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Can We Stop Using Contrast in RA MRI Clinical Trials? Quantitative MRI Demonstrates Similar Responsiveness for Contrast and Contrast-Free Synovitis Assessment.

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Background: Use of contrast agent (gadolinium, Gd) in MRI trials of rheumatoid arthritis (RA) increases risk of side effects, cost, and discourages recruitment. A reliable method to accurately quantify synovitis without Gd is highly desirable.

Objectives: The objectives of the study were to compare quantification and change in different synovitis measures using Gd enhancement and voxel classification in fat-saturated T2 images without Gd, using active appearance models (AAMs) for quantitative 3D assessment.

Methods: MR images of the hand were acquired from 45 established, active (mean (SD) DAS28 5.4 (1.1)), seropositive RA patients who received a cycle of rituximab therapy in an open label study. Participants were imaged at 0, 3, 6, 9 and 12 months; 34 had all 0/3/6 images. Pre- and post-Gd VIBE images and pre-Gd T2 TSE images with fat saturation were acquired. VIBE images were searched using AAMs to identify bones and capsular structures and generate 3D ROIs. Volume which enhanced with Gd (Gd synovitis) was calculated using the pre- and post-contrast VIBE images. T2 images were registered with the VIBE images and T2 synovitis volume was identified using a voxel classifier trained using T2 voxels registered to voxels which enhance with Gd. RAMRIS scoring was performed by a single experienced reader blinded to time point. Agreement between the methods was judged using Bland-Altman plots. The amount of change found by the 2 methods was judged using a paired t-test for the subset with all images, and a mixed model method for the complete dataset. All quantitative values were adjusted for differences in scale using total bone area at baseline. Voxels identified by the methods were visually compared.

Results: DAS28 improved by mean (SD) 1.7 (1.4) over 12 months. T2 synovitis volumes were systematically higher than Gd synovitis by 1547 mm3; (33%): most of this difference was in the wrist (+39%), with the MCP joints 19% higher. Bland-Altman plot showed that agreement between the measures was unaffected by the size of the measurement (not shown). Both methods showed very similar change in volume over time over 6 months in a subset of 34 participants (Figure 1). Reduction in T2 synovitis was significant at 3 months, with both methods significant at 6 months. Using a mixed model for all participants over 12 months, the mean monthly change (95% CI) for T2 synovitis was -2.3% (-3.4,1.2), $p<0.001$; Gd synovitis -2.7% (-4.8,-0.6), $p=0.013$. RAMRIS synovitis showed no significant change using either the subset data, or the mixed model on the full set. Visual assessment of all 170 3D images showed good agreement in all cases, with wrist T2 synovitis volume often larger compared to the Gd synovitis volume (Figure 2).

Conclusions: Synovitis assessed in T2 TSE images is a slightly different construct to that detected with contrast agents; the volume measured is likely to include synovial fluid. T2-detected synovitis identifies a higher volume of enhancing tissue than Gd synovitis, but an almost identical amount of volume change using sensitive quantitative analysis. MR imaging trials without the use of contrast agent seem a practical alternative to those using contrast.

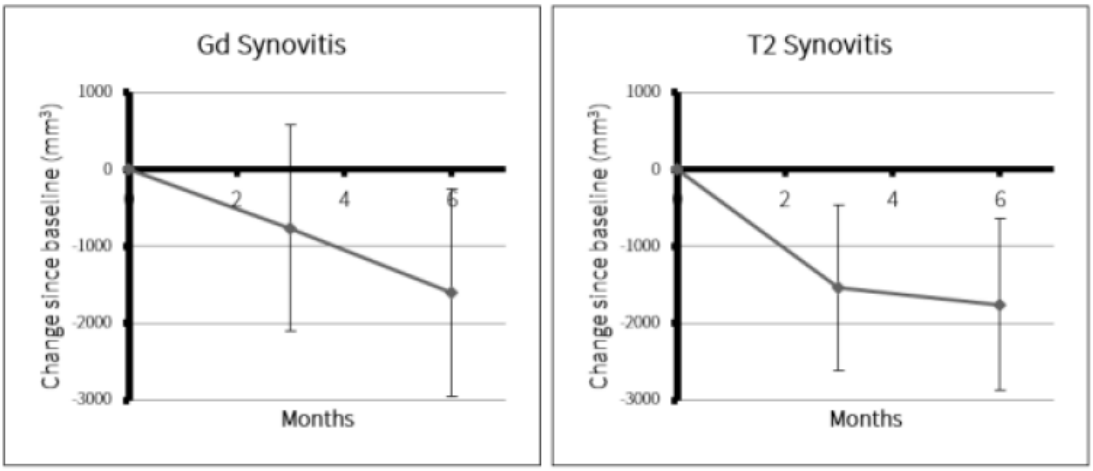

Figure 1 - Change from baseline in subset with all timepoints at 0, 3 and 6 months. 34 patients had all of 0, 3 and 6 month timepoints. Graphs show change in synovitis volume (microliters or mm3) for the 2 measures, showing 95% confidence limits for change from baseline using a paired t-test.

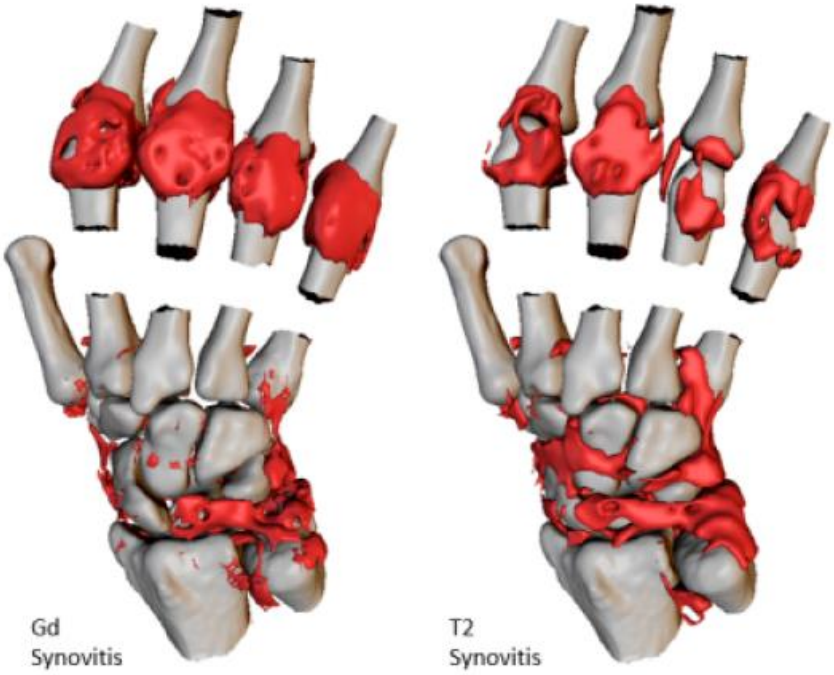

Figure 2 – Typical patient result showing Gd synovitis (left) and T2 synovitis. Overall pattern of synovitis identified is very similar in all patients; synovial voxels are shown in red. T2 synovitis systematically report a higher volume (19% of the Gd synovitis value in the MCP joints on average, 39% of the Gd synovitis value in the wrist on average). This image shows this typical bias with more synovial voxels in the wrist.