A comparative study of the relative sensitivities of various MRI parameters in measuring response to treatment with infliximab and methotrexate in patients with rheumatoid arthritis

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Introduction: Synovitis is primary abnormality in rheumatoid Arthritis (RA). The recent development of new targeted therapies in RA and ethical constraints preventing the comparison of a new trial drug with a placebo has fuelled the need for imaging techniques that are sensitive, not only for diagnostic and prognostic purposes, but also for monitoring treatment response. Detecting a difference in response between a drug and placebo may not be difficult, but detecting differences between active treatments requires relatively higher sensitivity. A number of parameters that can be derived from dynamic contrast-enhanced magnetic resonance imaging (DEMRI) are sensitive measures of inflammation and hence synovitis in RA. This pilot study aims to investigate the comparative sensitivities of different MR based measures in detecting treatment response to two different therapies. The first group of patients were treated with infliximab and methotrexate (hereafter referred to as the 'infliximab group'), whilst the other group were on methotrexate alone (the 'methotrexate group').

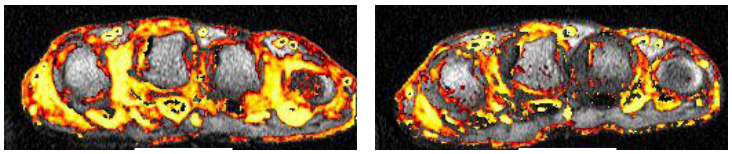
Methods: Twenty patients with active RA as defined by the American College of Rheumatology (ACR) criteria (1) and clinically diagnosed metacarpophalangeal (MCP) joint disease were randomised to receive the trial drug infliximab, with methotrexate, or methotrexate alone in a prospective, double blind, parallel design, and actively controlled clinical trial. The patients all had symptom duration of less than 12 months, with a mean duration of 6 months, and had had no prior treatment with any disease-modifying anti-rheumatoid drugs (DMARDs) or oral corticosteroids. Infliximab was given at the standard dose of 3mg/kg body weight at baseline, two weeks, and six weeks then eight weekly thereafter. DEMRI measurements were obtained from the MCP joints of the dominant hand at baseline and at 14 weeks into treatment using a Philips 1.5T Gyroscan ACS-NT MRI scanner (Philips Medical Systems, Best, The Netherlands). The DEMRI sequence acquired 20 spoiled T1-weighted gradient-echo images from each of the six axial slices before during and after the injection of a bolus of the contrast agent Gd-DTPA (2). Analyze software (Mayo Clinics, New York) and processing software developed in-house and described previously (3) were used to calculate values of ME and IRE on a pixel-by-pixel basis and the respective values were displayed as colour overlays superimposed on conventional greyscale images of anatomy (Fig 1(a) and (b)). Regions of interest (ROIs) were manually traced around the enhancing synovium for joints 2 to 5 in each slice for all six slices of the DEMRI data set - the first MCP joint was not considered as it is too far out of the plane relative to the other joints (2). The sum of the IRE and ME values together with the volume of enhancing tissue within the ROIs was calculated together with the sum of grey scale values obtained by subtracting the pre-contrast- from the post-contrast-images.

Results: Fifteen of the 20 patients had usable scans at baseline and at 14 weeks, 7 being in the infliximab plus methotrexate group and 8 in the methotrexate only group and 60 joints were therefore examined. A Student's t-test showed that there were no statistically significant differences in synovitis prior to treatment in patients assigned to each treatment arm. Paired t-tests for each treatment group showed significant improvement from baseline to 14 weeks for the infliximab group whilst patients treated with methotrexate alone actually showed a very slight worsening, which was not statistically significant. The infliximab group was used to compare the sensitivity of the 4 different MR parameters and the results show that IRE gave the largest percentage change with treatment (table 1).

Table1: % Change in the mean of the sum of values for each of the five parameters at baseline and at 14 weeks. p-values for the with-in group changes in synovial inflammation are indicated in parentheses.

	% Change	
Parameters	**Infliximab**	**Methotrexate**
IRE	-55.90 *(0.0031)*	+18.27 *(0.721)*
ME	-42.80 *(0.0293)*	+6.90 *(0.776)*
Subtracted sum	-31.04 *(0.0757)*	-
Enhancing Volume	-16.19 *(0.0369)*	+0.95 *(0.937)*

Figure 1(a) and (b): (a) *Pre* and (b) *Post*- week 14 infliximab treatment conventional grey scale axial MR image of the MCP with superimposed parametric colour maps of initial rate of enhancement (IRE)



1(a) **1(b)**

Conclusion: The MR results in this study show that at 14 weeks treatment there is a much greater reduction in synovial inflammation in patients treated with infliximab and methotrexate, relative to patients treated with methotrexate alone. This observation is consistent with other conventional (non-MR based) clinical patient assessments and suggests that the measured MR parameters are a valid method for assessing response. This study was designed to establish the comparative sensitivities of the various MRI parameters used for measuring synovitis and response. Examining two treatment groups instead of one ensured that any apparent differences in the change in synovial inflammation over the trial period are due to treatment and not the result of the natural progression of the disease. The results of the study indicate that IRE shows the largest change with treatment and that this is statistically significant.

References:

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