

# Monitoring Joint-Space Narrowing in Rheumatoid Arthritis with 1.5T Whole-body MRI and 0.2T Extremity MRI in a Multi-site Clinical Trial: IMPRESS

FRI0446  
EULAR 2010

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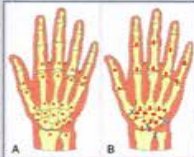
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## Background and Objectives

MRI is increasingly being used in clinical trials of rheumatoid arthritis (RA) because of its superiority over X-ray in detecting and monitoring change in bone erosion, osteitis and synovitis. However, in contrast to X-ray, the MRI scoring method most commonly used in clinical trials, RAMRIS<sup>1</sup>, does not currently include joint-space narrowing (JSN). This limitation has been an obstacle to substituting MRI for X-ray in clinical trials, as demonstration of erosion suppression has not always ensured suppression of JSN<sup>2</sup>. Cross-sectional studies have shown MRI to be sensitive for JSN in the hand and wrist, and to correlate well with X-ray<sup>3,4</sup>; although, longitudinal sensitivity to change has not yet been confirmed. In this study we monitor change in JSN with 0.2T extremity MRI (E-MRI) and conventional 1.5T whole-body MRI (C-MRI) in a multi-site clinical trial.

## Methods

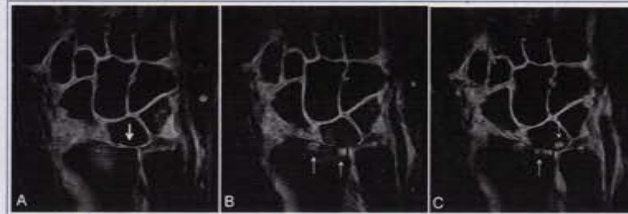
31 active RA patients from a clinical trial (IMPRESS) who were randomized equally into treatment with either rituximab + methotrexate or placebo + methotrexate had their dominant hand/wrist scanned at baseline, 12 weeks and 24 weeks using C-MRI at 3 clinical sites. 23 of these patients also had E-MRI of the same hand/wrist at each visit. For this exercise, only coronal T1-weighted 3D gradient-echo scans were reviewed. E-MRI scans had 0.346 cc voxels. C-MRI scans had 0.216 cc voxels and included spectral fat-suppression. All patients were scanned using a specially designed frame to ensure reproducible joint positioning between visits. One radiologist [CP] scored all C-MRI images blinded to visit order. The same radiologist similarly read all E-MRI images on a separate occasion blinded to the C-MRI results. Erosions were scored using the RAMRIS scale<sup>1</sup>. JSN was scored using a previously validated 9-point scale<sup>5</sup>: 0 = normal, 0.5 = equivocal, 1.0 = minimal (definitive disease), 1.5 = minimal with progression, 2.0 = moderate – severe, 2.5 = partial bone-on-bone, 3.0 = complete bone-on-bone, 3.5 = partial ankylosis, 4.0 = complete ankylosis. Data from the two treatment arms were pooled for this analysis.



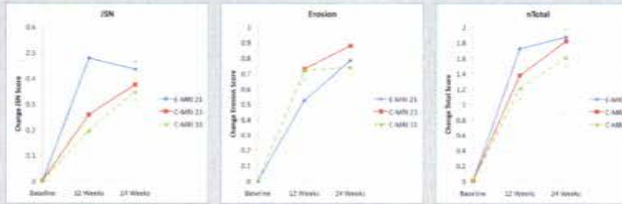
**Fig. 1.** Locations evaluated for erosion (A) and JSN (B). A. Erosions were scored in the 10 bones of metacarpophalangeal joints (MCP) 1-5 and all 15 bones of the wrist. B. JSN was scored in proximal interphalangeal joints (PIP) 1-5, MCP 1-5 and 15 joints in the wrist (all but carpometacarpal-1 [CMC-1], scapholunate, trapezoidiform and radioulnar joints). CMC-1 was excluded because of the high frequency of osteoarthritic JSN in this location. The scapholunate joint was excluded because rupture of the scapholunate ligament often widens this joint. The trapezoidiform joint was excluded because it is not well visualized in the coronal plane. The distal radioulnar joint was excluded because it is not load bearing and because of difficulty reproducibly aligning the joint on serial MRI examinations. The maximum score for erosion was 250. The maximum score for JSN was 100.

## Results

Of 2325 joints in the C-MRI group and 1725 joints in the E-MRI group, 4% and 2%, respectively, were outside the field of view and could not be assessed. The majority of these were PIP joints. Scores agreed well between C-MRI and E-MRI (ICC: 0.87-0.94 cross-sectionally and 0.74-0.88 for change). As shown in Fig 3, mean JSN score increased at 12 and 24 weeks. Statistical significance was reached in both groups at 24 weeks. However, when only the 23 patients who had both E-MRI and C-MRI were analyzed, only E-MRI reached statistical significance.



**Fig. 2.** JSN progression of radioulnar joint. C-MRI of the wrist shows thin but present cartilage over articular surfaces of radioulnar joint (large arrow) at baseline (A) associated with Grade-1 JSN. Follow-up C-MRI at 12 weeks (B) and 24 weeks (C) show progressive loss of cartilage over both articular surfaces of this joint accompanied by grade-3 JSN. Note development and progression of bone erosions (small arrows) in the radius and ulna on these follow-up scans.



**Fig. 3.** Change in JSN, Erosion and normalized-Total (nTotal) scores. nTotal = Erosion score + normalized JSN (nJSN) score. nJSN score = JSN score × 250/100, to give JSN equivalent weight to erosion. \* p < 0.05

## Discussion

Cross-sectional studies<sup>3,4</sup> have shown both C-MRI and E-MRI to be sensitive to JSN in RA, but to our knowledge this is the first study to demonstrate the ability of either type of MRI to monitor longitudinal change in JSN in a time-blinded multi-site clinical trial. Both E-MRI and C-MRI demonstrated significant progression of JSN in 24 weeks with only 23 and 31 patients, respectively. E-MRI's slightly better performance in this regard may have been because E-MRI covered more PIP joints than C-MRI did and/or because of differences in contrast-to-noise ratio or spatial resolution between the two techniques. Regardless, both techniques performed impressively. Moreover, adding JSN allowed determination of a total MRI damage score (Fig. 3), analogous to that used in X-ray Sharp scoring. Unfortunately, radiographs were scheduled only at baseline and 12 months, so direct longitudinal comparison of the two modalities was not possible at this point in the trial. However, earlier analysis showed strong cross-sectional agreement between MRI and X-ray at baseline<sup>5</sup>.

That MRI is good at monitoring JSN is not surprising. Firstly, MRI's tomographic viewing perspective obviates the projection of the rims of the concave articular components of joints over the joint space, as occurs with X-ray. However, MRI's greatest advantage is its ability to visualize articular cartilage directly rather than only estimate its thickness through joint-space width, as with X-ray. Ligamentous laxity/rupture and interpositioning of synovium or effusion between articular surfaces undermines JSN as a measure of cartilage loss, and reduces its sensitivity to change. Thus, further optimizing E-MRI and C-MRI protocols for cartilage delineation, and adapting the JSN score described in this report to one for scoring cartilage loss directly may further improve the utility of MRI for monitoring joint destruction in RA.

These findings suggest that MRI may offer a viable alternative to X-ray in multi-site clinical trials of RA. With the recent shift to active-comparator study designs, which require longer study durations and more patients to demonstrate therapeutic superiority, and the increasing difficulty in recruiting RA patients into trials, there is greater need for more sensitive methods, such as MRI, to offset the escalating costs, patient exposure and logistical challenges associated with these trends.

## References / Acknowledgements

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- Funding and study drug were provided by F. Hoffmann-La Roche Ltd., Genentech Inc., and Biogen IDEC Pharmaceuticals.