Benefits of ultrasonography in the management of early arthritis

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WORD COUNT: 3953
Introduction: To assess ultrasonography's (US) performance to detect structural damage in the initial evaluation of early arthritis (EA) using the ESPOIR cohort.

Methods: ESPOIR is a French multi-centric early arthritis cohort. Four centers assessed structural damage by both X-rays and US examination at baseline. X-rays of hands and feet were read firstly by the center's clinical investigator (usual reading), then in the X-ray coordinating center (central reading). Four trained examiners evaluated US images blindly from clinical data to detect erosions on the second and fifth metacarpophalangeal (MCP2 and 5) and the fifth metatarsophalangeal (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; and C-reactive protein level 22.7 mg/L; and 79.4% fulfilling rheumatoid arthritis ACR criteria. US revealed 42 patients (36.8%) 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 patients (8.8%), including 8 with X-ray evidence of erosion(s) on MCP3 and 4 and on the carpe. Both techniques combined revealed 52 erosive disease (45.6%). US detected erosion in 75 joints (11%) and X-rays in only 11 (1.5%). Only 3 joints with erosion(s) detected on X-rays were missed on US.

Conclusion: US detected 6.8-fold more joints with erosions than X-rays in 1.4-fold more patients (3-fold more with the usual reading). US combined with X-rays is of helpful diagnostic value in early arthritis.

KEYWORDS:
- Rheumatoid Arthritis
- Arthritis, Rheumatoid/diagnosis
- Ultrasonography
- Radiography
- ESPoir 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 rheumatoid arthritis (RA), joint damage occurs within the first 2 years after symptoms appear.[1] Others have demonstrated early versus 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 early arthritis, 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 in actual studies, structural damage in rheumatoid arthritis (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 stages 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 magnetic resonance imaging (MRI) than with routine techniques.[9,10] Szkudlarek et al., comparing conventional radiography and US to MRI, showed US with higher sensitivity than X-rays or clinical examination for 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 early detection of erosive diseases in early arthritis. 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

ESPOIR is a French multi-centric cohort of adults with early arthritis, who had at least two swollen joints for at least 6 weeks and less than 6 months and were not under treatment with disease-modifying antirheumatic drugs. 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 (DAS 28) and the Health Assessment Questionnaire (HAQ) score, C-reactive protein level, erythrocyte sedimentation rate (ESR), and positivity for IgM rheumatoid factor (RF) and anti-CCP antibodies. Fulfillment of RA by the American College of Rheumatology (ACR) criteria was noted. Moreover, at the end of the inclusion visit, the local investigator had to state the diagnosis that seemed the most likely (preferred diagnosis) and to express the level of confidence in RA diagnosis on a visual analog scale (0, “RA diagnosis excluded,” and 100, “RA diagnosis almost certain”).

Ultrasonography (US)

Of the 813 patients from the ESPOIR cohort, 126 underwent baseline US examination in 4 evaluation centers (Brest, Le Kremlin-Bicêtre, Montpellier and Paris). Each center had only one examiner who was either a radiologist or a trained rheumatologist. The patients underwent US examination randomly depending on the examiner availability. Two centers used the Aplio®, TOSHIBA device; the two others the Technos MPX®, ESAOTE. 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. 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 targeted joints were the second and fifth metacarpophalangeal (MCP2 and 5) and the fifth metatarsophalangeal (MTP5) joints for the detection of bone erosion (6 joints per patient); the MCP2 to 5 and MTP5 joints for the detection of synovitis (10 joints per patient). Joints were examined on palmar, dorsal, lateral and 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 OMERACT criteria. Synovitis in B mode, power Doppler mode and erosions were assessed as present or not on each selected joint. Synovitis in Power Doppler mode and bone erosions were also noted.
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according to semi-quantitative scores: for erosion: grade 0, no erosion; grade 1, erosion ≤ 1 mm; grade 2, erosion 1-2 mm; grade 3, erosion 2-4 mm; grade 4, erosion > 4 mm);[14], for synovitis in Power Doppler mode grade 0, no flow in the synovium; 1, flow ≤ 1/3; 2, flow ≤ 2/3; 3, flow > 2/3).[15] The inter-examiner reliability was assessed on selected images, blindly from clinical data and other examiner results: 20 images of in B mode and 30 images of synovitis in power Doppler mode were sent to each examiner. Examiners had to assess the presence or absence of synovitis in B mode and score synovitis in power Doppler mode according to the semiquantitative score previously defined.

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: 1) in the center by the ESPOIR investigator (usual reading) who assessed the presence or not of typical RA lesions (erosive disease) in the images; 2) X-ray images were then collected in the coordinating center (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.

Statistical analysis

Erosive disease was defined by the presence of at least one erosion by US on the 6 selected joints, or by the presence of at least one erosion or joint space narrowing on X-rays. At the joint level, only the 6 selected joints were assessed by both techniques. 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) and to compare the capacity of US and clinical examination to detect a synovitis. The intraclass correlation coefficient (ICC) was calculated to analyse interobserver reliability. A p < 0.05 was considered significant. All statistical analysis involved use of STATA® software (StataCorp LP, TX, USA).

RESULTS

Clinical, biological and ultrasonographic data were available for 126 patients, although X-ray date were missing for 12. (Figure 1).

Patient 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
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Slightly older. At inclusion, the disease was active (50.8% had a DAS 28 score higher than 5.1 and 41.3% a score between 3.2 and 5.1). A total of 35.7% of patients showed positivity for anti-CCP antibodies, and 42.9% positivity for IgM RF. Nearly 80% fulfilled the ACR criteria at the inclusion visit.

Inter-examiner reliability study

The reliability between the 4 examiners was excellent with very good agreement on the intraclass correlation coefficient (ICC) (0.82 for synovitis in B mode and 0.92 for synovitis in power Doppler 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 the 114 patients with both X-rays and US data, erosive early arthritis was detected in 42 (36.8%) by US versus 30 (26.3%) by X-rays in central reading (ratio = 1.4, p = 0.05) and only 14 (11.2%) by X-rays read by the local investigator (ratio = 3.3, p ≤ 0.001). US detected erosive disease in 22 patients (19.3%) not detected by X-rays. Nevertheless, US of the 6 targeted joints failed to detect erosive disease in 10 patients (8.8%) that were so detected on X-rays (only 3 patients (2.4%) in usual reading). Of these patients, 8 had erosions located on other joints (third and fourth MCP joints and the carpe) and only 2 had erosions on the joints targeted by US. Combining both techniques, 52 cases of erosive arthritis (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-rays central reading displayed similar capacity to detect erosive diseases. However, US still detected significantly more frequently erosive disease than X-ray read by 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’s level)

Both X-rays and US data were available on the 682 joints (i.e., 6 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 ≤ 0.001 ; see Table 3). US missed only 3 joints that were considered erosive on X-rays. The most frequent site for erosions was the MTP5 joint (42% of the US-detected erosions; see Figure 2). Considering the erosive joints detected by US, 61.2% showed
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concomitant mode-B synovitis and only 40% had concomitant PD activity. Erosions detected on X-rays were not associated significantly with PD+ synovitis at baseline or with clinically swollen or tender joints.

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. US detected 346 (34%) joints with synovitis versus 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. Pulse Doppler activity was found in 58% of B mode synovitis. Only one third of these synovitis were tender and only half were swollen (Table 4).

DISCUSSION

This descriptive study has shown that US, performed for patients with early arthritis 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. 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.[16]

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 [REFERENCE.??]. 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 3 faces of the joints. However, erosions on MTP1 are difficult to distinguish from that with degenerative disorders. We therefore 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
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with daily clinical practice. With such a focused US investigation, the mean duration of the examination was approximately 15 to 20 min per patient, whatever the center.

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 why we found 10 patients with erosive disease (8.8%) missed by US. In these patients, radiography revealed erosions located on joints which were not explored with US except for one MCP5 and one MTP5 joints. Further research and international recommendations are needed to determine the optimal tradeoff between US data acquisition and fair erosion detection capacity. Meanwhile, US cannot replace radiography for detection of erosion, and both techniques combined show complementary efficiency and displayed the best results.

US has frequently been depicted as examiner-dependent. Our study was multicentre which may introduce discrepancies between centers. To reduce this risk, the 4 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-observer and intra-observer agreements (kappa = 0.52-0.82).[18-22] 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 synovitis on only half of the clinically swollen joints. If our study wasn’t designed to demonstrate which method is the best, others have shown better inter- or intra-observer reliability with US.[22-24] As in the literature, we did not find at baseline any association between PD activity and either swelling or tender joints, nor the detection of erosions by US or X-rays. A possible explanation could be that PD activity (i.e., synovial hyperemia) precedes bone erosions and may not be present anymore when erosions become detectable. In fact, the evolution of PD activity was well correlated with clinical and biological improvement in a therapeutic trial of adalimumab.[26] PDUS has shown promising results in evaluating joint inflammation, with some possible histopathological correlation.[25] Somehow, PD activity has shown it’s 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.
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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. compared MRI and US, with computed tomography evaluation as a reference method, in erosion detection in 17 RA and 4 healthy control patients:[27] 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 to 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. performed such a prospective study of 49 cases of assessed RA;[28,29] 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 of X-rays for its early diagnostic value in early arthritis. Further longitudinal study of the ESPOIR cohort will enable us to assess the long-term prognostic value of US early erosions.

ACKNOWLEDGMENTS

An unrestricted grant from Merck Sharp and Dohme (MSD) was allocated for the first 5 years of the ESPOIR study. Two additional grants from INSERM were obtained to support part of the biological database. The French Society of Rheumatology, Abbot, Wyeth and Amgen also supported the ESPOIR cohort study. We also wish to thank Nathalie Rincheval for expert monitoring and data management, V. Devauchelle for expert x-ray image reading and all the investigators who recruited and followed the patients (F. BERENBAUM, Paris-Saint Antoine; MC. BOISSIER, Paris-Bobigny; A.CANTAGREL, Toulouse; B. COMBE, Montpellier; M.DOUGADOS, Paris-Cochin; P FARDELOONNE et P BOUMIER, Amiens; B. FAUTREL, P BOURJEOIS, Paris-La Pitié; RM. FLIPO, Lille; Ph. GOUPILLE, Tours; F. LIOTE, Paris- Lariboisière; X. LE LOET et O VITTECOQ, Rouen; X MARIETTE, Paris-Bicetre; O MEYER, Paris Bichat; A.SARAUX, Brest; Th SCHAEVERBEKE, Bordeaux; J. SIBILIA, Strasbourg).

REFERENCES
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## Baseline characteristics

<table>
<thead>
<tr>
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<th>Patients with US n = 126</th>
<th>Others ESPOIR patients n = 687</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>50.3 +/- 1.1*</td>
<td>47.9 ± 0.5</td>
</tr>
<tr>
<td>Female</td>
<td>78.6%</td>
<td>76.4%</td>
</tr>
<tr>
<td>Duration of symptoms (days)</td>
<td>102.6</td>
<td>103.2 ± 53</td>
</tr>
<tr>
<td>No. swollen joints / 28</td>
<td>7.74 +/- 5.6</td>
<td>7.1 ± 5.3</td>
</tr>
<tr>
<td>No. tender joints / 53</td>
<td>7.44 +/- 6.4</td>
<td>8.6 ± 7.1</td>
</tr>
<tr>
<td>DAS 28 score</td>
<td>5.04 +/- 1.3</td>
<td>5.2 ± 1.5</td>
</tr>
<tr>
<td>HAQ score</td>
<td>0.85 +/- 0.64*</td>
<td>1 ± 0.7</td>
</tr>
<tr>
<td>C-reactive Protein (mg/l)</td>
<td>22.7 +/- 44.1</td>
<td>22.2 ± 32</td>
</tr>
<tr>
<td>ESR (mm 1st hour)</td>
<td>31 +/- 24.2</td>
<td>29.1 ± 24</td>
</tr>
<tr>
<td>IgM RF positivity</td>
<td>42.9%</td>
<td>48.2%</td>
</tr>
<tr>
<td>Anti-CCP antibodies positivity</td>
<td>35.7%</td>
<td>39.5%</td>
</tr>
<tr>
<td>Typical RA radiographic signs</td>
<td>26.3%</td>
<td>22.2%</td>
</tr>
<tr>
<td>ACR criteria fulfilment</td>
<td>79.4%</td>
<td>83.4%</td>
</tr>
</tbody>
</table>

**Table 1**: Patients characteristics at baseline (mean ± sd or %)

DAS 28= disease activity score on the 28 joints; HAQ = Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide; RA = rheumatoid arthritis.

* p = 0.02
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<table>
<thead>
<tr>
<th>Patients (n = 114)</th>
<th>X-ray non erosive disease</th>
<th>X-ray erosive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>US non erosive disease (n = 72)</td>
<td>62 (54,4%)</td>
<td>10 (8,8%)</td>
</tr>
<tr>
<td>US erosive disease (n = 42)</td>
<td>22 (19,3%)</td>
<td>20 (17,5%)</td>
</tr>
</tbody>
</table>

Exact McNemar significance  \( p = 0.05 \)
Ratio = 1.4 [1.02; 1.9]

**Table 2 : Detection of erosive disease by ultrasonography (US) and radiography**

Ultrasonography (US) detects 1.4-fold more patients with erosive disease than X-rays.
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<table>
<thead>
<tr>
<th>Joints (n = 682)</th>
<th>X-ray non erosive joints</th>
<th>X-ray erosive joints</th>
</tr>
</thead>
</table>
| US non erosive joints  
(n = 607) | 604 (88,6%) | 3 (0,4%) |
| US erosive joints  
(n = 75) | 67 (9,8%) | 8 (1,1%) |

Exact McNemar significance  $p \leq 0.001$

ratio = 6.8 [3.8; 12]

**Table 3 : Detection of bone erosion on targeted joints by ultrasonography (US) and radiography**

Ultrasonography detects 6.8-fold more joints with erosion than X-rays
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<table>
<thead>
<tr>
<th>B mode synovitis (n = 346)</th>
<th>Clinically not swollen joints</th>
<th>Clinically swollen joints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No PD activity</strong>&lt;br&gt;(n = 147)</td>
<td>89 (61%)</td>
<td>58 (39%)</td>
</tr>
<tr>
<td><strong>PD activity</strong>&lt;br&gt;(n = 199)</td>
<td>95 (48%)</td>
<td>104 (52%)</td>
</tr>
</tbody>
</table>

Table 4: Pulse Doppler (PD) activity and clinical assessment of swollen joints

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

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Figure 1 Flow chart

Espoir Cohort
n = 813

Ultrasonography
n = 126

Missing X-rays
n = 14

6 joints x 114 patients for erosion analysis

10 joints x 126 patients for synovitis analysis

Erosion analysis: 682 joints with full data

Synovitis analysis: 1008 joints with full data

Il faut revoir le 3ème cadre : mettre les patients avec Radio à Brest =114
Mettre une flèche horizontale entre le 2ᵉ et le 3ᵉ cadre pour indiquer les 12 radios manquantes
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Figure 2 Site of erosions

- MTP 5 (48%)
- MCP 5 (22%)
- MCP 2 (32%)

Legend:
- Grade 1: ≤ 1 mm
- Grade 2: 1 < x ≤ 2 mm
- Grade 3: 2 < x ≤ 4 mm
- Grade 4: > 4 mm
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Key messages

- US on 6 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 early arthritis.