considering the erosive joints detected by US, 61.2% showed concomitant B-mode synovitis, and only 40% had concomitant PD activity. Erosions detected on X-rays were not associated significantly with synovitis with PD activity at baseline or with clinically swollen or tender joints.

TABLE 4. B-mode synovitis, Power Doppler activity and clinical assessment of swollen joints

US	n	Clinically swollen joints No, n (%)	Clinically swollen joints Yes, n (%)
Synovitis on mode B			
No	662	515 (78)	147 (22)
Yes	346	184 (53)	162 (47)
Synovitis with PD positive signal			
No	147	89 (61)	58 (39)
Yes	199	95 (48)	104 (52)

Only half of the B-mode synovitis with PD activity was found swollen by clinical examination. There is a weak correlation between PD activity and clinical findings.

Comparison between US and clinical examination to detect synovitis

Data were available for 1260 joints (i.e. 10 US-assessed joints in 126 patients). US detected slightly more synovitis than clinical examination: 346 (34%) joints with synovitis by US vs 309 (30.6%) clinically swollen joints. But there was only a fair agreement between both detection methods ($\kappa = 0.25$). US confirmed only 52% of the clinically swollen joints, and found synovitis in 26% of the clinically not swollen joints. B-mode synovitis was present on only 36% of the tender joints. PD activity was found in 58% of B-mode synovitis. Only one-third of these joints were tender and half of them were swollen (Table 4).

Discussion

This descriptive study has shown that US, performed for patients with EA on a limited number of joints, detected 6.8-fold more joints with erosion in 1.4-fold more patients than standard radiography (3.3-fold more than with usual reading). These results are consistent with those from previous studies of patients with assessed RA. Wakefield et al. [16] showed with 40 RA patients [mean duration of disease 5.5 (range 2–11) months] that US, performed on the MCP joints of the dominant hand, detected 6.5-fold more joints with erosions in 7.5-fold more patients than that detected with X-rays.

Our study is original with regards to the choice of a limited number of joints for US. Previous studies in RA had identified MCP1, -2 and -5 joints for the hands and the MTP1 and -5 joints for the feet as the preferred sites for finding erosions [16, 17]. In these sites, US was better than X-rays and even MRI for the detection of erosions [18]. This finding can be explained by the better accessibility for examination of these joints than MCP3 and -4, with the ability to apply the transducer on three faces of the joints. However, erosions on MTP1 are difficult to distinguish from that with degenerative disorders. Therefore, we excluded this joint in our study. Limiting the number of joints is interesting to keep the duration of US examination in reasonable timeframe and make it compatible with daily clinical practice. With such a focused US investigation, the mean duration of the examination was ~15–20 min/patient, whatever the centre.

If performing US on a limited number of joints reduces the time for examination, it may also decrease its capacity to detect erosions. This observation may explain as to why we found 10 (8.8%) patients with erosive disease missed by US. In these patients, radiography revealed the erosions located on joints that were not explored with US except for one MCP5 and one MTP5 joint. Further research and international recommendations are needed to determine the optimal trade-off between US data acquisition and fair erosion detection capacity. Meanwhile, US cannot replace radiography for the detection of erosion, and when both the techniques are combined, they show complementary efficiency and display the best results.

US has frequently been depicted as examiner dependent. Our study was multi-centre, which may introduce discrepancies between centres. To reduce this risk, the four examiners applied the same definitions previously described for synovitis, PD activity and erosions. In addition, we aimed to stay close to real clinical practice, and previous studies have reported moderate to good inter- and intraobserver agreements ($\kappa = 0.52$–0.82) [19–23]. The reliability exercise in our work was in the same range.

Our study confirmed that US detected more joint inflammation than clinical examination. It is striking to observe the mismatch between both detection methods at the joint level, especially when US confirmed the synovitis on only half of the clinically swollen joints. If our study was not designed to demonstrate which method is the best, others have shown better inter- or intra-observer reliability with US [23]. As in the literature, we did not find any association between PD activity and either swelling or tender joints at baseline, nor the detection of erosions by US or X-rays. A possible explanation could be that PD activity (i.e. synovial hyperaemia) precedes bone erosions and may not be present anymore when erosions become detectable. PD US has shown promising results in evaluating joint inflammation, with some possible histopathological correlation [24]. In fact, the evolution of PD activity was well correlated with clinical and biological improvement in a therapeutic trial of adalimumab [25]. Somehow, PD activity has shown its variability with the type of device used, and further studies seem necessary to validate it as a prognostic factor for poor outcome. Longitudinal data are needed to progress in the understanding of such mechanisms.

Whether early erosions detected by US, but not by X-rays, are true erosions and associated with a poor structural outcome is uncertain. Døhn *et al.* [26] compared MRI and US with CT evaluation as a reference method in erosion detection in 17 RA and four healthy control patients; the sensitivity of US and MRI was 42 and 68%, respectively, and specificity 91 and 96%, respectively. Erosion-like lesions were seen in all four controls. In another study, when compared with MRI as the reference method, US showed even higher values of sensitivity and specificity; MRI-detected erosions were also detected in 7 of the 20 healthy controls [11]. A longitudinal study is necessary to investigate erosion outcome evaluated by both US and X-rays with patients as their own controls. Backhaus *et al.* [18, 27] performed such a prospective study of 49 cases of assessed RA; US at baseline had detected 5 of the 12 newly appeared erosions seen on radiography after 2 years. The planned follow-up of the ESPOIR study is 10 years, which will enable to assess the prognostic value of early erosions detected by US.

In conclusion, this study demonstrates the interest of US in complement with X-rays for its early diagnostic value in EA. Further, longitudinal study of the ESPOIR cohort will enable us to assess the long-term prognostic value of US early erosions.

Rheumatology key messages

- US on six joints detects 6.8-fold more joints with erosions than X-rays in 1.4-fold more patients.
- US combined with X-rays is of helpful diagnostic value in EA.

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