Dynamic contrast-enhanced, extremity-dedicated MRI identifies synovitis changes in the follow-up of rheumatoid arthritis patients treated with rituximab

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Abstract

Objective

The aim of this study is to assess prospectively the effect of rituximab (RTX) on MRI features of wrist joint disease in patients affected by rheumatoid arthritis (RA).

Methods

Ten patients (6F/4M, mean age 52.9±15.5 years) diagnosed with IgM rheumatoid factor, anti-CCP positive, RA according to the 1987 ACR criteria were treated with a single course of RTX (2 infusions of 1000 mg, 15 days apart). MRI of the dominant hand was performed with a 0.2T extremity-dedicated machine using pre and post contrast T1 weighted SE, turbo 3D, and STIR sequences at baseline, and after 4 and 24 weeks. MRI was analysed using the OMERACT-RAMRIS score and the dynamic contrast-enhanced (DCE-MRI) technique for wrist synovitis, which calculates the enhancement ratio as both rate of early enhancement (REE) and relative enhancement (RE). The corresponding ME and IRE parameters were calculated also through a computer-aided semi-automated method on the mean of three MRI slices and on a small ROI positioned in the area of maximum enhancement.

Results

DAS significantly decreased during the study period (ANOVA for repeated measures, p=0.005). The RAMRIS score did not change along the study, whereas the dynamic MRI values RE, IRE and ME on the small ROI significantly decreased. RE, but not the RAMRIS synovitis score, significantly correlated with DAS at baseline, 1 and 6 months (p=0.005, 0.04, and 0.0007, respectively).

Conclusion

RTX confirmed good clinical efficacy, which was paralleled by a significant decrease in dynamic MRI results for wrist synovitis. On the contrary, the traditional RAMRIS measures did not change.

Key words

MRI, rheumatoid arthritis, rituximab, dynamic MRI

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Introduction

Rituximab (RTX), a mouse/human chimeric, monoclonal anti-CD20 antibody, is an effective and safe treatment for patients with rheumatoid arthritis (RA) (1). Magnetic resonance imaging (MRI) of the joints, including dynamic contrast enhanced MRI (DCE-MRI), can assess changes of synovial membrane activity and bone structure more precisely and in a shorter period of time than conventional imaging techniques (2). This pilot study is concerned with a prospective evaluation of the effect of RTX on hand MRI features in 10 RA patients. Changes of synovitis scores were evaluated over 6 months by both the outcome measures in rheumatology (OMERACT) RA MRI scoring system (RAMRIS) (3) and DCE-MRI analysed by the traditional (4) and computer-assisted (5) techniques.

Patients and methods

Ten IgM rheumatoid factor (RF) positive, anti CCP-positive, RA patients (6 women, mean age 52.4±15.7 years), diagnosed according to the ACR criteria (6), were studied. Disease duration was 6.3±3.2 years. The patients had a baseline DAS 28-CRP >3.2; they had not responded to traditional DMARDs and 7 of them also to one or more anti TNF-α agents. A single course of RTX (2 infusions of 1000 mg, 15 days apart) was administered after the first MRI examination. The infusions were preceded by 100 mg methylprednisolone intravenously. Concomitant treatment protocols included methotrexate, which was administered in all patients (mean weekly dose 14±4.5 mg) and prednisone, which was administered in 6/10 patients (mean daily dose 4.8±4.5mg). The following data were recorded at baseline, and after one, three and six months: number of tender and swollen joints (28 joint count), visual analogue scales of pain and general health, ESR, CRP, and functional capacity measured by HAQ. RF and anti CCP antibodies were measured at baseline, and after three and six months. CD 19+ cells were counted at baseline and after 6 months: paired results were not available in three patients due to technical reasons.

MRI of the dominant hand was performed with a 0.2T extremity-dedicated machine (Artoscan C, Esaote, Genoa, Italy) using pre- and post-contrast T1 weighted SE (slice thickness 5 mm, TR 100 ms, TE 16 ms, number of excitations 1), turbo 3D (slice thickness 0.6–0.8 mm, TR 860 ms, TE 26 ms, number of excitations 1), and STIR (slice thickness 3 mm, TR 1900 ms, TE 24 ms, number of excitations 1) sequences at baseline, and after 1 and 6 months. MRI was analysed using the RAMRIS method (3), which includes the evaluation of synovitis, bone oedema, and erosions of distal radium and ulna, wrist and metacarpophalangeal joints. The RAMRIS score for synovitis was calculated only on the wrist joint, because the low field of view of dedicated extremity MRI requires two different positioning for the wrist and the metacarpophalangeal joints, with gadolinium enhancement feasible in one location only. In addition, the DCE-MRI technique for wrist synovitis was performed as previously reported (4). The enhancement ratio was calculated on a small ROI of the synovial membrane both as rate of early enhancement (REE) and relative enhancement (RE). The intraclass correlation coefficients (ICC) for intrareader and intereader repeatability of the RAMRIS score were 0.90 (95%CI 0.86–0.93) and 0.84 (95%CI 0.82–0.86), respectively. The same figures for the evaluation of DCE-MRI were 0.93 (95%CI 0.89–0.96) and 0.86 (95%CI 0.83–0.88) for REE and 0.96 (95%CI 0.94–0.98) and 0.83 (95%CI 0.81–0.85) for RE. DCE-MRI results were also analysed using the Dynamika software version 4.4, a computer-aided semi-automated method for quantitative analysis (Image Analysis Ltd, www.imageanalysis.org.uk) (7). It includes motion reduction functionality algorithms able to reduce artifacts associated with hand movement during the examination. The imaging processing software analyses dynamic slices on a voxel-by-voxel basis for the whole slice or in a user defined "region of interest" (ROI). In the present study, (a) the mean of the three different slices of the wrist joint in a manually outlined ROI including all the synovial mem-

brane and (b) a small ROI of 35 mm^2 in the first slice tangential to the radius were considered. The small ROI on a single slice was considered because comparable to the original DCE-MRI method (4) and more rapid to calculate. The signal intensity *vs*. time curves are extracted from each voxel and automatically assigned to one of four patterns of contrast uptake described as either "no enhancement", "persistent", "plateau" or "wash-out". The "no enhancement" and "persistent" patterns are typical for disease unaffected tissues and background. The "plateau" and "wash-out" are typical for tissues with large perfusion such as inflamed joints or blood vessels. Furthermore, parameters characterising contrast uptake dynamics such as maximum enhancement (ME), calculated as maximum increase in the post-contrast signal intensity divided by the baseline signal intensity, and initial rate of enhancement (IRE), calculated as increase in signal intensity in %/second from time of onset of enhancement to ME is reached, are extracted. From each set, the following parameters were used for further analysis: the sum of voxels with the patterns of persistent, plateau and wash out enhancement (N_{total}), IRE, ME, N_{total} x IRE, and N_{total} x ME. The N_{total} represents a measure of the volume of inflammation, IRE and ME reflect the degree of inflammation, and their product is a composite measure of volume and degree of inflammation.

This pilot study, which was an open, prospective investigation following the declaration of Helsinki (Eudract 2007-001754-11), was approved by the ethics committee of the University of Genova. All patients gave their informed written consent to the study procedures and to the publication of its results. The study was sponsored by Roche Italy, which firm had no influence on manuscript preparation.

Statistical significance of changes in clinical, laboratory, and MRI data over time was assessed by ANOVA for repeated measures with Bonferroni correction (parametrical data) and with the Friedman's test (non-parametrical data). The Wilcoxon's test for paired samples was used to assess differences at two points in time. Correlations were evaluated with the Spearman's correlation coefficient. All statistical calculations were performed with MedCalc version 9.6.4.0 (Belgium).

Results

High disease activity (DAS 28 ≥5.1) was present in 9/10 patients (mean DAS at baseline 5.8±0.9). During the study period, DAS significantly decreased (p=0.005) (Table I). A moderate DAS EULAR response was seen at one month in 4/10 patients, at 3 months in 5/10 patients and at 6 months in 8/10 patients. Of the remaining patients, three had good response and two no response at 3 months; one had good response and one no response at 6 months. IgM RF, anti CCP antibodies, CD19+ cell count (from 135.5 cells/µl [29–438] to 10 cells/µl [1–382]) and the three components of the RAMRIS score did not change across the study (Table I). The DCE-MRI value RE significantly decreased between baseline and 6 months (p=0.021) (Fig. 1). Of the values obtained with the semi-automated method, those calculated as mean of the three slices did not change during treatment. Conversely, ROI-based IRE and ME significantly decreased during the follow-up (p=0.03 and p=0.04, respectively) (Fig. 2). RE, but not the RAMRIS synovitis score, significantly correlated with DAS at baseline, 1, and 6 months (p=0.005, 0.04, and 0.0007,

Table I. Changes of clinical, laboratory and MRI findings in RA patients treated with one course of rituximab.

	Baseline	1 month	3 months	6 months	*p*
DAS 28	5.7±0.8	5.3±1.6	4.3±1.5	4.4±1.4	0.005
Tender joint count	14.5±6.5	12±9.5	8.7±8.2	8.6±8.6	0.04
Swollen joint count	8 (4–20)	9 (2–24)	3.5 (0–17)	5 (0–20)	0.11
HAQ	1.8±0.7	1.5±0.8	0.8±0.7	0.9±0.7	0.002
CRP (mg/L)	21.6 (5.7–87.3)	23.5 (3.4–73.1)	10.9 (3.4–37.4)	23.4 (3.4–90)	0.88
IgM rheumatoid factor (IU/ml)	570.9 (48.5–2660)	ND	241.8 (39.8–1140)	281.2 (20.8–994)	0.13
Anti CCP antibodies (U/ml)	55.2±33.4	ND	41.9±32.3	122.2±247.8	0.61
OMERACT RAMRIS synovitis score (0–9)	3.4±1.6	2.3±2.8	ND	2.4±1.7	0.22
OMERACT RAMRIS bone oedema score (0–69)	23.2±13.6	23.8±15.7	ND	24±14.7	0.88
OMERACT RAMRIS erosion score (0–230)	7.9±3.7	8.1±3.6	ND	9.1±4.4	0.15
REE	0.36±0.27	0.49±0.51	ND	0.36±0.26	0.89
RE	67.0±42.4	57.9±51.9	ND	40.1±21.7	0.07
IRE	0.01±0.004	0.01±0.005	ND	0.01±0.004	0.53
ME	1.93±0.22	1.87±0.15	ND	1.86±0.21	0.32
N_{total}	696.2±432.1	756.8±497	ND	764.7±441.4	0.20
N_{total} x IRE	5.4 (2.3–30.5)	5.2 (.07–23.7)	ND	4.4 (0.3–7.9)	0.69
N_{total} x ME	1084.5 (281.5–3375)	853.3 (9.1–3710.9)	ND	896 (31–2073.9)	0.76
IRE ROI	0.01±0.004	0.008±0.005	ND	0.005±0.002	0.03
ME ROI	1.89±0.28	1.82±0.42	ND	1.60±0.26	0.04
N_{total} ROI	63.2±11.7	58.2±19.6	ND	55.5±16.7	0.09

Values in brackets are measure units or range of the MRI variables; results are expressed as means±SD when parametrical and as median (range) when non-parametrical; ND: not done.

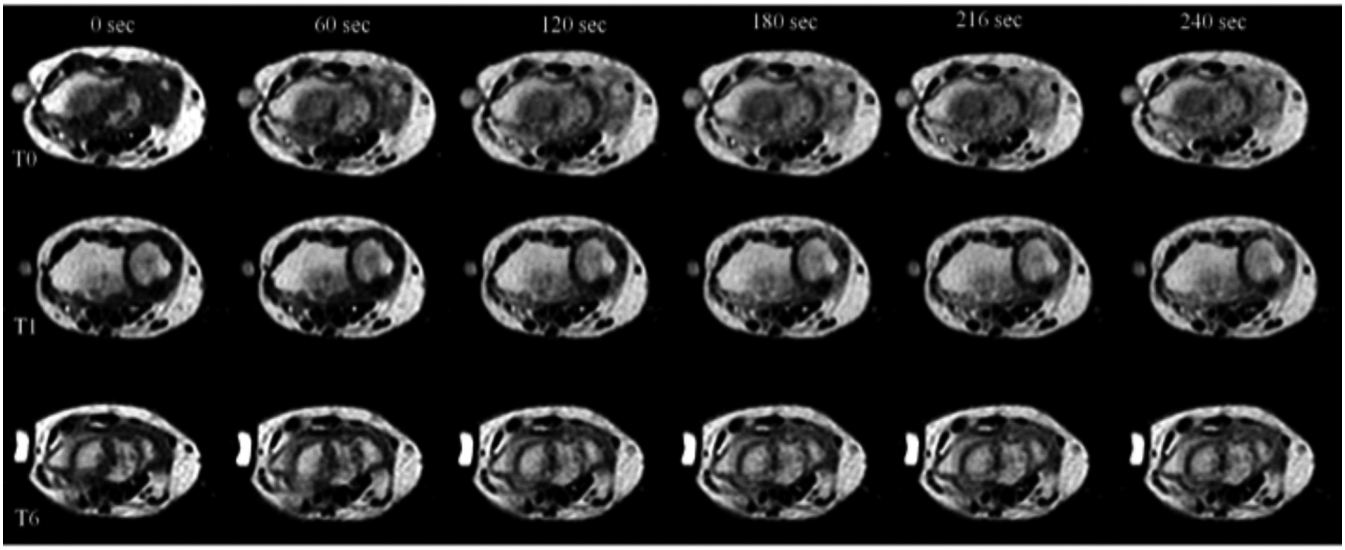

Fig. 1. Representative dynamic contrast-enhanced MRI of the wrist in a patient with rheumatoid arthritis. Sequences in the left column show the pre-contrast images, followed by those acquired after 60, 120, 180, 216 and 240 s, respectively. The first row corresponds to baseline examination (t0), the second to the examination performed after one month of treatment (t1), and the third to the 6-month examination (t6). In the represented patient, RE decreased from 136.8 (t0) to 83.4 (t1) and 52.3 (t6). The sequences are spin echo (TR/TE: 100/16 ms; matrix: 160x128; FOV: 150x150).

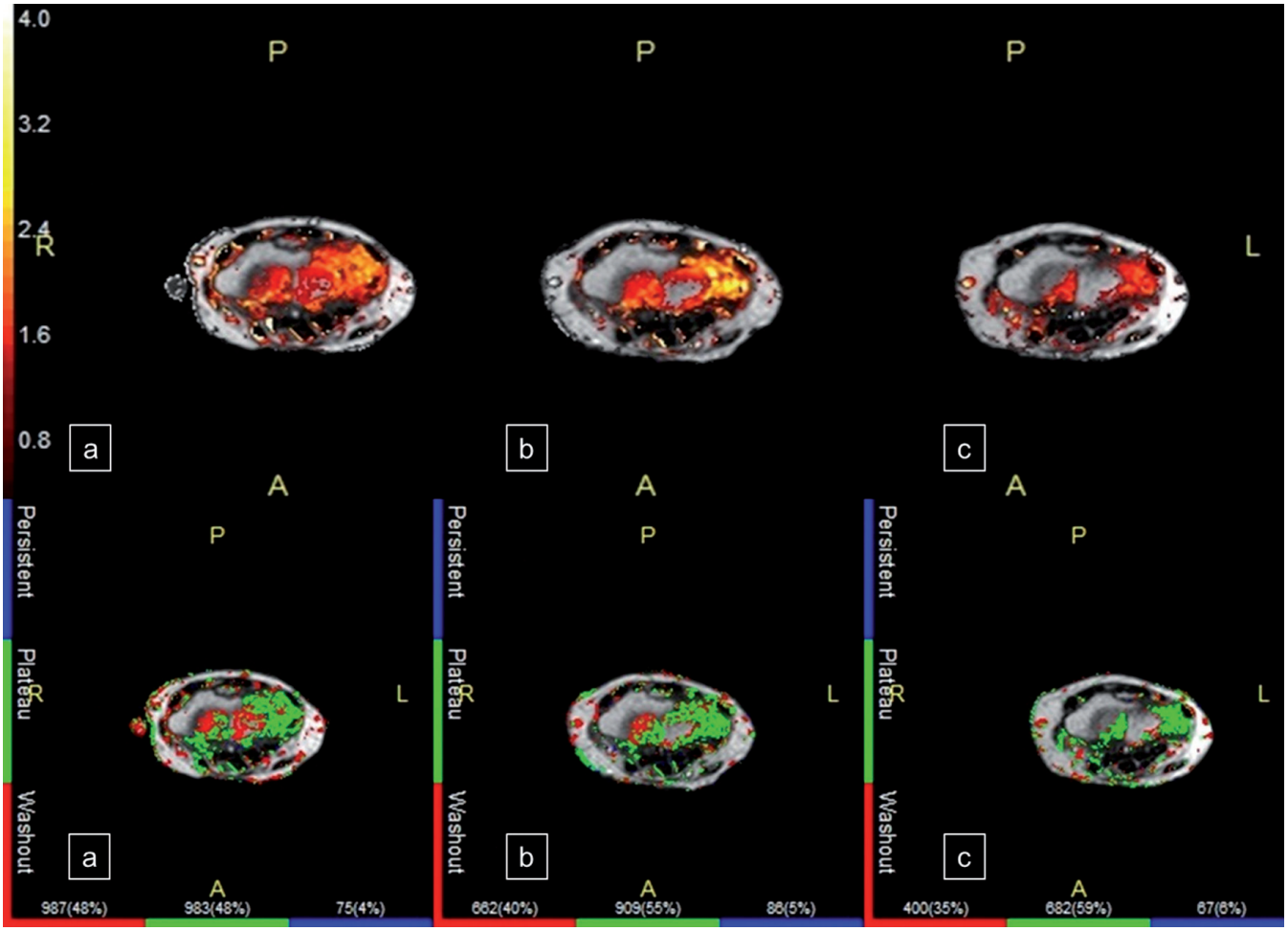

Fig. 2. The representative parametric maps of dynamic, contrast-enhanced MRI data of maximum enhancement (ME) superimposed on axial T1-weighted sequences of the wrist are shown in the upper row. The enhancement decreases from baseline (**a**), to months 1 (**b**) and 6 (**c**). In the lower row, gadolinium maps show all enhancing voxels, which are colour-coded according to enhancement patterns as explained on the Y-axis (the sum of voxels with plateau and washout enhancement is N_{voxel}). Note the almost complete disappearance of voxels with wash-out pattern and the decrease of those with plateau pattern.

respectively). IRE and N_{total} correlated with DAS 28 at baseline only (p=0.003).

Discussion

RTX showed good clinical efficacy on RA symptoms, confirming the data reported in the literature (1). Clinical improvement was paralleled by a significant decrease in the DCE-MRI RE, and ROI-based IRE and ME values for wrist synovitis. Interestingly, the traditional RAMRIS measures did not change, confirming the data by Moller Dohn *et al*. (8), who showed that the RAMRIS synovitis, bone oedema, and erosion scores did not change even after one year of RTX treatment. There are different possible explanations for the apparent lack of sensitivity of the RAMRIS score in the short term found in our study. The 2nd MRI was performed at one month from RTX infusion when disease improvement was probably still scarce; the 3rd MRI was performed, as in the previously cited study (8), at 6 months, when efficacy of the RTX course was declining. The optimal timing for MRI during RTX treatment is probably three months after infusion, as suggested by clinical data. Bone oedema probably needs a longer interval to improve. Finally, the number of patients was small, making more difficult to show treatment-induced changes. The erosion score remained unchanged, an observation that could support the concept of a protective role exerted by RTX on the development of new erosions. A non-significant increase of the erosion score was seen at 1 (+0.2) and 6 (+1.2) months in our patients whereas in the previous study a non-significant decrease at 6 (-0.5) and 12 (-2.4) months was observed (8). This difference may be ascribed to the difference in baseline mean erosion score in our as compared with the Moller Dohn *et al*. study (7.9 *vs*. 31).

DCE-MRI proved better than the RAMRIS score in evaluating short-term changes of synovitis. It has been used to evaluate response to RTX in a retrospective study of the metacarpophalangeal joints of 10 RA patients (9). In this study, the volume of inflamed synovial membrane and REE significantly decreased after 26 weeks. We recorded a similar improvement after the same time interval, although in our study only RE decreased. REE is derived from the slope of the curve of initial diffusion of the contrast agent in the vessels of the synovial membrane, whereas RE represents the steady state of contrast diffusion. The two measures are strictly correlated but probably indicate different disease-related mechanisms. In a previous study, we have shown that RE, but not REE, predicts the fulfilment of ACR criteria and both RE and REE predict the need of immunosuppressive treatment in patients with early, undifferentiated arthritis (10). Finally, it is also possible that the use of two MRI machines at the opposite end of the power spectrum (3T and 0.2T) can explain the differences.

DCE-MRI results were evaluated also by the Dynamika software. Since it is not known which of the many features deriving from this analysis are best suited to evaluate changes of synovitis during RA treatment, we studied different possible options, including persistent, plateau, wash-out, persistent+plateau, plateau+wash out, IRE, and ME, and the combinations thereof. In addition, evaluation was performed on the complete synovial membrane of the three consecutive slices after manual outlining to exclude superficial blood vessels that could interfere with the examination. This analysis did not yield significant modifications after treatment. A second approach was based on the identification of a small ROI where enhancement was more pronounced and its follow-up in the subsequent examinations. This method showed a change of ME, IRE, and N_{total}, which resulted significant only for the first two parameters. A possible explanation of this discrepancy relies on the finding that adjacent areas of the synovial membrane of the same joint may show different degrees of inflammation (11). Consistently, they also may behave differently in response to treatment. Considering the total surface of the synovial membrane may obscure treatment-related changes in more inflamed areas. In the conventional technique, RE significantly correlated with DAS 28, whereas in the computer-aided technique the most reliable parameter was IRE. REE, the equivalent of IRE in the conventional technique, had poor reproducibility when examinations on the same subject were repeated three days apart (5). This may be due to its dependence on the assumption of maximum enhancement occurring after 55", which is overcome by the fully automated data acquisition of the computer-aided method.

Our study may be limited by some weaknesses. The number of cases is small, a common finding in papers on MRI evaluation of RTX efficacy (8, 9), although DCE-MRI has been studied on a larger number of patients (4, 5, 10, 12). These results should therefore be confirmed in a larger trial. However, a significant decrease of RE, ME and IRE in spite of the low number of patients indicates a high sensitivity of the method. A dedicated MRI machine with a low field of 0.2 T was used. The proficiency of low-field dedicated machines in arthritis, as compared with high-field machines, is debated (13). However, several investigations have shown that both are comparable for the evaluation of synovitis and erosions of the hand in RA patients (14, 15). The sensitivity of dedicated MRI for the detection of bone oedema may be lower, although the introduction of new sequences has improved its performance. In addition, bone oedema has been recently demonstrated as the most specific finding in RA in a study with extremity-dedicated MRI (16). However, we cannot exclude that bone oedema could have been underestimated in our study. Finally, 0.2 T dedicated MRI cannot fully appreciate the articular cartilage of the small joints of the hand. This aspect has been recently evaluated with a 1.5 T MRI machine in a subgroup of RA patients from a clinical trail on RTX (17).

One of the advantages of extremity-dedicated MRI is the good acceptance by the patients. In our study, all 10 enrolled patients could perform the 3 subsequent examinations without problems and all the 30 MRI examinations could be evaluated. By contrast, in a study with a 3-T MRI machine a number of patients could not tolerate the examination (9). Finally, patients were evaluated after only a single course of

RTX. Our positive findings, in spite of this limitation, might suggest that a prolonged RTX treatment could achieve even better results.

Conclusion

In conclusion, we have shown that DCE-MRI results are improved after a single course of RTX. DCE-MRI is a promising method for the follow-up of treatment in RA patients, being able to detect even small synovitis changes. This finding supports the use of MRI in order to evaluate the results of clinical trial in a shorter time than before.

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