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BRIEF REPORT

Rapid improvement in rheumatoid arthritis patients on combination of methotrexate and infliximab: clinical and magnetic resonance imaging evaluation

Lai-Shan Tam · James F. Griffith · Alfred B. Yu · Tena K. Li · Edmund K. Li

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Abstract The objectives of this study was to assess, using clinical and magnetic resonance imaging (MRI) criteria, the efficacy of combination infliximab therapy in patients with active rheumatoid arthritis (RA) refractory to methotrexate (MTX) treatment and to ascertain whether the changes in MRI parameters correlate with the clinical response. Four infusions of infliximab (3 mg/kg) at weeks 0, 2, 6, and 14 were added to a stable background dose of MTX in 19 patients with active disease. Clinical parameters were assessed before each infusion and at week 14. Dynamic contrast-enhanced MRI examination of the most severely affected wrist was performed at baseline and week 14. Synovitis severity, volume of synovitis, and synovial perfusion indices were evaluated. Significant improvement in all clinical disease activity parameters was seen at week 14 with reduction in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and DAS28. Sixty-eight percent of patients achieved ACR20. MRI disease activity parameters also significantly decreased after treatment with reduction in grading of synovitis, volume of active synovitis, and perfusion enhancement slope. Significant positive correlations were seen between the baseline volume of synovitis and the pain score (r=0.65), patient global score (r=0.68), and health assessment questionnaire (HAQ) score (r=0.46). In conclusion, addition of infliximab to methotrexate rapidly reduces inflammation in long-standing patients with RA. Assessment of enhancing synovial volume and perfusion indices on serial MRI examination was helpful in documenting the effect of treatment over this short period.

Keywords Infliximab · MRI · Perfusion enhancement slope · Rheumatoid arthritis · Volume of active synovitis

L.-S. Tam (✉) · T. K. Li · E. K. Li
Department of Medicine and Therapeutics,
The Chinese University of Hong Kong,
Shatin, Hongkong, People's Republic of China
e-mail: tamls_813@yahoo.com

J. F. Griffith · A. B. Yu
Department of Diagnostic Radiology and Organ Imaging,
The Chinese University of Hong Kong,
Shatin, Hongkong, People's Republic of China

Introduction

The efficacy of infliximab has been well demonstrated in patients with rheumatoid arthritis (RA) [1]. Magnetic resonance imaging (MRI) is more sensitive for the detection of both inflammatory (synovitis) and destructive (erosive) joint changes than clinical examination and radiography [2]. In patients with early disease treated with methotrexate (MTX)–infliximab combination, MRI revealed significant improvement in synovitis and erosions at 1 year [3]. In patients with refractory RA, significant reduction in the volume of the enhancing inflammatory tissue had been demonstrated 1 year after treatment with infliximab and MTX [4] or adalimumab [5] but not with anakinra using the OMERACT evaluation [6]. Synovitis is the primary pathology of RA, which is most likely to show change over a short period of time if patients are given a potent therapy. The aim of the present study was to ascertain whether the assessment of enhancing synovial volume and perfusion indices on serial MRI examination is a useful indicator of responsiveness to treatment in refractory RA using infliximab and MTX.

Table 1 Clinical and MRI disease activity parameters before and after methotrexate and infliximab combination therapy

Variable	Baseline	Week 14
Clinical parameters		
Swollen joint count (0–28)	7.9 (5–10)	3.8 (1–6), p=0.000
Tender joint count (0–28)	9.5 (3–15)	5.2 (1–7), p=0.002
Patient global assessment of pain (VAS 0–100)	61.7 (50–75)	33.7 (11–53), p=0.000
Patient global assessment of disease activity (VAS 0–100)	59 (50–73)	31.6 (14–41), p=0.002
Health Assessment Questionnaire (HAQ)(1–3)	1.49 (1.25–1.75)	1.25 (1.0–1.5), p=0.000
DAS28	5.3 (4.57–6.31)	4.13 (3.1–4.9), p=0.001
C-reactive protein (mg/l)	21.6 (5.1–32.6)	8.4 (0.1–11.2), p=0.007
Erythrocyte sedimentation rate (mm/1st h)	68.7 (38–100)	41.1 (21.5–51), p=0.007
MRI parameters		
Synovitis grade (RAMRIS) (0–9)	5.8±2.3	4.7±2.0, p=0.002
Volume of active synovitis (ml^3)	20.3±7.1	14.9±7.6, p=0.003
Maximum enhancement (%)	190±39%	169±44%, p=0.07
Enhancement slope (%/s)	3.7±2.0	2.5±1.4, p=0.002

Materials and methods

(a) Patients and clinical assessment

Nineteen consecutive female patients with active RA, who fulfilled the American College of Rheumatology 1987 criteria for RA, were enrolled in this open label, single arm, 14-week study involving concomitant treatment with MTX and infliximab with clinical and MRI assessment before and after treatment. Active RA was defined as the presence of four or more swollen and tender joints and at least two or more of the following: morning stiffness that lasted at least 45 min, erythrocyte sedimentation rate (ESR) Westegren of at least 28 mm/h, and a serum C-reactive protein concentration of at least 2.0 mg/dl.

All patients were female, mean age of 49±10 years, seropositive in 84%, disease duration, 11±7 years, methotrexate resistant on a median dose of 15 (12.5–15) mg/week initiated at least 3 months before baseline. Doses were kept stable during the trial, as were doses of oral prednisolone (one patient) and nonsteroidal anti-inflammatory drugs. No intramuscular or intra-articular steroid was given. All patients received MTX and four infusions of infliximab at 3 mg/kg body weight, at baseline (week 0), weeks 2, 6 and 14. All subjects provided signed informed consent and the protocol was approved by the Ethics Committee, Chinese University of Hong Kong. Standard clinical assessments were performed at baseline and at weeks 2, 6, and 14 (Table 1).

(b) MR imaging technique

MRI examination of the most severely affected wrist was performed at baseline and 14 weeks. MRI examinations were performed on a 1.5-T imaging unit (Siemens Sonata, Siemens Limited, Germany), utilizing a small (17 cm×37 cm) flex coil positioned on the dorsum of the wrist. Each wrist was examined separately with the arm by the side and the patient prone. Coverage extended from the distal forearm to the mid-phalanges. Signal sequences comprised of axial T1-weighted (TE: 21 ms, TR: 420 ms, 4-mm thickness, field-of-view: 120 mm, matrix: 160×512), T1-weighted fat-suppressed (TE: 21 ms, TR: 622 ms) pre-contrast and T1-weighted gradient-echo sequence (TR/TE: 2.7/0.95, flip angle: 15°, 4-mm thickness, number of slices: 11, field-of-view: 1,050 mm), and T1-weighted fat-suppressed (TE: 21 m, TR: 622 ms) post-contrast sequences. For dynamic imaging, a total of 20 dynamic images were obtained. A bolus of gadoteric acid (Dotarem; Guerbet, Aulnay, France) at a concentration of 0.15 mmol/kg body weight was injected at a rate of 2.5 ml/s (Spectris, Medrad, Indianola, PA, USA) through a 21-gauge intravenous catheter inserted into the contralateral hand. Dynamic MR imaging started at the same time the contrast medium injection started.

MR imaging analysis

At baseline and post-treatment, three MR imaging parameters of disease activity were assessed.

(a) Synovitis severity was graded in three regions (distal radioulnar joint, radiocarpal joint, and the intercarpal and metacarpophalangeal joints) (Figs. 1a and 2b). A score of 0 represented normal (no synovitis) while scores of 1–3 represented mild, moderate, and severe synovitis, respectively [7]. Readers were not blinded to

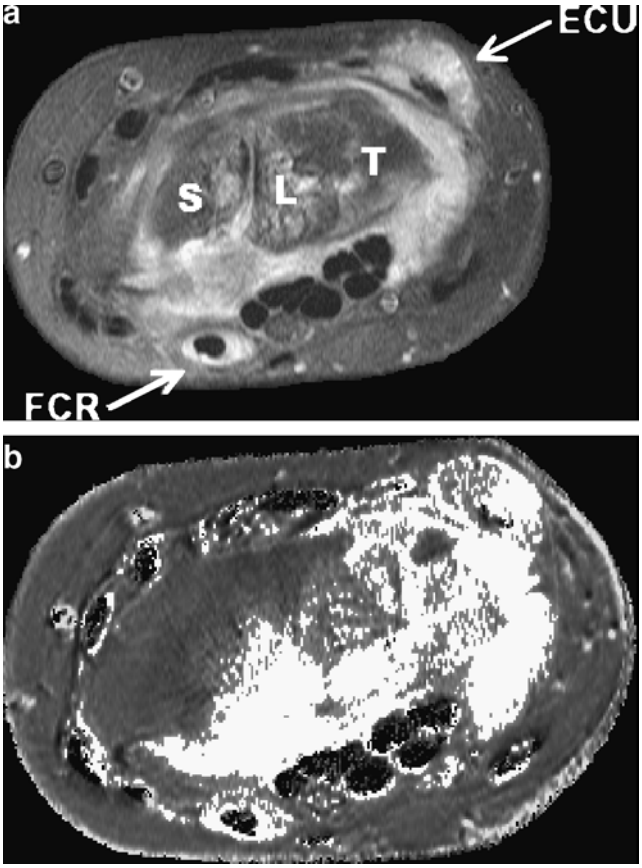

Fig. 1 **a** Pretreatment T1-weighted fat-suppressed axial image of the wrist at the level of the proximal carpal row after contrast. Synovial enhancement is present around the proximal carpal bones (*S* Scaphoid, *L* lunate, *T* triquetrum) and also around the extensor carpi ulnaris (ECU) and flexor carpi radialis (FCR) tendons. **b** Pretreatment enhancement map of image (**a**). Voxels with enhancement greater than thenar muscle enhancement (mean±2.5 SD) are *highlighted*. The pretreatment volume of enhancing synovium, measured on serial images though the wrist and hand, in this case was 18.7 ml

chronology of MR examinations. Images were read paired and in chronological order.

(b) Volume of synovitis [4, 8, 9] was measured though preparation of an enhancement map of each axial image by dividing the signal intensity for each voxel on the post-contrast T1-weighted images by the corresponding voxel on pre-contrast T1-weighted images. Pre- and post-contrast image registration was performed using statistical parametric mapping software (available at http://www.fil.ion.ucl.ac.uk/spm/). A threshold level (equivalent to mean thenar muscle enhancement plus 2.5 standard deviations) was applied using a separate software package (available at http://www.sph.sc.edu/comd/rorden/mricro.html). Skin, blood vessels, and superficial subcutaneous tissues were manually erased such that remaining tissue represented enhancing synovial tissue. Summation of pixel counts from contiguous axial images yielded the volume of enhancing synovium compatible with active synovitis (Figs. 1b and 2b).

(c) Synovial perfusion indices [4, 10, 11]. On T1-weighted images, a region of interest (ROI) within the largest single area of enhancing synovium was drawn manually. Time–intensity perfusion curves were developed and processed using a standard software package (available at http://www.sph.sc.edu/comd/rorden/mricro.html). Two perfusion indices of the time–intensity curve were measured, namely, maximum (ME) enhancement and enhancement slope (Fig. 2c). Maximum enhancement was defined as the maximum percentage increase in signal intensity from baseline (I_{base}). Enhancement slope (ES) was defined as the rate of enhancement between 10 and 80% of the maximum signal intensity difference between maximum signal intensity (I_{max}) and I_{base}. These perfusion indices were calculated thus:

$$ME = \frac{(Imax - I_{base})}{I_{base}} \cdot 100\%$$

and

$$ES = \frac{(Imax - I_{base}) \cdot 0.8}{I_{base} \cdot (t_{80\%} - t_{10\%})}$$

where $t_{10\%}$ and $t_{80\%}$ are the time intervals when the rise in signal intensity reaches 10 and 80% of the maximum signal intensity difference between I_{base} and I_{max}, respectively.

Data analysis

Variables were described as mean±1 SD. Student *t* test was used to test for differences in pre- and post-clinical and MRI parameters. Pearson correlation test was applied to assess relationship between paired data. Logistic regression was used to assess whether any clinical and MRI parameters at baseline is associated with clinical response [American College of Rheumatology (ACR) 20 response and the European League Against Rheumatism (EULAR) response] at week 14. General linear model was used to assess the association between the clinical response (ACR 20 response and EULAR response) and the changes in the various MRI parameters. SPSS for Windows v11.5 was used for all statistical analyses. A 5% significance level was applied for all tests ($p<0.05$).

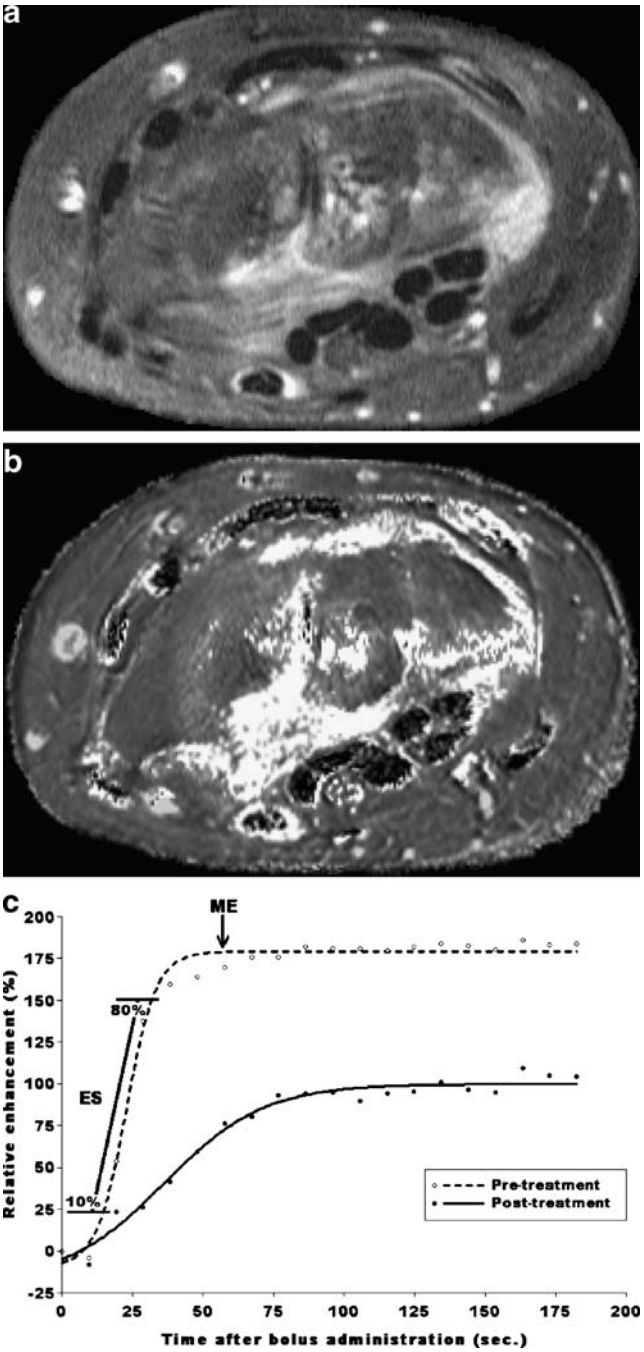

Fig. 2 **a** Post-treatment T1-weighted fat-suppressed axial image of the wrist at the same level as Fig. 1a. The degree of synovial enhancement present is appreciably less than before infliximab/methotrexate combination. **b** Post-treatment enhancement map of image (**a**). The number of voxels with synovial enhancement has appreciably decreased compared to the pretreatment enhancement map (Fig. 1b). The post-treatment volume of enhancing synovium in this case was 15.9 ml. **c** Time–intensity curves, derived from dynamic post-contrast images, for a single patient pre- and post-treatment. Maximum enhancement (ME) was defined as the maximum percentage increase in signal intensity from baseline. Enhancement slope (ES) was defined as the rate of enhancement between 10 and 80% of the maximum signal intensity difference between baseline and ME. Maximum enhancement and enhancement slope decreased after infliximab/methotrexate combination therapy

Results

Clinical findings

Clinical parameters pre- and post-treatment are shown in Table 1. At baseline, all patients had clinically active RA with mean 28 joint count Disease Activity Score (DAS-28), score 5.31±1.06. All clinical disease activity parameters were significantly reduced at week 14 except the duration of early morning stiffness (Table 1). By week 14, 68, 26, and 16% of patients have achieved ACR 20, 50, and 70, respectively. Sixty-eight percent of the patients also achieved the EULAR response.

MRI findings

MRI parameters pre- and post-treatment are shown in Table 1. Significant positive correlations were seen between the baseline volume of synovitis and the pain score (r=0.65), patient global score (r=0.68), and function as reflected by the health assessment questionnaire (HAQ) score (r=0.46). All MRI disease activity parameters were significantly reduced at week 14 except for maximum enhancement (Table 1). No clinical or MRI parameters were found to be predictive of patients likely to respond to combination therapy using logistic regression. General linear models were employed to investigate the effect of treatment between patients with or without clinical response. No significant interactions were found, with the exception of an interaction between the group who achieved EULAR response criteria according to the DAS 28 score and MR-determined enhancing synovial volume (p=0.02). The direction of interaction indicated that the absolute change in volume after treatment was higher for the EULAR nonresponders than for responders. This can be explained by the greater initial enhancing volume in the nonresponding group compared to that in the responding group (means: 24.2 and 18.5 cc, respectively; t test for inequality of means nearing significance at p=0.09). When we analyzed percentage reduction rather than absolute reduction, this effect was no longer apparent, i.e., the difference between responder and nonresponders was no longer significant.

Discussion

This open label pilot study confirms the efficacy of a combination of methotrexate and infliximab in patients with RA, refractory to treatment with MTX alone. Rapid clinical response, together with reduction in synovial inflammation, was demonstrated by dynamic perfusion MRI examination over a short period of time.

MR imaging has been used as an outcome measure in many RA clinical trials on account of specific advantages over radiography [2–4, 8, 9, 11, 12]. Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) system utilizes a semi-quantitative scoring system based on the severity of erosions, marrow edema, and synovitis [7, 13]. Our study was designed to focus on the severity of synovitis, the primary pathology of RA, and the most likely to show change over the short duration of this study (14 weeks). Three aspects of synovitis were evaluated. First, grading of severity of synovitis as per the RAMRIS scoring system was performed [7, 13]. This method has good intra- and inter-reader reliability but may be limited in detecting small changes in severity of synovitis [13]. Second, a quantitative volumetric estimation of active synovitis was performed. Quantitative measure of synovial volume, although time-consuming, may be more precise [12] and more responsive to change than semi-quantitative measures [9, 11, 12] and allows evaluation of both articular synovitis (as in the RAMRIS system) and adjacent tenosynovitis. Synovial volume was measured by quantifying the number of voxels of enhancing synovium on serial images through the wrist and hand [10, 11]. After exclusion of non-synovial soft tissue, all joint or tendon sheath tissue, enhancing to a greater degree than thenar muscle, was considered as hyperemic synovium indicative of active synovitis. Third, dynamic imaging of synovial perfusion was performed. Dynamic MR perfusion imaging is a good indicator of synovial disease activity [10, 11], and directly addresses one of the main pathways of infliximab action, i.e. a reduction in synovial vascularity and perfusion. Infliximab reduces circulating levels of cytokine vascular endothelial growth factor (VEGF) [14]. VEGF is a potent angiogenic peptide, which is thought to induce synovial neovascularization and endothelial leakage, thereby, facilitating deposition of inflammatory agents into the synovium and joint [14]. Two indices of synovial perfusion were assessed, namely, maximum enhancement and enhancement slope. Both indices are derived from the first-pass phase of signal enhancement and are considered to represent arrival of contrast material into the arteries and capillaries of the tissues under study and diffusion into the extracellular space [15]. The usual measure used for enhancement parameter is 10–90%. The reproducibility of our technique is not known yet. We currently are in the process of performing an animal-based study to measure this. The results will not be available for 2 months.

Nearly all clinical and MRI parameters assessed showed a significant improvement after infliximab treatment. Assessment of enhancing synovial volume and perfusion indices on serial MRI examination was useful to document the effect of treatment over this short period. Patients who had the least clinical response actually had the largest absolute reduction in synovial volume. The reduction in synovial volume achieved with therapy was probably not sufficient to manifest as a clinical response. When percentage reduction in synovial volume was assessed, this was similar across all patients. Therefore, MRI assessment allows one to demonstrate improvement in patients which may not be apparent clinically. In conclusion, this study supports the value of MRI for accelerated assessment of drug therapy on synovitis in patients with refractory disease.

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