EXTENDED REPORT

Prospective 7 year follow up imaging study comparing radiography, ultrasonography, and magnetic resonance imaging in rheumatoid arthritis finger joints

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Objective: To perform a prospective long term follow up study comparing conventional radiography (CR), ultrasonography (US), and magnetic resonance imaging (MRI) in the detection of bone erosions and synovitis in rheumatoid arthritis (RA) finger joints.

Methods: The metacarpophalangeal and proximal interphalangeal joints II–V (128 joints) of the clinically dominant hand of 16 patients with RA were included. Follow up joint by joint comparisons for erosions and synovitis were made.

Results: At baseline, CR detected erosions in 5/128 (4%) of all joints, US in 12/128 (9%), and MRI in 34/128 (27%). Seven years later, an increase of joints with erosions was found with CR (26%), US (49%) ($p < 0.001$ each), and MRI (32%, NS). In contrast, joint swelling and tenderness assessed by clinical examination were decreased at follow up ($p = 0.2$, $p < 0.001$). A significant reduction in synovitis with US and MRI ($p < 0.001$ each) was seen. In CR, 12 patients did not have any erosions at baseline, while in 10/12 patients erosions were detected in 25/96 (26%) joints after 7 years. US initially detected erosions in 9 joints, of which two of these joints with erosions were seen by CR at follow up. MRI initially found 34 erosions, of which 14 (41%) were then detected by CR.

Conclusion: After 7 years, an increase of bone erosions was detected by all imaging modalities. In contrast, clinical improvement and regression of synovitis were seen only with US and MRI. More than one third of erosions previously detected by MRI were seen by CR 7 years later.

Accurate assessment of disease activity and joint damage in rheumatoid arthritis (RA) is important for monitoring treatment efficiency and for predicting outcome of the disease. This requires sensitive imaging methods for detection and monitoring of the disease process.

Of all imaging modalities, conventional radiography (CR) has the best established role in identifying progressive joint damage in RA. However, it has long been recognised that CR is insensitive in detecting soft tissue lesions—for example, synovitis, and usually does not detect early erosive lesions.^{1–3} Magnetic resonance imaging (MRI) has shown strength in detecting early inflammatory changes.^{4–6} However, MRI is expensive and the need for contrast agents to detect active synovitis has meant that MRI has become not a general imaging modality but a problem solving tool in the diagnostic management of RA.⁷ Recent technological advances have made musculoskeletal ultrasonography (US) a promising tool for the assessment of patients with rheumatic diseases, with strengths in visualising soft tissue inflammatory processes^{8–11} and early bone erosions^{1–3, 12} in different joints; however, validation studies to assess reader dependability are still needed.¹³

Validity measures for US in RA have recently been summarised. They concluded that further determination of its discriminant validity and reproducibility is still needed.¹³ In particular, further longitudinal data on musculoskeletal US are needed.¹³ Up to now, the course of US bone erosions have been followed systematically only by Backhaus *et al.*² In 49 patients with various arthritides, MRI, US, and CR

findings for the clinically dominant hand were analysed at baseline and after 2 years. MRI and US signs of synovitis decreased, whereas the number of bone erosions detected by MRI and US increased. More patients showed erosive progression with US than with CR, suggesting that US has a higher sensitivity to change. To contribute to validity studies for the evaluation of longitudinal imaging data in musculoskeletal US we decided to re-examine patients with RA who were available after 7 years with all imaging techniques previously used.

We present the first long term data comparing clinical examination (CE), CR, US, and MRI in the detection of bone erosions and synovitis in finger joints of a small cohort of patients, including 16 patients with RA. An additional aim was to monitor erosions by different imaging modalities during treatment with disease modifying antirheumatic drugs (DMARDs) and to determine whether radiographically occult finger joint erosions—previously detected by US and MRI—would be seen by CR 7 years later.

PATIENTS AND METHODS

Sixteen patients with RA (11 women, 5 men, mean age 58.6 years, range 27–75) according to the American College of Rheumatology criteria¹⁴ were included in the study. All

Abbreviations: CE, clinical examination; CR, conventional radiography; CRP, C reactive protein; DMARDs, disease modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; MCP, metacarpophalangeal; MRI, magnetic resonance imaging; OMERACT, Outcome Measures in Rheumatology (working group); PIP, proximal interphalangeal; RA, rheumatoid arthritis; US, ultrasonography

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patients were recruited from the Rheumatological Outpatient Clinic, Department of Rheumatology and Clinical Immunology, Charité University Hospital Berlin. Their mean disease duration was 14.7 years. All patients had been or were being treated with DMARDs (methotrexate: all patients, additionally sulfasalazine one patient, leflunomide one patient). Serum measures of inflammation (erythrocyte sedimentation rate (ESR), and C reactive protein (CRP)) were assessed in all patients.

All patients underwent follow up assessment in the same way as 7 years ago (in 1996), as described by Backhaus *et al.*¹ CE, US, CR, and MRI were performed of the clinically dominant hand (right hand = 10, left hand = 6) and included in the analysis. Proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints II–V were selected for evaluation (eight joints; total 128 joints). Follow up comparisons for the presence of erosions and synovitis were performed joint by joint. All evaluations were performed blinded to baseline results and to the other imaging result. Owing to the technical progress over 7 years, it was not possible to perform the examinations with the same imaging devices. Both CE and imaging studies were performed on the same day at follow up.

For CE, special care was taken in the clinical examination of the PIP and MCP joints. A binary scoring system was used to assess each joint as normal (0) or abnormal (1) for joint tenderness and soft tissue swelling. CE was performed by two experienced examiners (JD, AKS).

The study was approved by the local ethics committee. All patients gave their written informed consent before investigation.

Imaging methods

Conventional radiography

CR of the hands was obtained in two planes. The presence of erosions was recorded for each joint and graded as normal (0) or abnormal (1), as described by Backhaus *et al.*¹

Ultrasonography

US was performed at baseline (in 1996) and follow up (in 2003) with two different imaging devices owing to technical progress.

At baseline, a 7.5 MHz linear array transducer in combination with an acoustic standoff (silicone) was used for better focusing (Ultramark 4, ATL, Bothell, USA), as described in detail by Backhaus *et al.*¹ At follow up, a 10–5 MHz hockey-stick linear array transducer without acoustic standoff was used (ATL, HDI 3500, Bothell, USA).

PIP and MCP finger joints II–V were examined in longitudinal and transverse planes from dorsal and palmar views with the hand in a neutral position. Radial and ulnar views were not carried out at baseline. These views were used at follow up, but not taken into account for direct joint by joint comparisons. Erosions were defined as an interruption of the bone surface visible in two planes. In US, two criteria of inflammation were evaluated: joint effusion was visible as a black, anechoic area, and thickening of the synovial membrane (synovial proliferation) was visualised by US as hypo- or hyperechoic structures within the region affected by effusion. In the following, both phenomena are described as “synovitis”. All findings were also graded as normal (0) or abnormal (1).

US images were evaluated by one experienced examiner at baseline (MB), while at follow up two experienced examiners (AKS, MB) reached consensus for the erosion and synovitis evaluation. In a former study, both examiners reached high interreader agreement with a κ value of 0.88 and 0.93.¹⁵ The investigators were unaware of the clinical findings. Readers were blinded to baseline results.

Magnetic resonance imaging

MRI of the clinically dominant hand was performed at baseline (in 1996) and follow up (in 2003) with two different imaging devices:

The baseline examination was performed with a 0.2 Tesla imaging device (Magnetom Open, Siemens, Erlangen, Germany) with the patients in sitting position and using a small flex coil. Three dimensional (3D) T₁ weighted gradient echo sequences were obtained before and after intravenous injection of gadodiamide (Gd-DTPA (Omniscan; Nycomed, Oslo, Norway) at a dose of 0.3 mmol/kg of body weight. At follow up MRI was performed with a 0.2 Tesla Esaote unit (Esaote C-Scan, Genoa, Italy). The protocol called for a T₁ weighted 3D gradient echo sequence in coronal slice orientation before and after administration of gadolinium diethylenetriamine pentaacetic acid (Magnevist; Schering AG, Berlin, Germany) at a dose of 0.2 mmol/kg body weight. Reconstructions in transverse section orientation were made.

An erosive joint lesion was defined as a joint related cortical defect with or without a decrease in the signal intensity of the adjacent subchondral bone marrow on precontrast T₁ weighted images. To determine synovitis, MR images were evaluated using the definition as recommended by the OMERACT MRI in RA working group.^{6, 16}

For further evaluation, the number of erosions and the presence of synovitis were determined for each joint and

Figure 1 (A) Detection of soft tissue lesions (synovitis/effusion) by CE, US, and MRI in 128 finger joints. (B) Detection of development in bone erosions by US, CR, and MRI in 128 finger joints.

Figure 2 (A) MRI and US show marked synovitis at MCP and PIP joints V at baseline (arrows). At follow up after 7 years no synovitis is present at MCP and PIP joints V with MRI, whereas minimal synovitis can be seen at PIP joint V with US. (B) Images of the same MCP II joint at baseline and follow up visit with three different imaging techniques. In radiography, there is no erosion at baseline, while there is an irregularity at the 7 year follow up (arrows). In US and MRI there are no erosions detectable at baseline, while there are clear erosions at the follow up visit.

Figure 3 Distribution of the detection of erosions (in %) by the different imaging modalities at follow up examination in (A) PIP joints, (B) MCP joints.

graded as either normal (0) or abnormal (1), as described in our previous study.²

Two experienced investigators analysed CR (K-GAH, MBo) and MRI (K-GAH, MBo) and reached consensus for erosion and synovitis. The investigators were unaware of the clinical findings and results of the respective other imaging modalities. Readers were blinded to baseline results. There were at least 3 months between the readings for CR and MRI.

Statistical analysis

The data were analysed by non-parametric methods. The McNemar test was used to analyse differences between the imaging modalities. All analyses were calculated with the standard software package Statistica (Tulsa, Oklahoma (USA)).

RESULTS

Clinical examination

A reduction in swollen joints was seen by CE (from 37 to 28 joints), however it was not significant ($p = 0.2$) (fig 1A). CE tenderness showed a significant decrease from 51 (40%) tender joints at baseline to 23 (18%) at follow up ($p < 0.001$) (fig 1B).

Comparing baseline and follow up visit, we saw a reduction of serum measures of inflammation: mean (SD) ESR decreased from 27.7 (15.7) mm/1st h (baseline) to 23.8 (15.4) mm/1st h (follow up), CRP decreased from 26.8 (26.8) mg/l to 0.65 (0.66) mg/l ($p < 0.001$), indicating a more active disease at the baseline visit.

Imaging techniques

Synovitis

We saw a significant reduction in synovitis with US with a decrease in synovitis from 106 joints (83%, baseline) to 66 joints (52%, follow up examination; $p < 0.001$). In agreement with US, a significant reduction in synovitis evaluation could also be detected by MRI (baseline 80 joints = 63%, follow up 53 joints = 41%, $p < 0.001$).

Erosions

An increase in the detection of erosions was seen by all imaging techniques (CR, US, and MRI). At baseline, 5/128 (4%) joints with erosions were detected by CR; 7 years later, a significant increase of joints with erosions was found with radiography (33 joints = 26%; $p < 0.001$). At baseline, 12 (9%) of all finger joints with erosions were detected by US with a significant increase to 62 affected joints (49%) at follow up examination ($p < 0.001$) (fig 1B). Thirty four (27%) finger joints had erosions at baseline when examined by MRI (fig 1B). An increase was also detected by MRI to 41 (32%) joints, which was, however, not significant compared with

baseline visit ($p = 0.2$). There were no significant differences of imaging data between the patients receiving methotrexate alone as compared with the patients who additionally received sulfasalazine or leflunomide.

Figures 2A and B show images of the course of synovitis and erosions with the different imaging techniques.

In a next step, we evaluated whether radiographically occult finger joint erosions, previously detected by US and MRI, would be seen by CR 7 years later: At baseline, erosions were not visible in 12/16 patients by CR. After 7 years, in 10/12 (83%) patients erosions were detected by CR in 25/96 (26%) joints. US initially detected erosions in 9/96 (9%) joints, of which two (22%) erosions were seen in CR at follow up. MRI found 34 erosions at baseline, of which 14 (41%) erosions were then detected in CR at follow up.

Distribution in the PIP and MCP joints

US was sensitive for the detection of very small fluid accumulations and proved better than MRI, especially in the PIP joints. Figures 3A and B show the distribution of erosions for the PIP and MCP joints II–V visualised by the three different imaging techniques. Interestingly, US detected far more erosions in PIP joints than MRI and even CR. For MCP joints, most erosions were detected by MRI, while US and CR detected fewer erosions. The distribution of finger joints affected shows that MCP IV was less often affected than MCP II, III, and V.

DISCUSSION

MRI is an established imaging technique for the detection of early inflammatory changes in RA joints.¹⁷ Musculoskeletal US is a rapidly emerging technique, especially for the detection of soft tissue lesions in inflammatory rheumatoid diseases.^{13–18} Several studies have proved the ability of US and MRI in the sensitive detection of synovitis and early erosive lesions,^{12–19–21} which is of major importance in the early treatment of RA. However, with the exception of a 2 year follow up study involving mainly RA and psoriatic arthritis finger joints² there are no longitudinal long term data for US, while MRI has been proved to be sensitive for the follow up analysis of bone damage.^{22–23} No data on the importance of US findings for later radiographic or functional status are available (that is, the prognostic value of US in RA is unknown).¹³ Some indirect support for a predictive value of US is provided by the high agreement with MRI findings.^{1–2–11–24}

In this study we collected the first long term data comparing CR, US, and MRI for the detection of bone erosions and synovitis in RA finger joints. During long term DMARD treatment we saw a significant reduction of synovitis with both US and MRI, but the reduction was

more evident with US. In CE a reduction of finger joint swelling was also assessed, although CE seemed clearly to underestimate the presence of synovitis in RA joints, which was also shown in previous studies.^{1 24 25} US was sensitive for the detection of very small fluid accumulations and proved better than MRI, especially in the PIP joints, which might explain the slightly higher percentage of joints affected by synovitis which were detected by US.

Follow up analysis of finger joint synovitis is an important task in controlling the effectiveness of treatment. However, for long term outcome, a precise analysis of erosions is essential. Although we saw a decrease in synovitis during long term DMARD treatment, we found an increase of finger joints with erosions with all imaging techniques. The difference between baseline and 7 year follow up was highly significant as detected by CR and US, but there was no significant difference with MRI between both time points.

A possible reason for the small number of erosions detected by US at baseline is the distinct difference in the quality of the US devices (fig 2). With a significantly lower resolution and the need to use an acoustic standoff pad it is likely that US missed a number of erosions at baseline. Also, it should be mentioned that neither ulnar nor radial aspects of the joints were evaluated by US, raising the possibility that some erosions might have been missed. A high number of erosions were already detected at baseline visit by MRI¹ and owing to our binary evaluation system no statistically significant further progression of MRI erosions was shown because of a ceiling effect (truncation of data because a score of 1 could not progress further as it is already the highest possible score),²⁶ which may help to explain our current results. Although it could be shown that low field MRI (0.2 Tesla) has similar sensitivities for bone erosions to those obtained with 1.5 Tesla MRI devices,²⁷ a better detection of bone erosions might have been achieved by using higher field MRI (>0.2 Tesla) devices.

The selection of patients with established disease (mean disease duration 14.7 years) might have had an impact on the study outcome. Our data are in agreement with the 2 year follow up study,² which recorded an increase of erosions with clinical improvement and regression of synovitis, but now more pronounced with MRI than with US. An increase in erosions in the wrist as detected by MRI despite clinical improvement was also described by McQueen *et al.*²³

Another aim of our study was to determine whether radiographically occult finger joint erosions, previously detected by US and MRI, would be detected by CR 7 years later. Nearly every second erosion previously detected by MRI presented on CR 7 years later, showing that erosions could actually be predicted by MRI. The reason why not all formerly detected erosions were seen later in the disease course by CR might be explained by healing processes, reader error, and technical limitations of x ray procedures.²⁸ US initially detected erosions in nine joints, of which two erosions were seen in radiography at follow up. Again, we explain this rather low percentage of erosions at baseline by the low quality of the US images 7 years ago. However, another explanation lies in the fundamental difference in the way in which CR and MRI generate image contrast. This is outlined by Peterfy,²⁹ but basically, the lucency associated with erosions on radiographs is due to the loss of cortical bone, not trabecular bone. CR is quite insensitive to trabecular bone loss. Consequently, the often larger intramedullary component of an erosion is typically not visible on radiographs. MRI, however, provides excellent delineation of abnormalities in the marrow space, and therefore can detect even large intramedullary erosions that are radiographically occult. Many of these erosions may not become detectable on radiographs even after many years.

For MCP joints, more erosions were detected by MRI than by US and CR. The distribution of finger joint erosions shows that MCP IV is less often affected than MCP II, III, and V, as also described by Wakefield *et al.*³ Interestingly, we saw a more frequent and distinct affection of PIP compared with MCP joints by US than by CR and MRI, which is in agreement with recently presented data.^{30 31} This underlines the importance of potentially including PIP joints in common scoring systems both for US and MRI—for example, the RA-MRI scoring system developed by the OMERACT MRI in an RA working group.³²

US has some advantages over MRI, because it is easier to perform examinations of all finger joints with US, although documentation is time consuming. In MRI examinations, especially in the dedicated systems which we used in this study, the region to be examined has to be defined before the examination is performed (for example, focus on PIP and MCP joints or wrist and MCP joints) owing to field of view and coil limitations. However, when limited to a field of view, it would probably be more useful to include the wrist and MCP joints rather than solely the PIP and MCP joints. On the other hand, with MRI, images can be obtained by a technician, whereas with US, several readers are needed to interpret and score both synovitis and erosions at a later time point.

For each method, two experienced readers reached consensus about synovitis and erosion findings, except for US which was evaluated by one experienced examiner at baseline. Although this might have had an influence on the interpretation of the pathological findings, we have recently shown that US performed by experienced examiners giving good interreader agreement results.^{15 33}

CONCLUSIONS

US and MRI are valuable imaging techniques for the visualisation and follow up analysis of synovitis and bone erosions in small finger joints of patients with RA. MRI seems to be better than US for the detection of early erosions because more erosions formerly detected by MRI were seen by CR at follow up. However, technical limitations of the US device at baseline have to be taken into account. MRI seems to be better for evaluation of erosions of MCP joints rather than PIP joints, while US was better than MRI for evaluation of PIP joints. Both techniques have their advantages and disadvantages. However, because US is an easy handling and low cost imaging technique, whereas MRI (as imaging “gold standard”) is rather expensive, we recommend US for quick evaluation of follow up analysis.

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