Clinical Outcome and Imaging Changes After Intraarticular (IA) Application of Etanercept or Methylprednisolone in Rheumatoid Arthritis: Magnetic Resonance Imaging and Ultrasound-Doppler Show No Effect of IA Injections in the Wrist After 4 Weeks

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ABSTRACT. ***Objective.*** To assess the magnetic resonance imaging (MRI) and ultrasound (US) changes in the wrist of patients with rheumatoid arthritis (RA) 4 weeks after an US guided intraarticular (IA) injection.

Methods. Contrast enhanced MRI and US-Doppler were performed at baseline and 4 weeks after IA injection of either 40 mg methylprednisolone (n = 12) or 25 mg etanercept (n = 13) in 25 patients with RA taking disease modifying antirheumatic drugs with a therapy-resistant wrist joint. All injections were US guided.

Results. There was an improvement in swollen target joint score ($p < 0.001$), tender target joint score ($p < 0.002$), and physician visual analog scale score ($p < 0.001$) after 4 weeks. Baseline MRI synovitis score was mean 5.08 (range 3–9) and was unchanged at followup in the whole group ($p = 0.52$) and between treatment groups ($p = 0.43$). MRI edema score (mean 4.46, range 0–29) in the total group was unchanged after 4 weeks ($p = 0.13$), whereas MRI erosion score increased in the total group from baseline, 17.88 (range 7–40), to 4 weeks, 18.25 (range 7–40) ($p < 0.001$). Neither US-Doppler color fraction (0.07) nor Resistive Index (RI) ($p = 0.36$) changed from baseline to 4 week followup.

Conclusion. In contrast to the clinical evaluation, imaging measures of relevance for the estimation of inflammation, US-Doppler, US RI, MRI synovitis, and bone-marrow edema did not change 4 weeks after a single IA injection of either methylprednisolone or etanercept in the wrist. Within the same period, erosive progression in some patients suggested that joints with active disease may deteriorate within as little as 1 month, and that this development is not arrested by 1 injection. Given the small sample size of our study further studies are required to confirm our results. (First Release Mar 1 2008; J Rheumatol 2008;35:584–91)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ETANERCEPT METHYLPREDNISOLONE
MAGNETIC RESONANCE IMAGING ULTRASOUND DOPPLER

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To obtain a more concentrated effect on the target joint and reduce the possibility of systemic adverse effects, intraarticular (IA) medication injections were proposed by Hollander in the 1950s[1]. Since then, IA injections have become a mainstay of the rheumatologist's armamentarium in cases of localized joints with nonresponse to systemic therapy[2]. Glucocorticosteroid IA injections are commonly used in the treatment of patients with rheumatoid arthritis (RA), although their repeated longterm use may also cause adverse effects[3]. The correct placement of the needle has been a matter of concern[4] because only about half of IA injections are performed into the right structure. Ultrasound (US) guided IA injections can help overcome this problem[5].

In parallel to the use of IA glucocorticoids, anti-tumor necrosis factor-α (TNF-α) medications have also been successfully used intraarticularly, although with varying response[6,7].

Magnetic resonance imaging (MRI) of the small joints of the hands and feet is a safe, sensitive, and accurate method to detect synovitis and bone erosions in patients with RA compared to the classical radiographic examination[8]. Indeed, MRI shows signs of bone erosion in patients with RA a median of up to 2 years before they become visible on conventional radiograph[9]. MRI also provides valuable information regarding bone marrow edema near the joint. Bone marrow edema reflects true bone marrow inflammation[10] and can be used as a prognostic marker for future bone erosions in the hand and feet in RA[11,12]. Low- (< 0.5 T) and high-field MRI can outline bone erosions, joint synovitis, joint effusion, and bone marrow edema in patients with RA[13], and image quality is comparable. However, cost and patient acceptance favor low-field MRI, which may replace high-field MRI for routine clinical examinations in patients with RA[13-17]. US-Doppler has also been evaluated for use in RA as a promising tool in the detection of inflammatory reactions[18-21].

We used low-field extremity dedicated MRI and state of the art US for monitoring wrist changes after IA injection of either etanercept or methylprednisolone in patients with RA recruited from a randomized, controlled, double-blinded study.

MATERIALS AND METHODS

The patients with RA included in our study were participants in a larger randomized, controlled trial of the clinical effect of IA injection in several joints of either etanercept or methylprednisolone[22]. After giving informed consent, all 25 patients treated in the wrist joints in that study were enrolled in the imaging examinations. The patients had RA diagnosed according to the American College of Rheumatology criteria[23], female/male ratio was 22/3, mean age 55 years (range 24–80 yrs), and mean disease duration 7.5 years (0–30 yrs). All patients accepted MRI and US evaluation at baseline and at followup. The patients were all receiving disease modifying antirheumatic drugs (DMARD; 15 methotrexate, 9 sulfasalazine, 1 gold), and were included in our study because of a wrist joint involvement resistant to systemic therapy. The study was randomized and double-blinded. The patients received US guided IA injections of 0.5 ml lidocaine 1% plus either 40 mg methylprednisolone (1 ml Depomedrol® 40 mg/ml) or 25 mg etanercept (1 ml Enbrel®, 25 mg/ml) in the wrist at baseline.

Clinical evaluation. All patients described the degree of wrist pain on a 100 mm visual analog scale (VAS) and completed the Health Assessment Questionnaire (HAQ). An independent clinician, blinded to the treatment, evaluated the number of tender and swollen joints (28-joint count), which were graded 0–3, with 0 = no activity and 3 = most prominent activity. The DAS28 was calculated. As the data of the treated wrist were part of this information, these were extracted and used for separate calculations. The clinician rated the patient disease severity on a VAS and biochemical blood tests, including IgM and C-reactive protein (CRP) concentrations, were performed.

MRI. Contrast enhanced MRI was performed at baseline and 4 weeks posttreatment. To select the most appropriate image protocol, all patients had both T1 spin-echo (SE) and 3D Turbo T1 gradient-echo images performed before and after intravenous injection of gadolinium as contrast agent. A better and more sensitive detection of erosive disease was noted using the 3D Turbo T1 sequence in contrast to the T1 SE sequence (data not shown; Figure 1). As a result, 3D Turbo T1 sequences were used throughout the study. These findings are in concordance with published data regarding sequence selection[13-15].

All MRI examinations were performed using a 0.2 T musculoskeletal dedicated extremity scanner (E-scan®, Esaote Biomedica, Genoa, Italy). Patients were examined in supine position with the hand along the side of the body. For signal collection, a receiver-only cylindrical solenoid wrist coil was used. The following pulse sequences were applied: gradient-echo scout, coronal T1 weighted spin-echo (TR/TE: 600/18 ms, fov/matrix: 180 × 180 mm/192 × 192, slice thickness 2.0 mm), coronal short-tau inversion recovery (STIR) (TR/TE/TI: 1310/24/85, fov/matrix: 200 × 170 mm/192 × 163, slice thickness 3.0 mm), and axial/coronal Turbo 3D T1 gradient echo (TR/TE: 38/16, fov/matrix: 180 × 180 × 100 mm/192 × 160 × 72, slice thickness 0.8 mm). After these images were acquired, an intravenous injection of gadolinium-DTPA (Magnevist, Schering AG, Berlin, Germany) was given at a dose of 0.2 mmol/kg of body weight. After the gadolinium injection, the coronal and axial T1 weighted 3D pulse sequences were repeated. Total scan time was 45 min. All images were evaluated on the scanner-processing console using the standard Esaote software program. The MRI data were paired and evaluated by the same independent observer in chronological order as recommended by van der Heijde, *et al*[24] for longitudinal radiographic studies and as suggested by Haavardsholm, *et al*[25] for longitudinal MRI studies of the wrist. The MRI observer was blinded to the clinical data. All images were evaluated by the same observer, who had 7 years of MRI expertise and 4 years of expertise in reading wrist MRI.

Disease activity was scored according to the Outcome Measures in Rheumatology [Clinical Trials] RA MRI score (OMERACT RAMRIS) evaluation standard for synovitis, bone-marrow edema, and erosions[26], and in cases of doubt, the OMERACT reference atlas was used[27].

Ultrasonography. This examination included a high-sensitive Doppler analysis of the perfusion of the target wrist joint as described[18,20]. The US examination was performed immediately before and on the same day as the MRI examinations at baseline and after 4 weeks. All examinations were performed by the same specialists with more than 20 years of experience in ultrasonography including 7 years with musculoskeletal US using a Sequoia® device (Becton Dickinson, Mountain View, CA, USA) with an 8–13 MHz linear array transducer and color Doppler and spectral Doppler applied. Single photos of the procedures were stored for blinded examination after the study. A computerized estimate of the relative area with perfusion and the color pixel fraction in the synovial tissue was calculated on each image. Resistance index (RI) for synovial blood flow, measured by Doppler technique, was determined in 3 randomly chosen arteries in the area of interest. The mean of the 3 values was chosen for further calculations. An independent observer blinded to the clinical data and the order in which the images were acquired evaluated the US images.

US guided injection. The US guided injection was performed on the dorsal side of the wrist with the transducer in the sagittal plane showing the distal end of the radius and the proximal part of the lunate bone as well as an extensor digitorum tendon in the image plane. Needle insertion was performed perpendicularly to the transducer and the drug injection was documented by recording an image-clip during injection with the needle tip in the image plane.

Statistics. All analyses were performed using SPSS® version 13 for Windows®. Correlations were estimated by Spearman's rho. Differences between baseline and followup were tested using paired 2-way Student t-test and differences between the 2 treatment arms were tested by using a simple general linear model with values at 4-week followup as dependent variable and using treatment as a factor (2 levels) and baseline values as a covariate.

In the Results section, estimated marginal means derived from these models are reported. This in effect eliminates minor differences in baseline values, allowing a difference in estimated marginal means to be an estimate of the true difference between the 2 groups.

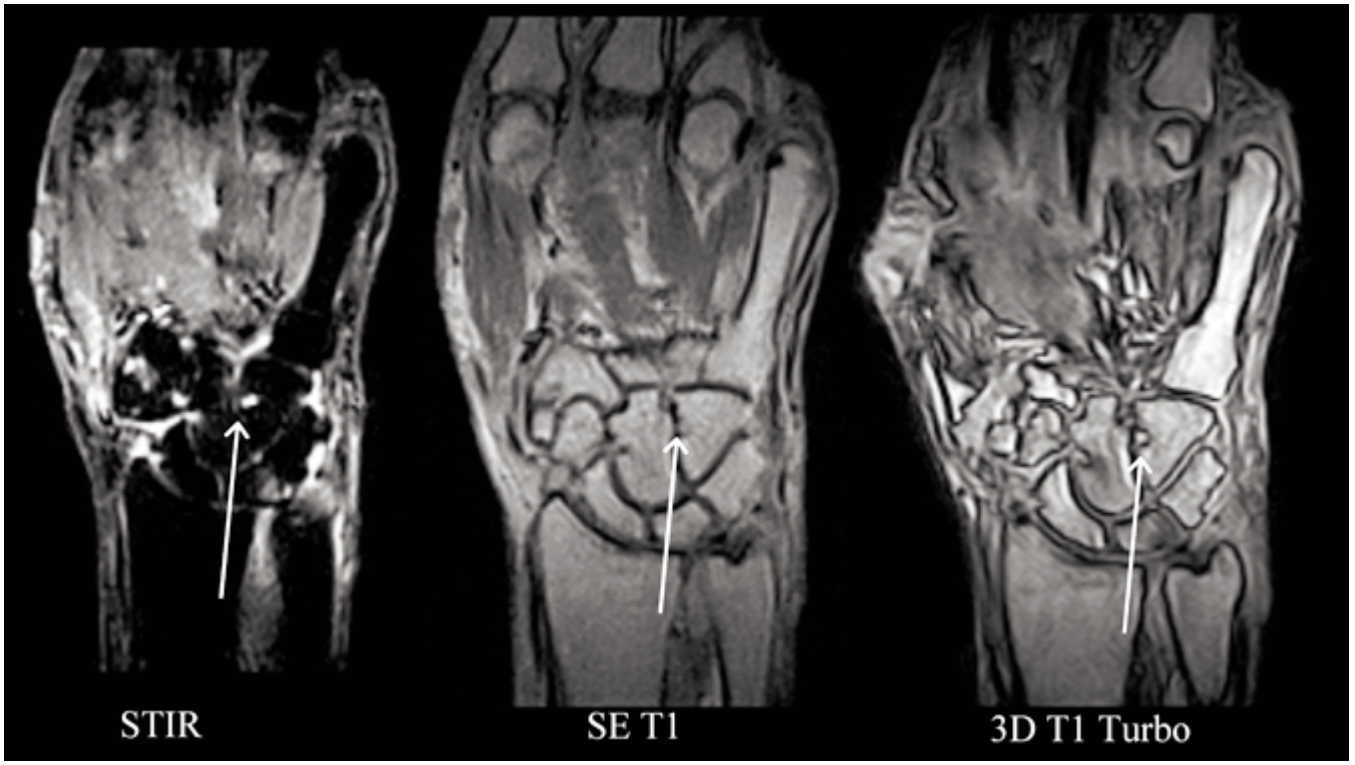

Figure 1. Sequence selection: for optimal image contrast of synovitis and erosion detection, the 3D T1 Turbo gradient-echo sequence is superior to the spin-echo (SE) T1. Arrow indicates an erosion in the hamate bone visible on the STIR but best seen on the coronal 3D T1 Turbo sequence. Both T1 images have gadolinium contrast.

Intrareader reliability of the different OMERACT MRI scores (synovitis, erosions, and bone-marrow edema) were evaluated in 10 randomly chosen patients and calculated using the 2-way mixed model single-measure intraclass correlation coefficient (ICC) for absolute values and were calculated for both the baseline and the followup scores as recommended by Haavardsholm, *et al*[25]. Sensitivity to change was calculated as the smallest detectable difference (SDD) described by Bland and Altman[28] and recommended as an outcome measure in longitudinal trials with MRI scores of the wrist in rheumatology[29]. The SDD shows the smallest detectable change score, within a 95% confidence interval (95% CI), that represents a "true" change and not a measurement error. Finally, the minimum detectable change (MDC) was calculated to express the SDD as a percentage of the maximum score[25]. P values < 0.05 were considered significant.

Ethics. The local Ethics Committee and the Danish Medicines Agency approved our study (KF 02-064/02). All patients signed an informed consent form. The protocol, a randomized, controlled study of intraarticular injections of etanercept or glucocorticoids in patients with rheumatoid arthritis (CCT-NAPN-13235), was submitted to Current Controlled Trials Ltd., Middlesex House, London, UK.

RESULTS

At baseline the patients in the 2 treatment arms (methylprednisolone and etanercept) did not differ regarding the distribution of sex (22 women, 3 men), mean age (55 yrs, range 22–80), mean duration of RA (7.7 yrs, range 1.9–30), IgM-rheumatoid factor (RF)-positive (n = 18), and mean DAS28 (4.2, range 2.1–6.6).

MRI. According to the OMERACT reference atlas for wrist joint pathologies in RA[27], in general, the patients had a mean total erosion and bone-marrow edema score at a relatively low level and a midrange mean total synovitis score (Table 1). No significant differences were observed in MRI scores between the 2 groups at baseline.

The global MRI synovitis score did not differ between the treatment groups at 4-week followup (estimated marginal mean: methylprednisolone 4.91 vs etanercept 5.24; p = 0.4); nor did the overall response score differ from baseline to 4-week followup (p = 0.52; Figure 2, Table 1). The overall MRI bone-marrow edema score was also unchanged after 4 weeks (p = 0.13; Table 1) and no group differences were found (estimated marginal mean between groups (p = 0.1). The global erosion score increased significantly at 4-week followup in both groups ($p < 0.001$; Table 1).

The ICC, SDD, and the MDC of the MRI scores are presented in Table 2 and the number of patients who showed a regression or a progression in the MRI scores before and after correction by the SDD are presented in Table 3.

Figure 3 shows an example of a patient with progression in total OMERACT erosion score higher than the SDD with a clearly visible erosive progression in the hamate bone.

US. All patients had moderate to high activity on US-Doppler at baseline. In general, the activity was distributed throughout the joint. Table 1 gives the mean color pixel frac-

Table 1. Clinical measures, MRI total OMERACT score, and ultrasound (US) score at baseline and at the 4-week followup in the total patient group. Data are mean (SD).

Measure	Baseline	4 Weeks	p
Swollen target joint	1.6 (0.6)	0.9 (0.8)	< 0.001
Tender target joint	1.72 (0.9)	0.8 (1.0)	< 0.001
Physician VAS	36.3 (25.1)	15.2 (15.7)	< 0.001
Patient VAS	43.3 (24.7)	32.2 (28.6)	0.09
MRI erosion score	17.88 (8.5)	18.25 (8.6)	< 0.001
MRI bone edema score	4.46 (7.2)	3.71 (6.6)	0.13
MRI synovitis score	5.08 (2.0)	4.96 (1.9)	0.52
US color pixel fraction	0.25 (0.18)	0.19 (0.14)	0.07
US Resistive Index	0.75 (0.13)	0.77 (0.10)	0.36

MRI: magnetic resonance imaging; VAS: visual analog scale.

tion and RI values of the wrists. There were no significant differences between the baseline measures in the 2 groups of patients. The US-Doppler was calculated as color fraction, which did not change significantly, but showed an improvement trend from the baseline value of 0.25 (range 0.06–0.77) to 0.19 (range 0.01–0.44) at the 4-week followup ($p = 0.07$). In addition, no significant changes were seen in RI, which was 0.76 at baseline in both groups and 0.77 at 4 weeks ($p = 0.36$; Table 1).

Clinical data. Both groups showed a significant improvement in the clinical measures of swollen target joint score ($p < 0.001$), tender target joint score ($p < 0.002$), physician evaluated VAS ($p < 0.001$), and an improvement trend in patient evaluated VAS ($p = 0.09$) (Table 1).

Clinical versus imaging data. Within the 2 groups, the clinical and imaging scores showed no significant correlations in the etanercept group at the 4-week followup, whereas in the methylprednisolone group changes in clinical target joint tenderness score correlated with both the change in the OMERACT synovitis score ($r = 0.60$, $p < 0.04$) and the change in color fraction index ($r = 0.68$, $p < 0.02$).

The other laboratory and clinical measures (IgM, CRP, HAQ, DAS28, and VAS) did not correlate with any imaging data (MRI and US) at baseline, nor at the 4-week followup.

DISCUSSION

This double-blinded, clinically controlled study attempted to assess the short-term efficacy of a single IA injection of either etanercept or glucocorticoid, which have both shown significant clinical effect within the first month[20,30-32]. This clinical response was not confirmed by imaging, as neither MRI nor US-Doppler could demonstrate a benefit of one such injection at the 4-week followup. This negative result was found in all measures tested with the 2 methods including synovitis and bone-marrow edema on MRI, and color-fraction index or RI-index on US, which represent very sensitive signs of inflammation[31]. The clinical observer in our study was blinded to the therapy and phase in therapy of the patients. A discrepancy between clinical and imaging efficiency may be partly explained by bias of the patient wishing to experience a positive effect.

A definite source of concern was our finding of a significantly higher erosion score at the 4-week followup, indicating that joints with active disease may deteriorate within as little as 1 month due to insufficient response to the injection, regardless of therapy. The erosions may be in a state of progress that cannot be arrested by a single injection of medication. This result should, however, be regarded with some reservation due to the SDD of the erosion score presented in Table 2. As can be seen in Table 3, only 1 patient had an increase in OMERACT erosion score exceeding the SDD. This patient had imaging evidence of erosive progression in the hamate bone (Figure 3). The changes in erosion configuration observed in this case may be regarded as a

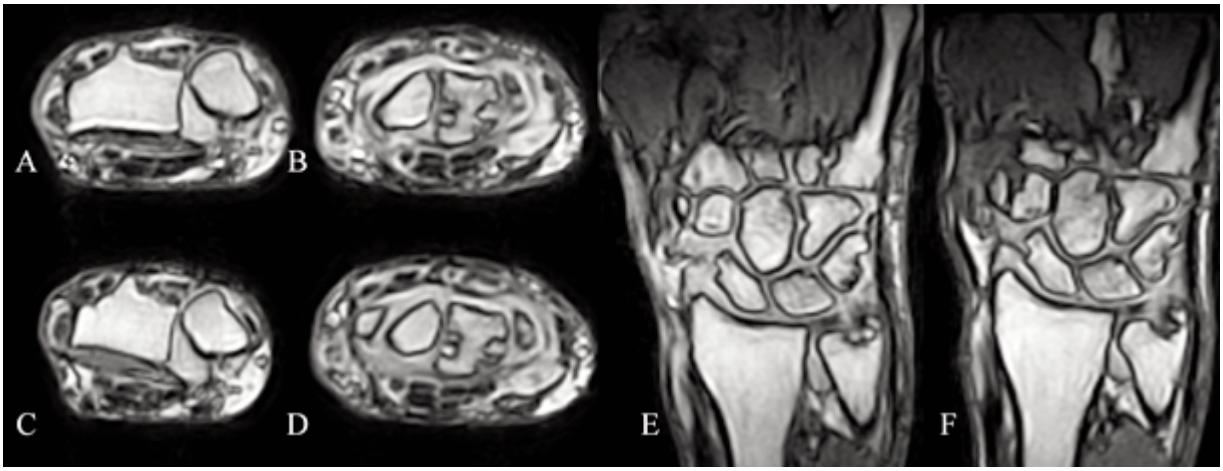

Figure 2. MRI of the wrist at baseline (A, B, E) and 4 weeks after IA injection of steroid (C, D, F). All images are postgadolinium. Note the synovitis score and visible erosions are unchanged. A, C: axial 3D Turbo T1 gradient-echo image of the radioulnar joint. B, D: axial 3D Turbo T1 gradient-echo image of the intercarpal joint. E, F: coronal 3D Turbo T1 gradient-echo image of the wrist.

Table 2. Intrareader agreement of the different OMERACT MRI scores determined by a 2-way mixed effect model (single measures with absolute values).

MRI Result	ICC Baseline	ICC Followup	SDD	MDC, %
Erosion score	0.96	0.95	1.89	4.75
Bone edema score	0.89	0.81	2.08	9.56
Synovitis score	0.89	0.95	0.86	9.56

ICC: intraclass correlation coefficient; SDD: smallest detectable difference; MDC: minimum detectable change.

true deterioration, as demonstrated recently by comparison with computerized tomography[33].

The intraobserver agreement values (Table 3) are all above 0.8, indicating a very good correlation, which is in agreement with published results on both high-field and low-field MR scanners[29].

Our disappointing 1-month imaging results are in contrast with the clinical impression of the injections in joints, which are commonly regarded as having a dramatic, immediate effect, as also found in our former study of injections[22,30]. However, the imaging measures can be regarded as more objective evidence that 1 injection in the wrist joint is ineffective after 1 month. Consequently, clinical measurements with subjective scores might give a false impression of response if used as the only criterion of success.

Our findings lend further support to the recent study by Brown, *et al* showing imaging documentation of continuing joint deterioration in patients with clinical remission, leading to the conclusion that "imaging assessment may be necessary for the accurate evaluation of disease status and, in particular, for the definition of true remission"[34].

Studies of the smaller and single-chambered metacarpophalangeal and the metatarsophalangeal joints have reported a good correlation between MRI and US synovitis evaluations[35,36]. Our imaging data were in contrast to these results, which might be explained by the wrist being a more complicated joint with less strict definitions of region of interest for MRI and US. A former study of the wrist from our own group showed a weak to moderate correlation between the MRI synovitis score and the US scores, and possible differences in patient selection may also be of importance for the results[31].

To our knowledge, ours is the first study to show indications of further bone destruction within as little as 4 weeks. None of our patients was treated with anti-TNF systemically, whereas all were treated with DMARD, suggesting an insufficient protection by DMARD from disease progression, at least in active solitary joints.

In clinical practice flares of arthritis in one of a few joints are commonly treated with a single injection, despite evidence that the effect of a single injection of methylprednisolone is unpredictable, with large variations in both clinical and imaging measures of inflammation (Doppler US and RI)[20]. A one-shot strategy must be regarded as delivering "rescue" medication and is not an alternative to changes in systemic treatment in cases of generally unsatisfactory treatment of RA. However, after planning our study, evidence has been presented of a more sustained effect of repeated injections of steroid into RA joints[2], but this was not the only therapeutic measure.

Our negative imaging findings could be explained by the relatively long interval of 4 weeks between imaging assessments, and we can only speculate whether both drugs had an earlier effect on inflammation in the days/weeks after injection. We have found indications of an earlier clinical and US response to etanercept when tested 1 week after IA injection[30].

Treatment failure may also be caused by incorrect placement of the IA injection due to poor technique[4]; however, in our series this problem was overcome by giving all injections under US guidance, with imaging documentation of the placement of the injected substance into the wrist joint. Even so, evidence has been presented of compartmentalization of the wrist with various degrees of communication between the compartments[37], and due to this anatomical variance, some authors suggest a triple injection technique for a whole-joint arthrographic evaluation[38-40]. Thus, treatment failure of a wrist injection may be caused by insufficient spread of the medication into all joint compartments, when using this small volume of 2 ml[41].

Our patient group had a long duration of disease, a moderate synovitis score according to the OMERACT RAMRIS, and a moderate Disease Activity Score, and they might

Table 3. MRI total OMERACT score and number of subjects with increased or decreased values at baseline and 4 weeks before and after correction of the smallest detectable difference (SDD).

Specific Score	MRI Scores, mean (SD) Baseline	4 Weeks	No. of Progressors	No. of Regressors	SDD	No. of Definite Progressors Corrected by SDD	No. of Definite Regressors Corrected by SDD
MRI erosion score	17.88 (8.5)	18.25 (8.6)	8	0	1.9	1	0
MRI bone edema score	4.46 (7.2)	3.71 (6.6)	1	5	2.1	0	2
MRI synovitis score	5.08 (2.0)	4.96 (1.9)	3	4	0.86	3	4

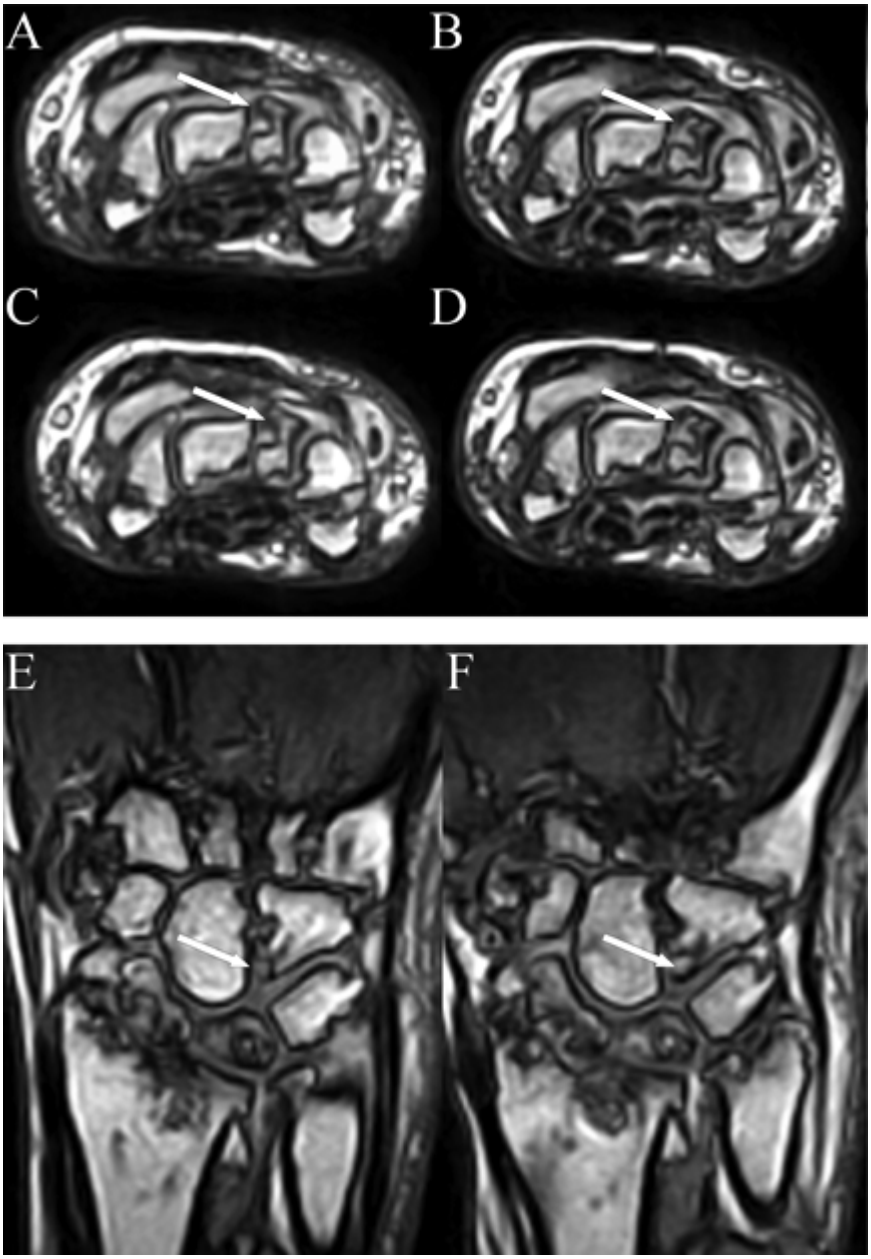

Figure 3. MRI of the wrist at baseline (A, E) and 4 weeks after IA injection of etanercept (B, F). All images are postgadolinium. A, B: axial 3D Turbo T1 image of the midcarpal region. Arrow indicates an erosion in the hamate bone, which markedly changes configuration 4 weeks after treatment. Despite the image plane not being identical, but out of plane by a few degrees, reformatting the baseline image (C) does not explain the configuration change (D), which we take as an indication of a true erosive progression. E, F: coronal 3D Turbo T1 image of the wrist. Arrows indicate the same erosion in the proximal part of the hamate bone as in A and B; the synovitis score is unchanged.

be relatively more resistant to the injections than would be seen in early arthritis. Whatever the reason for the neutral and possibly negative outcome, our patients should have been treated more aggressively. In particular, the potential aspect of rapidly progressing erosions in wrist joints must challenge the usual reluctance to treat patients with biologics or IA injections. In Denmark, as in many other countries, biologics are used as the last resort, despite these drugs seemingly giving patients a higher chance of arrest of erosions than traditional DMARD[42-44].

Finally, the OMERACT RAMRIS synovitis score could be insensitive to changes in the very short term as it is not the ideal method to follow up IA injections. In this perspective the effect of IA glucocorticoid injections in the knee has

been successfully evaluated in the past by calculation of synovial membrane volume and dynamic MRI[45], and a new dynamic sequence for the low-field scanner has successfully been evaluated for discriminating active disease from inactive disease in patients with RA[46].

Neither MRI nor US measures revealed a significant effect 4 weeks after treatment with a single IA injection of either methylprednisolone or etanercept in the wrist of patients with RA. Further, we present MRI evidence of significant, progressive erosive disease in active joints within 4 weeks that could not be arrested by a single IA injection. Thus an injection into a joint does not seem to have a sufficient effect on arthritis and should not be used as a sole measure against flares.

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