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Magnetic Resonance imaging of joints following intra-articular treatment and procedures in arthritis

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Acknowledgements

Preface and original manuscripts

The present thesis is based on three papers listed below (referred to by roman numerals in the text).

I   Mikael Boesen, Lars Boesen, Karl Erik Jensen, Marco Amedeo Cimmino, Søren Torp Pedersen, Lene Terslev, Merete Koenig, Bente Danneskiold-Samsøe, Henrik Røgind and Henning Bliddal; *Dissociation between imaging evaluation and clinical outcome in rheumatoid arthritis: MRI and ultrasound Doppler show no effect of intra-articular injections in the wrist after 4 weeks*
J Rheumatol. 2008 Apr;35(4):584-91. Epub 2008 Mar 1.
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II   Mikael Boesen, Karl Erik Jensen, Søren Torp-Pedersen, Marco A Cimmino, Bente Danneskiold-Samsøe, and Henning Bliddal; *Intra-articular distribution pattern after ultrasound-guided injections in wrist joints of patients with rheumatoid arthritis.*
Eur J Radiol. 2007 Oct 10; [Epub ahead of print]

III   Mikael Boesen, Karl Erik Jensen, Etienne Qvistgaard, Carsten Thomsen, Bente Danneskiold-Samsoe, Mikkel Østergaard and Henning Bliddal. *Delayed gadolinium-enhanced magnetic resonance imaging (dGEMRIC) of hip joint cartilage: better cartilage delineation after intra-articular than intravenous gadolinium injection.*
Acta Radiol. 2006 May;47(4):391-6

Abbreviations

2D	Two- dimensional
3D	Three-dimensional
ACR	American College of Rheumatology
CNR	Contrast-to-noise ratio
CRP	C-reactive protein
dGEMRIC	Delayed gadolinium enhanced magnetic resonance imaging of cartilage
DMARD	Disease modifying antirheumatic drugs
FOV	Field of view
GAG	Glycosaminoglycan
Gd-DTPA	Gadolinium-diethylenetriamine penta-acetic acid (DTPA) contrast agent
HAQ	Health assessment questionnaire
IA	Intra-articular
i.v	Intra-venous
MCP	Metacarpophalangeal joint
MPR	Multi-planar reconstruction
MRI	Magnetic resonance imaging
OMERACT	Outcome measures in rheumatoid arthritis clinical trials
PACS	Picture Archiving System
RA	Rheumatoid arthritis
RF	Rheumatoid factor
ROI	Region of interest
SD	Standard deviation of the mean
SE	Spin echo
SNR	Signal-to-noise ratio
STIR	Short tau inversion recovery
T	Tesla
T1-w	T1-w-weighted
T2W	T2-weighted
TI	Inversion time
TNF-α	Tumour necrosis factor alpha
TR	Repetition time
US	Ultrasound

Summary

Rheumatoid arthritis (RA) and osteoarthritis (OA) are two chronic disease entities with variable disease course that affect the joints of millions of people around the world, and can lead to severe disability with major socioeconomic impact. In general the joint damage in both RA and OA is monitored by x-ray, even though this modality tends to show only late disease manifestations within the joint. Thus there is a need for more sensitive imaging modalities for detecting early disease manifestations, which with proper systemic and/or intra-articular (IA) treatment potentially can halt the disease progression, and prevent or retard future disability. Magnetic resonance imaging (MRI) is an established and sensitive tool that offers an unparalleled discrimination among articular soft tissues by direct visualization of all components of the joint simultaneously.

The aim of study I and II was primarily to evaluate the effect of two intra-articular drug treatments injected US guided into the wrist joint of patient with RA (study I) and secondly to examine the distribution pattern of such an injection (study II), which we suspected could be a possible explanation of treatment failure in some patients. To evaluate the treatment effect in study I, we used state of the art low-field MRI before and 4 weeks after IA treatment, and used the recommended RAMRIS scoring system by the OMERACT group to monitor the treatment changes. To track the distribution pattern within the wrist in study II, we used low-field MRI before and immediately after the US guided injection.

In short, most of the patients in study I had a significant clinical effect of a single IA injection into the wrist in both treatment groups, but neither low-field MRI nor US parameters revealed a group effect 4 weeks after treatment with either methylprednisolone or etanercept. In fact we present evidence of a significant erosive progression among the patients. This result should however be regarded with reservation due to the calculated intra-observer variation and calculated smallest detectable difference (SDD) of the erosion score, which could explain all but one of the observed patients with erosive progression. In this patient we present imaging evidence of a likely erosive progression in the hamate bone, which is, as far as we know, the first time this is presented within a time span of 4 weeks.

Nevertheless, one IA injection into the wrist joint does not seem to have a sufficient effect on the overall arthritis activity in the studied patient group and should not be used as the only treatment measure against its flares. Based on our results it may be speculated whether a relevant effect of the IA treatment requires more than one injection; in such cases experiences in larger populations remain to be obtained with glucocorticoid, etanercept and other anti-TNF-α agents.

The diversity of distribution patterns within the wrist joint among the RA patients could be an explanation of the variation in treatment responses seen after IA injections, which is supported by the fact that the distribution of contrast on MRI in study II showed a random and patient specific pattern. The degree of distribution increased with the synovitis score, while no association was found with the erosion- and bonemarrow oedema scores. Thus, injecting patients with more severe synovitis might be associated with a more complete diffusion into the wrist, possibly increasing the efficacy of the injection. The results also indicate that injection into the proximal central part of the wrist cannot be regarded as sufficient to treat the whole wrist joint in most patients. Thus based on our results we suggest that patients who do not respond clinically to IA injections in the wrist joint, could have their distribution pattern examined to clarify whether an effect might be obtained by additional injections elsewhere in the joint if the distribution of the injected drug is blocked by either anatomical variation or expanding pannus.

In any case we suggest that imaging should monitor the IA injections effect on the inflammation, using both US-Doppler and possibly dynamic MRI on short-term and conventional MRI on long-term follow-up to substantiate a true regression in disease activity and erosive arrest. This is as also recommended in a recently published study showing imaging documentation of further erosive progression 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".

In study III the aim was to test whether an i.v or an IA "delayed Gadolinium enhanced MRI of cartilage" (dGEMRIC) method could increase the SNR and CNR in the thin cartilage of the hip joint using a conventional 3D T1-w cartilage sensitive gradient echo sequence on a clinical 1.5T scanner. We found that both the i.v and IA dGEMRIC method significantly increased the SNR and CNR in the hip joint

cartilage as well as the visual delineation compared to non-enhanced images. Among the two dGEMRIC techniques the IA administration of Gd-DTPA gave an even better delineation of cartilage and significantly better SNR and CNR than the i.v. administration. In conclusion, as ultrasound guided IA therapies in the hip joint are increasingly used, our results indicate that a more exact status of the joint cartilage may easily be obtained in the same procedure by adding Gd-DTPA to the IA injection with subsequent delayed MRI. This could provide a tool to evaluate more subtle cartilage damage and may potentially be useful for a more precise monitoring of cartilage volume changes and effects of newer therapies in OA.

Danish Summary

Reumatoid artrit (RA) og slidgigt/osteoartrit (OA) er to meget almindelige led sygdomme i befolkningen, der præsenterer sig med uforudsigelige sygdomsforløb som oftest er smertefulde, og som kan medføre svær invaliditet med store sociale og økonomiske konsekvenser for personen og samfundet. Til at vurdere graden af ledskade og monitorere sygdomsudviklingen anbefaler de store internationale medicinske selskaber at bruge røntgenbilleder. Ulempen ved røntgenbilleder er at de kun viser de sene sygdomsmanifestationer i form af led- og knogleforandringer, fordi røntgenbilleder ikke kan visualisere bløddelsforandringerne. Derfor er der brug for en mere følsom metode til at vurdere de tidlige sygdomstegn i form a bløddelsforandringerne i leddet, hvormed man med målrettet systemisk eller intra-artikulær terapi kan bremse sygdomsudviklingen på et tidligt stadie og derved forhåbentlig forhindre fremtidig leddestruktion og invaliditet. Magnetisk resonans billeddannelse (MRI) opfylder kravene til et sådant billeddannende værktøj, idet MRI har etableret sig som et følsomt værktøj, der på overlegen vis kan visualisere alle bløddele i leddet på samme tid.

Formålet med studie I var at vurdere og måle og visualisere den potentielle effekt af en ultralydsvejledt injektion af to forskellige betændelsesdæmpende behandlinger i håndleddet hos RA patienter. Behandlingen blev injiceret ultralydsvejledt for at sikre en korrekt placering. Til at vurdere behandlingseffekten i studie I undersøgte vi patienterne med en "state of the art" lavfelt MR-skanner umiddelbart før den ultralydsvejledte injektion, samt 4 uger efter og anvendte det internationalt anbefalede RAMRIS score system udviklet af OMERACT gruppen..

I studie II undersøgte vi fordelingen af en sådan ultralydsvejledt injektion i håndleddet, idet vi mistænkte at fordeling i de forskellige områder i håndleddet måske kunne forklare behandlingssvigt hos nogle patienter. Igen brugte vi lavfelt MR før og umiddelbart efter injektionen til at visualisere fordelingen af injektionen.

Vores resultater viste at patienterne i studie I oplevede en betydelig klinisk bedring af deres ledsymptomer efter 4 uger uanset behandling, hvorimod hverken lavfelt MR eller ultralyd-Doppler viste en forbedring af de billeddiagnostiske parametre. Faktisk fandt vi at nogle patienter fik en forværring af deres leddestruktions (erosion) score. Dette resultat skal dog tages med forbehold idet den statistiske måleusikkerhed ved det anvendte scoresystem kunne forklare alle på nær én patients forværrring. Hos denne patient har vi MR- billeddokumentation for en sandsynlig forværret leddestruktion i en håndledsknogle, hvilket er første gang dette er synliggjort efter bare 4 uger ved brug af lavfelt MR. Uanset om den målbare effekt af forværring kan forklares af statistisk måleusikkerhed, er faktum at patienterne, trods klinisk bedring, ikke viste tegn på billediagnostisk bedring, hvorved vi må konkludere at én injektion i håndleddet hos disse patienter ikke har været tilstrækkelig til at have en effekt på de inflammatoriske parametre såsom synovitis, knoglemarvsødem, hvorfor vi må betragte patienterne som utilstrækkeligt behandlet. Vi kan på baggrund af vore resultater kun gisne om at mere end én injektion i samme håndled er nødvendig for at have en målbar effekt på betændelsesparametrene, hvilket et større behandlingsstudie med flere patienter formodentlig kan besvare.

I studie II forsøgte vi at besvare hvorledes en ultralydsvejledt injektion i håndleddet fordeler sig, når man benytter et standardiseret injektionssted som anbefalet i litteraturen. Vores resultater viste at der er stor forskel på kommunikationen mellem de mange små led der udgør håndleddet, idet vi observerede at fordelingen var tilfældig og uafhængig af alder og varigheden af RA. Fordelingen var korreleret til graden af synovitisscoren på MR, men korrelerede ikke med knoglemarvsødem- eller erosionsscore, hvilket vi tolker som at patienter med svær grad af synovitis måske har en større fordelingsgrad af behandlingen, og derfor muligvis også en bedre effekt, hvilket et studie med flere patienter og behandlings monitorering, formentlig kan afklare. Vores resultateter angiver også at man hos de fleste af vores patienter ikke kan betragte det anbefalede standardinjektionssted som tilstrækkeligt til at opnå en

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fordeling af behandlingen til hele håndleddet. Baseret på vores erfaringer fra studie I og studie II anbefaler vi at undersøge patientens håndledsfordeling hvis de ikke umiddelbart responderer på en ultralydsvejledt injektion, for at klarlægge om en mulig forklaring på den manglende effekt er at fordelingen i håndleddet er begrænset af enten en anatomisk variation eller ekspanderende betændelsesvæv (pannus). Disse patienter kan måske have effekt af flere injektioner andre steder i leddet. Endelig anbefaler vi at overveje avanceret billeddiagnostik til at monitorere effekten af injektioner i håndleddet med f.eks ultralyds-Doppler og dynamisk MR til korttidsopfølgningen og standard MR til langtidsopfølgning, for at synliggøre en ægte regression af sygdomsaktiviteten og knogledestruktionen. Denne konklusion er i tråd med et nyligt publiceret arbejde der demonstrerede billeddiagnostisk forværring af knogledestruktionen efter 1 år hos RA patienter, der klinisk var kategoriserede som værende uden sygdomsaktivitet. Forfatterne konkluderede således at "imaging assessment may be necessary for the accurate evaluation of disease status and, in particular, for the definition of true remission"(1).

I studie III var formålet at teste om to forskellige dGEMRIC metoder enten en i.v- eller en ultralydsvejledt IA metode, kunne øge signal-støj ratioen (SNR) og kontrast-støj ratioen (CNR) i den tynde hofteledsbrusk hos patienter med tidlige slidgigtsymptomer. Vi brugte en konventionel 3D-gradient ekko brusksekvens på en klinisk 1.5T MR skanner. Vi fandt at begge metoder øgede SNR og CNR i hofteledsbrusken sammenlignet med den ikke kontrastforstærkede baselineundersøgelse. Af de to dGEMRIC metoder gav IA- metoden den bedste afgrænsning af brusken samt den højeste SNR og CNR sammenlignet med i.v- metoden. Som konklusion kan dGEMRIC metoden anvendes klinisk til at forbedre signal- og kontrastforholdene i hofteledsbrusken, og i de tilfælde hvor det er muligt anbefaler vi IA- metoden, hvilket sandsynligvis vil være mulig i nær fremtid, da ultralydsvejledte IA- behandlinger i hoften benyttes i stigende grad. Ved at benytte ovenstående kliniske dGEMRIC metoder til forbedret bruskfremstilling i en MR skanner, har vi et værktøj der muligvis kan forbedre diagnostikken af mindre brusklæsioner samt formentlig kan bruges til bedre at afgrænse hofteledsbrusken hvilket muliggør en forbedring af bruskvolumen målinger der i stigende grad anvendes til at monitorere effekten af nye bruskbeskyttende behandlinger ved slidgigt.

Introduction

Rheumatoid arthritis (RA) and Osteoarthritis (OA) are two chronic disease entities with variable disease course that affect the joints of millions of people around the world, and can lead to severe disability with major socioeconomic impact. In general the joint damage in both RA and OA is monitored by x-ray, even though this modality tends to show only the late disease manifestations within the joint such as reduced joint space, erosions, ankylosis and subluxation (2). In RA x-ray erosions may develop rapidly as erosions are seen in 10-26% of patients within 3 month of disease onset and is present in 75% of patients within 2 years(3). In OA cartilage repair is poor, and as joint space narrowing is an indirect measure of cartilage degradation on x-ray, this modality is insensitive and is not ideal for early disease recognition. Thus there is a need for more sensitive imaging modalities for detecting the early soft tissue disease manifestations, which with proper systemic and/or intra-articular (IA) treatment, potentially can halt the disease progression and prevent or retard future disability.

With the introduction of magnetic resonance imaging (MRI) in clinical practice during the 1990's, MRI has been extensively used to investigate, diagnose, follow and monitor the evolution as well as the treatment effects in both RA and OA. Compared to x-ray, MRI offers an unparalleled discrimination among articular soft tissues by direct visualization of all components of the joint simultaneously. Over the last decade MRI has contributed to a better understanding of both RA and OA, and is today considered an important and invaluable tool in both research protocols as well as in clinical management of both diseases.

When I started the studies of this thesis the following was known:

High-field MRI of the small joints of the hands and feet was a safe, sensitive and accurate method for detection of synovitis and bone erosions in joints compared to the classical x-ray examination in patients with RA(4-6). In fact, MRI showed signs of bone erosion a median of 2 years before it appeared on x-rays(7). MRI also provided valuable information regarding bone marrow oedema in bone near the joint, and bone marrow oedema could be used as a prognostic marker for disease progression and future bone erosions in the hand and feet(8;9). In addition it was shown in a previous study at the Parker Institute, that both low (<0.5T) and high-field (>0.5T) MRI could outline bone erosion, joint synovitis, joint

effusion and bone marrow oedema (10). The image quality seemed to be comparable, but cost and patient acceptance indicated that low-field MRI might replace high-field MRI for clinical routine examinations(10-12).

In OA of the knee, bone marrow oedema had also shown to be a predictor of progress(13), and compared to x-rays, MRI allowed the knee joint to be evaluated as a whole(14) and could be useful in imaging cartilage abnormalities. Cartilage thickness was considered an important parameter for the evaluation joint damage and high-field MRI was expected to be the best method for accurate cartilage measurements, however, MRI still had limitations because of insufficient signal to noise ratio (SNR) and problems regarding quantification of cartilage volume (15), especially in joints with thin cartilage such as the hip joint (16;17). When we started the studies, research had also indicated that "delayed Gadolinium enhanced MRI of cartilage" (dGEMRIC) approximately two hours following intra-venous (i .v) Gadolinium and subsequent T1-mapping could image the early and subtle molecular changes of the glycoseamineglycan content in the cartilage on high-field 1.5 T MRI scanners(18-20). The clinical impact of this method has been debated in several papers but further investigations regarding clinical application as well as optimal magnetic field strength was needed(18;19;21-23). In addition, no group had published the use of the dGEMRIC technique to increase the signal to noise (SNR) and contrast to noise (CNR) in the cartilage of the hip joint by use of a clinical T1-w 3D cartilage sensitive sequence, nor was it known whether an IA approach gave superior cartilage visualization compared to the standard i.v method.

In conclusion the focus of this thesis was to use MRI for monitoring of IA injections. Thus we used low-field MRI to monitor the treatment effect and the distribution pattern of IA- injected drug in the wrist joint of patients with RA, and finally we used high-field MRI to test a novel dGEMRIC approach to increase the SNR and CNR of the hip joint cartilage.

This thesis was based on the following hypotheses and aims:

Hypotheses

- Low-field MRI can visualize synovitis, bone marrow oedema and erosive destruction in the wrist joint and demonstrate a regression of disease activity 1 month after IA therapy in patients with RA.

- Injecting drugs ultrasound- guided into the proximal part of the wrist joint of patients with persistent RA using one standard injection site provides an even distribution of the drug to all the joint compartments.

- IA Gadolinium will improve the clinical evaluation and possible quantification of cartilage using the dGEMRIC technique in patients with hip OA.

Aim

The aim of this study was to:

1. Use low-field MRI to evaluate and score the synovial changes, bone marrow oedema and bone erosions according to the OMERACT RAMRIS criteria in the wrist joint of patients with RA before and 4 weeks after IA therapy.

2. Use low-field MRI in a double-blinded study to monitor the treatment effect 4 weeks after either IA glucocorticoid or IA etanercept injected into the wrist joint of patients with RA.

3. Use low-field MRI to investigate the compartmental and spatial distribution pattern after injection of an ultrasound guided IA drug solution in the wrist joint of patients with persistent RA.

4. Apply a new dGEMRIC method for increasing the SNR and CNR in cartilage imaging of the hip joint in OA patients

5. Compare two dGEMRIC methods for improving clinical cartilage imaging of the hip joint using either i.v (indirect) or IA (direct) administration of Gadolinium (Gd-DTPA) contrast.

Ethical considerations

MRI is without ionising radiation and repeated examinations of joints with either inflammatory or degenerative diseases is therefore safe. However, some safety considerations are to be taken as mentioned in the MRI section. Placebo treatment was not used in the treatment study I, because patients

with active RA disease receiving placebo over even as short a period as 6 month may develop irreversible damage to their joints as seen in previous studies (24;25). Approval from the ethical committee was granted to the randomized treatment studies I and III. We did not seek approval from the local ethical committee in study II due to the fact that this was a pilot study. We found no ethical conflict in study II since a clinical indication of an IA injection in the wrist joint was present in all cases, and the use of IA Gadolinium is a recommended technique for joint arthrography. In all studies the patient received full information about the procedures and we had a written agreement of participation. The patients were also informed that they could withdraw from the studies at any time.

Background

MRI in general:

It is beyond the scope of this thesis to describe the basic principles of the MRI technique, as this has been described in more than 100 textbooks and has been discussed in more than 10 academic theses from Denmark. In the following it is assumed that the basic principles of MRI theory are known, as I will discuss the aspects of pulse sequence choice in joint imaging.

Generally 3 types of sequences are used in clinical musculoskeletal imaging, being spin echo (SE), gradient echo (GRE) and inversion recovery.

Spin Echo(SE) sequences

The spin-echo sequences are the oldest type of sequence and properly still the most used in MR imaging of the joints(26). In SE sequences, a 90° pulse flips the net magnetization vector into the transverse plane(27). As the spinning nuclei go through T1, T2, and T2* relaxation, the transverse magnetization is gradually dephased. A 180° pulse is applied at a time equal to one-half of TE to rephase the spinning nuclei. When the nuclei are in phase coherence, an echo is observed and read. Sequences that have a relative short TR and relative short TE are used to obtain T1 weighting (T1-w) in the images. Those with a long TR and short TE result in proton-density weighting and when both the TR and the TE is long, T2

weighting (T2-w) is achieved(27). In general T1-w images best depict the anatomy due to high signal to noise, and, if Gadolinium contrast is used, they also may show enhancement of the pathologic entities by reducing the T1 value and the relaxation time. However, T2-w images or the STIR (see below) provide the best depiction of disease, because most tissues involved in a pathologic process have a higher water content than normal, and the fluid causes the affected areas to appear bright on T2-weighted and STIR images (27;28). With the introduction of MRI, SE sequences were time-consuming and therefore not used frequently. However, advances in MR imaging- and computer technology enabled a reduction in acquisition time with the use of fast or turbo SE that uses several echoes to make the image within the same TR. Thus image time is reduced by a factor equal to the number of echoes used, which makes this sequence type more suitable in clinical practice (27).

Short tau inversion recovery (STIR) sequences

In STIR sequences, an inversion-recovery pulse is used to null the signal from fat. The inversion recovery sequence is an SE sequence in which a 180° preparatory pulse is applied to flip the net magnetization vector 180°, in order to null the signal from a particular entity like fat. When the RF pulse ceases, the spinning nuclei begin to relax. When the net magnetization vector for fat passes the transverse plane (the null point for that tissue), a 90° pulse is applied, and the SE sequence then continues as before with a 180 degree pulse at TE/2(27;28). The interval between the 180° pulse and the 90° pulse is the inversion time (TI). TI for fat is usually 140-170ms in high-field MR scanners(28) and approximately 80-100ms in low-field scanners(10), and at that TI, the net magnetization vector of fat is very weak, so when the vectors are flipped by the 90° pulse, there is little or no transverse magnetization of fat, so that no signal is generated at the echo time and fat appears dark. The other tissues exhibit signal intensities from low to high in tissues with a stronger net magnetization vector such as water(27;28). The STIR sequence thus provides excellent depiction of bone marrow oedema, which may be the only indication of an occult fracture or an indication of more aggressive disease in RA and OA(8;9;13). In addition the STIR sequence is not affected by magnetic field inhomogeneities (27), which is a huge advantage in low-field MR scanners, where they are the only usable fat suppression sequence, as spectral fat suppression is

not possible due to a reduced spectral separation between water and fat which restricts the ability to perform frequency selective fat suppression(27).

Gradient Echo (GRE) Sequences

Recently GRE type sequences have been introduced in musculoskeletal imaging and are being increasingly used. In a GRE sequence, an RF pulse is applied that partly flips the net magnetization vector into the transverse plane (variable flip angle)(27;28). Gradients are then used to dephase (negative gradient) and rephase (positive gradients) the transverse magnetization and because gradients do not refocus field inhomogeneities, as the 180^0 pulse does in the spin echo experiment, GRE sequences with long TE's are T2* weighted rather than T2 weighted(27;28). The use of gradients to de- and rephrase the transverse magnetisation along with the lower flip angles (typically 15-65) makes the GRE sequences very fast compared to the conventional spin-echo sequence, mainly because the repetition time TR is markedly reduced (27;28) . This also enables the making of 3D volume scans with isotropic voxels within a reasonable time frame and still achieving high image quality (28;29). Furthermore 3D GRE sequences also make it possible to reduce the slice thickness to sub-millimetre resolution which is an advantage when looking at small structures, such as small erosions in the bones of patients with RA, compared to the typical slice thickness of 2-5 millimetre used in the 2D spin-echo sequences(28;29).

Low-field MRI

The E-scan® (Esaote®, Genoa, Italy) 0.2T MRI scanner which we used in study I and II, is a low-field extremity scanner with a permanent magnet that has MR qualities and physics similar to those of conventional whole-body systems. It is designed with open access to the imaging volume, which allows examination of not only the distal extremities, but also the shoulder and hips in children and small adults. The permanent magnet poles are located above and below the table, making it a vertical field scanner, and the table can be positioned around the magnetic pole, which helps with a more comfortable patient positioning. The main advantages of extremity MR scanners compared to whole-body, high-field scanners are lower purchase and maintenance costs, low weight, and ease of installation in a limited

space, making them suitable for in-office and emergency room installation(30). Another advantage of extremity scanners is that claustrophobic patients and children, who may otherwise require sedation, tolerate them better(10;30). Finally the disease entity may be occult on x-ray, such as is the case in numerous musculoskeletal injuries and diseases such as subchondral bone injuries, bone marrow infections and inflammatory joint diseases. A delay in treatment can thus occur if MRI is not applied, and as the capacity of high-field scanners is limited, the low-field equipment might fill in this place in the future(30).

The main disadvantage of low-field scanners is that the image quality is reduced compared to whole-body, high-field scanners, mainly due to a poorer SNR. In general, SNR, contrast, and resolution increase with field strength and the literature has suggested that in order to compensate for the increased SNR in low-field scanners, the voxel volume and/or acquisition time must be increased (30). Increasing the voxel volume by increasing the slice thickness or the FOV makes the detection of signal abnormalities more difficult secondary to reduced spatial resolution. 3D imaging can improve the SNR compared to 2D techniques, however, the longer acquisition times can lead to an increased risk of patient motion and hence reduced image quality, even though the movement artefacts are less problematic in low-field imaging(30). Additional factors, such as RF penetration, optimized pulse sequences, and improvement in coil design and sensitivity also play a crucial and significant role in the SNR benefit at different field strengths(31). Hence the newer generations of low-field MR scanners have improved in many of the mentioned factors, especially with the introduction of optimized fast spin echo- and gradient echo sequences as well as improved coil designs, low bandwith technology and long gradient echoes which can be noticed in the image quality that is significantly better today than 10 years ago(30;32). Care must be taken to not compensate for the inherently poor SNR at 0.2T with voxel dimensions that are too large to provide adequate spatial resolution for evaluation of joint structures. Thus sequence optimization and protocol improvement are still mandatory when the scanner is installed, but after such a calibration low-field scanners today produce images of diagnostic quality, even though the images are subjectively noisier compared to high-field(30;32). As previously mentioned another major disadvantage of low-field imaging is the reduced spectral separation between water and fat, which restricts the ability

to perform frequency selective fat suppression. Fat suppression is an invaluable technique in musculoskeletal imaging because it is used to demonstrate bone-marrow pathology and increase the contrast between Gadolinium enhanced tissue and adjacent fat in high-field imaging. An alternative method to suppress fat signal, which can be performed by low-field scanners, is the STIR sequence that is extremely useful for demonstrating bone marrow oedema. Unfortunately the STIR sequence is incompatible with Gadolinium enhancement, thus MR arthrograms and contrast-enhanced studies have, in theory, a reduced diagnostic value on low-field scanners, mainly due to lack of a robust T1-fat-suppressed imaging sequence (32).

In musculoskeletal MRI, the CNR is also a clinically relevant parameter because it determines the extent to which adjacent structures can be distinguished from one another (33) but compared to the SNR, the CNR is more dependent on imaging parameters and not as strongly dependent on field strength, which make this parameter less compromised in low-field imaging (34;35).

Rheumatoid arthritis (RA)

RA is a chronic inflammatory joint disease with an unpredictable course (36). In two thirds of the cases, RA begins with symmetric arthralgia and arthritis in the small joint of the hands and feet, and the disease process can lead to severe skeletal changes and destruction of the affected joints(37), thus RA has a great impact on all aspects of life due to the joint- related symptoms as well as general malaise and tiredness. As no pathognomonic test exists for RA, the disease is a "syndrome" diagnosis based on case history, clinical signs, laboratory abnormalities and x-ray manifestations. The classification criteria for RA along with therapeutic recommendations were published by the American College of Rheumatology (ACR) in 1988(38) to define a more uniform group of patients, The RA criteria have made the diagnosis RA more specific, but even though these criteria are still not diagnostic, they are generally useful since they help to ensure a uniform patient group for comparing experiences and treatment results between countries and clinical treatment centres.

The actual consensus of RA treatment involves early onset of disease modifying anti-rheumatic drugs, DMARDs (39;40) with supplementary IA drug therapy with glucocorticoid in target joints not

responding to systemic treatment (41). The IA glucocorticoids are well tolerated, however, the effect varies considerably from a few months to a year (42;43). In the ACR criteria, x-ray of the joints is considered the standard reference for detecting and quantifying the erosions in RA, while x-rays cannot reliably detect changes in the synovial membrane (44), x-rays tend to show the late disease manifestations, and as the synovial changes are believed to precede the erosions because the synovial changes are seen in patients months to years before an erosion develops(45;46), early detection of inflammatory joint changes is crucial for guiding the treatment strategy. Hence there is a need for more sophisticated imaging modalities capable of accessing the soft tissue changes. The need for a change in imaging strategy is also supported by the introduction in recent years of new biological drug treatments such as systemic anti-tumor necrosis-factor alpha (anti TNF-α) (ex. etanercept (Enbrel®)). These drugs have shown promising results and have revised the treatment strategy in patients with RA (47), but as the drugs are very expensive, there is a need for more sensitive imaging modalities that can access the early inflammatory treatment response. But even with these potent and effective drugs, IA treatment is still necessary in joints with aggressive forms of the disease that do respond to the systemic treatment. The drugs are either the traditionally known glucocorticoids or, on experimental basis, anti-TNFα(48). IA treatment in wrists has recently been evaluated with ultrasound(US)-Doppler at the Parker Institute(43) and the safety aspects of IA injections of anti-TNF-alpha (etanercept) in the wrist joint of patients with RA have also been investigated at the Parker Institute(48). A randomized study comparing the clinical outcome 4 weeks after ultrasound guided IA injection of either glucocorticoid or etanercept in several joints has been published (49), showing that the patient receiving glucocorticoid had a better clinical outcome regarding pain, joint swelling and clinical evaluation compared to etanercept.

Course of the disease

The clinical presentation is heterogeneous with a wide spectrum of age at onset, degree of joint involvement, and severity. At the onset of symptoms it is difficult to predict which patients will follow a more severe disease course though various predictive parameters have been indicated.

Suggested predictors of poor outcome are a large number of joints involved, poor functional status, the presence and a high titre of rheumatoid factor (RF), a low haemoglobin level, a high platelet count, elevated erythrocyte sedimentation rate (ESR) and/or c-reactive protein (CRP) level, already present bone erosions on x-ray(50) and bone marrow oedema on MRI(8;9). A positive RF is associated with the development of erosions (51;52), and patients with RA who remain RF negative have better prognosis than those who are positive(53;54).

Laboratory tests

More objective measures of clinical status and disease activity are the laboratory tests. In RA it is the acute phase proteins and the RF that are of interest.

CRP is part of the acute phase response, which means that it increases at least 25% in plasma concentration after inflammatory stimuli (55). Its production in the liver is stimulated by the cytokines interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) derived from the inflamed synovium. CRP increases very rapidly over hours as part of the acute response , peaks in 2 to 3 days and in contrast to the erythrocyte sedimation ratio (ESR)it may return quickly to baseline (55). It has been shown to reflect disease excercabations and remissions (56) and is therefore suitable for the estimation of disease activity and treatment response – especially when measured sequentially. Due to the high sensitivity and amplitude CRP is the choice of acute phase proteins in rheumatology. It is however important to note that the CRP reflects the sum of the disease from all involved joints which synthesize it, and that it is an insensitive marker for local flares in a single joint.

RF is included as one of the classification criteria made for RA. It is an antibody against the Fc-part of the immunoglobulin M. However, not all RA patients have elevated RF and it may occur in the absence of RA. With sufficient stimulation in e.g. chronic infections, any individual may develop RF and the specificity of the test is low. Elevated RF is present in other inflammatory diseases like mixed connective tissue disease and systemic lupus erytomatosus and elevated levels are also present in 3-5% of the normal population and the frequency increases with age. Nevertheless subjects with RF have a 40-

fold risk to develop RA(57) and of those subjects developing RA the age of onset is associated with the prevalence of circulating RF(58).

Joint assessment

A joint with disease activity is defined by the presence of tenderness on pressure, pain on passive movement and/or swelling other than bony proliferation (59). Soft tissue swelling is detectable by palpation along the joint margins and fluctuations are characteristic features and may influence the range of joint movement. Joint tenderness is present by pressure and passive movement of the joint by the examiner. The maximum pressure to elicit tenderness should be exerted by the examiner's thumb and index finger sufficient to cause whitening of the examiner's nail bed (60).

In the estimation of the disease activity the ACR recommend an evaluation of 68 joints for tenderness and 66 for swelling (the latter not including the hips) but a reduced 28 joint count was suggested by H.A. Fuchs and colleagues in 1989(61) for evaluating easily accessible joints commonly affected in RA. The 28-joint count has been shown to correlate to the 66/68 joint count when assessing changes in relation to therapy (62).

The clinical assessment of joint swelling and tenderness may be either qualitative (presence or absence of swelling) or quantitative (graded from 0-3) and inter-observer agreement depends on which type of assessment is used. The inter-observer agreement for the qualitative joint assessment has been shown to be better than the quantitative joint assessment (63), but the quantitative joint assessment improves the reliability of the joint assessment in measuring disease activity (64). The joint assessment should be performed by the same assessor because the intra-observer variation is low (65), even though this is rarely the case in clinical practice. The inter-observer variation is high(59), but may be improved with training(66).

Other measures of disease activity

The tender and swollen joint assessment is supplemented by several other measures of disease activity. The functional status may be evaluated by questionnaires, most commonly applied as the health

assessment questionnaire (HAQ) (67). In early arthritis the inflammatory symptoms are the main predictors of physical disability, and in late stage RA the joint destruction may be more important, both indicated by the HAQ (68). As an objective measure of performance of the RA patients, isokinetic muscle strength measurements have been applied in several studies (69) and the HAQ score has been shown to correlate with isokinetic muscle strength in a longitudinal study(70).

The severity and duration of morning stiffness is recorded in minutes. A quantitative assessment of pain on a 100 millimetre (mm) visual analogue scale (VAS) and patient and physician global assessment of disease activity are all useful parameters to follow during the course of the disease (71).

Treatment

Treatment of RA aims at preventing, reducing, or at least retarding the destructive processes that lead to joint destruction and impaired function. Optimal management of the disease does not only require early diagnosis but also timely introduction of drugs that reduce the probability of irreversible joint damage(40). To prevent joint destruction, disease modifying anti-rheumatic drugs (DMARD) such as methotrexate (MTX), sulphasalazine, anti-malaria drugs, oral glucocorticoids and more recently leflunomide and TNF-α blocking agents such as infliximab and etanercept are used. MTX is the most commonly employed DMARD therapy, and is also the first choice in patients with high disease activity whereas patients with low disease activity are more likely to receive sulphasalazine or anti-malaria drugs and then MTX if the treatment fails (72). Recently the TNF-α drugs have changed the treatment strategy, especially in patients that do not respond to the traditional DMARDs, as the drugs have been shown to control inflammation and retard destruction (73-75). In conclusion early initiation of therapy, and rapid disease control is considered important as the destructive process can be quite rapid and detectable on x-rays after only a few months (76-78). In clinical practice the joint count, pain and global disease assessment play a prominent role in determining whether a treatment change is needed (79).

IA treatment

Despite successful systemic DMARD and/or TNF-α treatment, local joint flares often occurs, in which case, IA treatment with glucocorticoids have become a mainstay of the rheumatologist's armamentarium

(80) in order to reduce the possibility of systemic adverse effects, since it was proposed by Hollander in the 1950s(81). One or a few injections in the same joint can improve the patient's clinical condition significantly by decreasing joint pain and swelling and lead to improved function. The effect varies from patient to patient but may last up to years (42) although the repeated long-term use can cause adverse effects(82). In addition IA treatment with betamethasone and oral methotrexate seems to halt the erosive progression on radiographs in patients with early RA and a poor prognosis (80). In parallel to the use of IA glucocorticoids, anti-TNF-α medications have also been successfully used intraarticularly, although the response to this treatment has varied (83;84), and the knowledge and experience concerning the treatment effect is still limited.

The correct placement of the needle for IA injections have been a matter of concern (85) because only about half IA injections are performed into the right structure, but US- guided IA injections can help to overcome this problem(86).

Clinical remission

There are several sets of criteria (EULAR, ILAR, WHO and ACR) for defining clinical remission in RA, but the studies of this thesis have used the criteria suggested by the ACR which include six signs and symptoms being 1) duration of morning stiffness not exceeding 15 minutes 2) no fatigue 3) no joint pain by anamnesis 4) no joint tenderness or pain on motion 5) no soft tissue swelling in joints or tendon sheets 6) erythrocyte sedimentation rate <30mm/hour for female and <20mm/hour for male(71;87)

The wrist joints articulations:

The wrist joint is a complex multi-compartmental joint, which often displays local disease flares in patients with RA, thus there is a need to understand the anatomy of the joint in order to properly evaluate the treatment procedure and imaging findings.

The wrist is composed of six articulations, from proximal to distal including: 1) The distal radio-ulnar joint, 2) the radio-carpal joint, 3) the intercarpal joint, 4) the piso-triquetral joint, 5) the four ulnar carpo-

metacarpal joint and finally 6) the trapezio-carpal joint(88). From arthrographic studies of the wrist joint approximately 10% of the of the "normal" population in the 3rd decade have communication between the radio-ulnar and the radio-carpal joint which raises to approximately 50% in the seventh decade(89). Communication between the radio-carpal and inter-carpal joints is seen in approximately 40% of scapholunate- and 55% of luno-triquetral articulations in randomly chosen cadavers older than 40 years (90). Despite the anatomical knowledge of the wrist joint as comprised of several synovial cavities with variation in communication, there is a longstanding assumption in rheumatology, especially concerning RA, that an injection of drug into the standard site (radio-carpal joint) will distribute into all relevant joint cavities of the wrist (91) due to destruction of the anatomic boundaries by the disease processes in RA.

In MRI studies of the wrist joint in rheumatology, the joint is usually defined as comprised of 1) the radio-ulnar joint, 2) the radio-carpal joint, 3) the inter-carpal joints and 4) the four ulnar carpo-metacarpal joints(92) (figure 1).
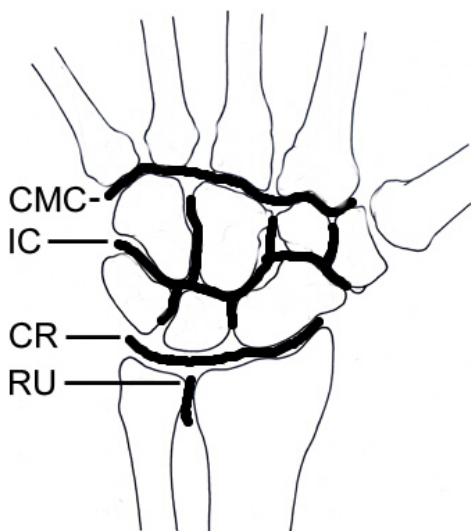
Figure 1

The wrist joint in RA MRI studies is defined as:

RU: the distal radio-ulnar joint, CR: the radio-carpal joint, IC: the inter-carpal joints and CMC: the four ulnar carpo-metacarpal joints.

(The drawing is presented by courtesy of Søren Torp-Pedersen, The Parker Institute)

Imaging modalities in RA

X-ray in RA

The imaging modalities used in rheumatology aim at providing the clinician with objective measures of disease activity/severity by the use of qualitative and quantitative parameters.

X-ray is the gold standard imaging in rheumatology for evaluating joint damage, and is still part of the classification criteria in RA(38). It may be used to define erosive damage in RA as well as progression

of the disease over time, and x-rays also serve as an invaluable tool in terms of differential diagnoses such as psoriatic arthritis that show distinct features on the x-ray, which can be helpful in making the correct diagnosis especially in patients with unspecific/unclassified arthritis. X-ray in RA demonstrate bone erosions, joint space narrowing as an indirect sign of cartilage thinning or loss, juxta-articular osteoporosis, bone cysts, or in late stages of disease joint subluxation, malalignment or ankylosis(93). However, the soft tissue changes that precede the bone changes are not visible (44) which is one of the major disadvantages of this imaging modality, thus, more sensitive modalities in term of soft tissue visualisation is recommended. Another disadvantage of X-ray is the use of radiation. X-rays of the hands and feet are commonly obtained in the posterior-anterior (PA) view but alternate radiographic views of the hands are recommended (e.g. the Nørgaard view(94)). However, the latter requires specific positioning which affects the reproducibility(93).

Several scoring systems, based on the PA view, are currently in use in the assessment of joint destruction in a semi-quantitative way. The three most used methods are the Sharp method (95), the Sharp/van der Heijde modification (96) and the Larsen method(97;98).

The Sharp method considers 17 areas for erosion and 18 areas for JSN in each hand/wrist. Each erosion scores one point, with a maximum of five points for each area (reflecting loss of more than 50% of either articular bone). Erosion scores range from 0 to 170. For JSN, one point is scored for focal joint narrowing, two points for diffuse narrowing of less than 50% of the original space, and three points if the reduction is more than half of the original joint space. Ankylosis is scored as four. (Sub)luxation is not scored. The score for JSN ranges from 0 to 144.

In 1989, van der Heijde modified the method described by Sharp in 1985. Erosion is assessed in 16 joints for each hand and wrist, and six joints for each foot. One point is scored if erosions are discrete, rising to 2, 3, 4, or 5, depending on the amount of surface area affected where complete collapse of the bone is scored as 5. The score for erosion ranges from 0 to 160 in the hands, and from 0 to 120 in the feet where the maximum erosion score for a joint in the foot is 10. JSN is assessed in 15 joints for each hand and wrist, and six joints for each foot. JSN is combined with a score for (sub)luxation and scored as follows:

0 = normal; 1 = focal or doubtful; 2 = generalised, less than 50% of the original joint space; 3 = generalised, more than 50% of the original joint space or subluxation; 4 = bony ankylosis or complete luxation. The score for JSN ranges from 0 to 120 in the hands and from 0 to 48 in the feet.

The Larsen score was developed in 1974, and is based on a comparison with a set of standard films. It differentiates six stages from 0 (normal) to 5, reflecting gradual, progressive deterioration, and provides an overall measure of joint damage in 15 joints of the wrist and 10 joints of the feet (this method was modified several times between 1974 and 1995). In 1995, Larsen devised a method to evaluate radiographs in long-term studies. The main differences from the original are deletion of scores for the thumbs and 1st MTP; subdivision of the wrist into four quadrants; deletion of soft tissue swelling and osteoporosis; distinction between erosions of different sizes. The grading scale ranges from 0 to 5: 0 = intact bony outlines and normal joint space; 1 = erosion less than 1 mm in diameter or JSN; 2 = one or several small erosions (diameter more than 1 mm); 3 = marked erosions; 4 = severe erosions (usually no joint space left and the original bony outlines are only partly preserved); and 5 = mutilating changes (the original bony outlines have been destroyed). The score ranges from 0 to 160.

The scoring systems have been validated in many clinical trials. In North America, the Sharp's method has been used extensively, whereas the Larsen method or the Sharp/van der Heijde method(96) has been used frequently in Europe. The Sharp/van der Heijde method, in contrast to the Larsen method, includes the feet in the joint assessment and has a better sensitivity to change while considerably more time-consuming(96).

The advantages of x-rays are that it requires simple, readily available x-ray films that are inexpensive. In addition it is the only recommended imaging modality in the ACR criteria and they have shown to be reproducible for clinical trials. With the current digital imaging technology the x-rays are obtained digitally and stored in PACS for convenient retrieval and re-analysis (99). However, considerable inter-observer variation must be taken into account (100) especially when dealing with multicenter trials, and the introduction of digital images with a significant lower image resolution compared to the classical x-ray and mammography films might change the sensitivity of the erosion detection.

MRI in RA

Since the first pilot study was published in 1988(101) comparing MRI to conventional x-rays in the wrist joint of RA patients, more than 200 publications using MRI in wrist RA have been published according to MEDLINE. When we started the work of the thesis, it was known that MRI was the non-invasive imaging modality of choice for visualisation of the inflamed synovium in patients with RA(9;102). MRI could also provide the possibility for detection of volume changes and changes in contrast enhancement following anti-inflammatory drug treatment(103;104). Furthermore, MRI was shown be a sensitive non-invasive method for detection and quantification of bone erosions, and is the only modality able to detect bone marrow oedema which is a predictor of future bone erosions (8). In fact bone marrow oedema was recently shown to reflect true bone marrow inflammation (105).

In the beginning of my thesis it was discussed whether MRI erosions were true erosions. However, a recent publication from 2006 by Dohn et al have settled this question by showing that MRI erosions can be considered true erosions when compared to computed tomography (CT) as the reference(106). In addition McQueen et al have published in 2006 evidence that erosions seem to start in the bone marrow through an inflammatory release of cytokines stimulating osteoclasts to resorb bone(107), which contribute to the understanding of the still unsolved controversy regarding the cause and effect relationship between synovitis and bony changes(108) in RA.

Low field MRI of the wrist and hand in rheumatology

With the introduction of extremity dedicated low-field (<0.5T) magnets there has been an interest in comparing the diagnostic performances of these patient friendly scanners to the existing high-field scanners. The low-field scanners are especially suited for the patient group with peripheral joint diseases, because the imaging in high-field scanners requires uncomfortable patient positioning compared to the low-field magnets. A study from our institution by Savnik et al(10) has shown that low- and high-field MRI showed a comparable number of erosions and number of joints with synovitis, which has also been confirmed by several groups (11;12;109). In fact it has been reported that low-field imaging reveals more erosions than high-field images, and the reason for this is still not clear, but coil selection choice of

pulse sequences and patient positioning in the high-field scanners have been suggested (109). High-field MRI is properly still the most used modality in research settings (6;103;110) although low-field publications has increased in the last couple of years(4;111-113).

For bone marrow oedema there are only few published studies comparing low- and high-field, and the most cited of these are the study by Ejbjerg et al(12) concluding that low-field MRI performed markedly poorer compared to high-field, but these data are based on images from an early generation of low-field scanners (Arthroscan®, Esaote) and a 1.0T (Impact®, Siemens) scanner. Hence a study with blinded comparison between a state of the art low- field and high-field MR scanner is needed, to reveal if this is still the case with today's technological improvements(114).

We used a state of the art low-field MRI scanner in study I and II of wrist RA for several reasons. 1) The scanner was readily available in our institution 2) The scanner had very high patient compliance which especially was mandatory in study I that included two MRI scan within 4 weeks and 3) The literature supported the image quality of the low-field scanner to be comparable to the images from high-field scanners in terms of diagnostic quality.

Sequence selection for joint imaging in low-field scanners:

Selection of optimized protocols and sequences for RA is mandatory especially in low-field dedicated MR scanners, that suffer from lower SNR compared to high-field scanners, in order to obtain the best possible signal and contrast between the different tissues. In the wrist joint, most groups recommend starting with a STIR sequence or a fat-saturated T2-w sequence (only high-field scanners) in the coronal plane for bone marrow oedema detection, followed by a 3D isotropic T1-w turbo gradient echo sequence; or a T1-w spin echo sequence in the coronal and axial plane before and after contrast for detection of erosions and synovitis. The isotropic 3D gradient echo sequence has the advantage of subsequent reconstruction in the orthogonal plane, why one can omit a scan plane and thus save time in the scanner (10-12).

Impact of Gadolinium contrast in synovitis scoring

Gadolinium contrast is mandatory for quantification of the synovial inflammation in RA in order to differentiate the enhancing inflamed synovium from the surrounding tissues and possible effusion. In addition a recent publication has shown that a double standard-dose of Gadolinium (0.2ml/kg) significantly increases the subsequent synovitis score in low-field scanners, compared to a standard single dose (0.1ml/kg).

OMERACT (Outcome measures in rheumatoid arthritis clinical trials)

The OMERACT group consists of several international experts from the field of rheumatology and musculoskeletal radiology that are working with MRI as an outcome measure in clinical trials, and who since the first publication in 1999 have been very active and published more than 20 papers (according to MEDLINE) regarding the use of MRI in RA. The group has contributed to most of the "corner-stones" in the field such as publication of a valid and reproducible RAMRIS (RA MRI score) scoring system along with basic recommendations of MRI sequences selection (115) and have introduced a reference atlas for scoring the key parameters; synovitis, bonemarrow oedema and erosions in the wrist and MCP joints (92;116). The recommended basic MRI sequences are: T1-w images before and after contrast in two orthogonal planes for erosion and synovitis scoring along with either a fat-saturated T2-w image or a STIR sequence for bone marrow oedema assessment (115). According to the RAMRIS score the degree of synovitis is scored on a scale from 0–3 for every examined joint area depending on an arbitrary grading of the synovitis from no synovitis over mild, moderate to severe (worst imaginable). Erosions are graded on a scale from 0-10 with intervals of 10% volume involvement, and bone marrow oedema is scored on a scale from 0-3 with intervals of 33% volume involvement. Long bones are scored to a depth of 1cm from the articular surface.

In Denmark the group is represented by professor Mikkel Østergaard, dr. Bo Ejbjerg and colleagues, and recently the group has suggested a scoring system for evaluation of both tenosynovitis and psoriatic arthritis (117;118).

In conclusion there are several advantages of MRI in RA as it provides a potential for whole joint tomographic assessment with high image quality in any plane, as well as discrimination and assessment of the soft tissue structures including the intra-articular and periarticular tissues without potentially harmful radiation. In this context MRI a safe and ideal tool to follow-up on treatment responses, and especially erosive progression, as no harmful radiation is applied. MRI is also the only modality that can access bone marrow oedema and the introduction of 3D MRI sequences with isotropic voxels (voxels with equal size in all directions), have also made it possible to reduce scan time due to the possibility of multi-planar reconstruction (MPR) without loss of image quality, which can increase the throughput of patients in the MR scanner. Finally, as the MRI technology relies on digital images, these are easily stored in Picture Archiving System (PACS) for convenient retrieval, re-analysis and quick sharing across hospitals and country borders.

The use of MR in RA is restricted by some patient-related circumstances like claustrophobia, pacemakers, pregnancy in the first trimester, existing alloplastic implants that destroy the image quality due to metallic artefacts etc. The imaging procedure may also be hampered by uncomfortable positioning of the patient especially in the high-field scanners, while this problem is overcome by the use of dedicated low-field extremity scanners (10) or the newly developed "midfield" (0.6-1.0T) open scanners. When compared, high-field MRI provides better image quality than low-field MRI; however, this does not necessarily translate into greater diagnostic power (30;32) as has been shown in the case of RA. The current literature has demonstrated a high diagnostic value of low-field scanners for musculoskeletal pathologies (30), but large well-designed comparative studies quantifying the clinical impact, efficacy, cost benefit and diagnostic capabilities of low- and high-field imaging are still needed in most clinical musculoskeletal applications (30;114). In general, the experience and training of the reader is likely to impact the interpretation of the images, thus low-field musculoskeletal MR images are probably best read by radiologists with experience from low-field systems.

Regardless of scanner field strength, more technical limitations of MRI in RA are availability, cost issues and the fact that MRI is also restricted to make contrast enhanced imaging of only one area that can fit in the scanner's field of view (FOV) due to the washout period of the Gadolinium contrast agent

of approximately 24 hours, impairing multiple contrast enhanced joint assessments/examinations on the same day.

Ultrasound in RA

Within the past decade, musculoskeletal US has become an established imaging technique for the diagnosis and follow-up of patients with rheumatic diseases (119;120). US is most commonly used in the assessment of soft tissue changes or the detection of fluid collections (121), but has also proven able to detect erosions in RA both actual changes and development over time (122).

Most musculoskeletal US is performed using grey-scale US, but newer US techniques include the use of colour- or power Doppler, which may be used in the assessment of vascularisation of the tissue as may occur in inflammatory conditions (123). So far, no standardised scoring methods have been developed, while guidelines for grey-scale US have been suggested (124).

The advantages of US are its non-invasiveness, portability, relative inexpensiveness, lack of ionising radiation, its repeatability and its ability for rapid "real-time" dynamic examinations of multiple joints in multiple planes at one sitting. US may also be used for guidance for aspirations, biopsy and injection of IA treatments – ensuring correct placement of the needle (125), and finally US has the advantage that with proper training the treating physician can perform the examinations. The most prominent disadvantages of using US are the intra- and inter-observer variation, and the lack of spatial orientation (126).

Osteoarthritis (OA)

OA is a common disease entity covering a group of chronic, non- inflammatory joint disorders with cartilage destruction, and may be regarded as a common joint failure that can be induced by disease entities of different aetiologies (127). Thus the development of OA seems to follow a common complex pathway with gradually evolving disease manifestations, including decreasing water content, degradation of cartilage matrix components, collagen fibers and glucose-amino-glycans (GAG))(128;129). The

process is irreversible due to the poor repair potential of the hyaline cartilage tissue, whatever the underlying aetiology (130).

OA is a major cause of morbidity and disability in the elderly and OA is the most common form of arthritis, affecting millions of people; approximately 70% of a population over 65 years (131). The incidence of hand, hip, and knee OA increases with age, and women have higher rates than men, especially after age 50, with knee OA showing the highest incidence compared to hand and hip(132). Hip OA is representing the second highest incidence next to knee (132). Before the age of 50, men have a higher prevalence and incidence of OA than women, presumably due to secondary changes after trauma, while after the age of 50 women have both a higher prevalence and incidence (133).

No international agreement has been reached regarding a common definition of OA, but it is generally accepted that the disease processes involves cartilage destruction, bony changes in the subchondral zone, and loss of function(134)

Several risk factors for OA development have been reported such as obesity (135), heredity (136), malalignment(129), cruciate ligament injuries(137), meniscal tears(138), Legg-Calvé-Perthes(139), congenital hip dislocation(140), slipped epiphysis(141), certain occupations like jobs with prolonged or repeated knee bending(142) and hip fractures(143). However, data from epidemiological studies are often difficult to interpret due to confounding factors and selection bias. Odds ratios representing increased risk of OA are usually modest, and generally associated with wide confidence intervals.

Classification and grading

Classification of this multifaceted joint disorder has to embrace the great disparity and is often the result of a consensus. Overall OA is classified into a s*econdary* form with a known trigging factor; e.g. trauma, congenital/developmental, metabolical or endocrine diseases; as opposed to an *idiopathic* or primarily OA of unknown source (144). The latter may be subdivided into a localized form, involving one joint, and a generalized form involving three or more independent areas(145).

Treatment

Current treatment strategies for OA include both non-pharmacological, pharmacological, and surgical interventions (146;147). Weight reduction with a sustained weight loss seems to be the best non-pharmacological treatment with moderate pain relief and functional improvement (148).

The medical treatment in OA mainly consists of various formulations of painkillers and supplementary therapy with glucocorticoids during painful inflammatory flares/reactions. Since no disease modifying drugs yet have been developed for improving the quality of the cartilage, all current recommended treatments aim at reducing symptoms, but do not have any direct impact on the continuing degradation of the cartilage. Currently there is an ongoing debate regarding treatments that can slow down or even halt the disease evolution and thus spare the cartilage. In this context the use of oral formulations of glucosamine and chondroitine sulphate have in some studies shown a beneficial effect on clinical as well as x-ray parameters in early and moderate cases of OA(149), but a recent meta-analysis published by the Cochrane group has concluded that there is yet no evidence to conclude a general effect of these substances(150). IA therapy has also been advocated in OA with hyaluronic acid(151) as well as glucocorticoids(152) however the efficacy of these IA drugs, especially hyaluronic acid is debated(153;154). Finally surgical treatment is regarded as the last treatment option with total joint replacement being the most radical one(147).

Course of OA

Disease progression characteristically is slow, occurring over several years or decades. At onset symptoms can be very subtle, morning joint stiffness may be the only early sign present, as the disease progresses, pain becomes more prevailing and is often the main reason for an OA patient to seek medical attention. Initially pain occurs during activity but can be relieved by rest, at this state usually no clinical signs of inflammation are present. Depending on which joint is affected the specific clinical picture can vary. In most cases the range of joint motion is gradually decreasing as a consequence of changes in bone formation, including formation of osteophytes. Ultimately malalignment and bony enlargement of

the affected joint may occur. Pain can become a permanent feature and even resting pain is typical in advanced hip OA.

The natural course of OA, without treatment, is diversified both in time and amplitude. OA pain in the hip joints may diminish or stagnate over time, often at the price of decreased range of motion (155) whereas in other joints like the knee, worsening both in function and pain can be overall intolerable. There is, however, casuistic evidence of reversibility in both symptoms and radiographic changes (156), leading to the assumption that the existence of a Disease Modifying OA Drug could become a reality (157). In conclusion since the disease evolution is slow, there is a need for sensitive imaging modalities and/or biomarkers to reduce the sample size in future studies evaluating potential disease modifying drugs.

Imaging modalities in OA

X-ray grading

In 1957 Kellgren and Lawrence (K&L) were the first to systematically use radiographic changes to asses the severity of OA (158). By combining the four characteristic features of OA and the subsequent deformation of subchondral bone, a four step grading scale was developed for the major sites involved. (Table 1)

Table 1	K&L grades of severity of osteoarthritis of the hip(158)
Grade 1	Possible narrowing of joint space medially and possible osteophytes around femoral head.
Grade 2	Definite narrowing of joint space inferiorly, definite osteophytes and slight sclerosis.
Grade 3:	Marked narrowing of joint space, slight osteophytes, some sclerosis and cyst formation and deformity of femoral head and acetabulum.
Grade 4:	Gross loss of joint space with sclerosis and cysts, marked deformity of femoral head and acetabulum and large osteophytes.

The K&L score has limitations, wherefore numerous modifications have been suggested (159;160) and the more recent overall grading of the hip OA emphasizes joint space narrowing, as the most common and prominent feature of the radiographic changes(161). Which of the published scoring systems should be regarded as the more valid is still to be clarified, nevertheless intra- and inter-reliability seem to be comparable(162). In the present study III, the K & L grading was chosen as one of the inclusion criteria as recommended in studies of hip OA (163).

MRI in OA

MRI is regarded as the most powerful soft tissue and joint imaging modality, and bone marrow oedema has been shown to be a predictor of worsening in knee OA (13), and compared to x-ray, MRI offers unparalleled discrimination among articular soft tissues by direct and tomographic visualization of all components of the knee joint simultaneously, allowing the knee joint to be evaluated as a whole organ. Thus MRI in OA can reliably image pathology such as; osteophytes, bone marrow oedema, sub- and periarticular cysts, meniscal tears, ligament abnormalities, synovial thickening, joint effusion, intra-articular loose bodies, and has been shown useful in imaging cartilage abnormalities (14;164;165).

MRI of cartilage

MRI provides the possibility for direct chondral imaging with the potential for evaluation of the regional thickness as well as the water content and cartilage matrix compositions throughout the joint (23;165). Most MRI data of cartilage imaging are derived from studying the knee, while similar good results regarding accuracy, sensitivity and specificity to cartilage lesions cannot be reproduced in joints with thinner cartilage such as the hip joint (16;17). In the past static two dimensional (2D) MRI using conventional T1-w- and T2-w spin echo sequences, did not provide accurate visualization of joint cartilage when compared to arthroscopy (166). Hence new 2D turbo spin-echo and three dimensional (3D) gradient echo MRI cartilage sensitive sequences were developed, which has increased the accuracy for surface evaluation and thickness measurements. However, no consensus regarding examination technique has yet been derived, although several have been suggested (23;167;168). Even though the

sensitivity regarding cartilage lesions detection has increased with the introduction of new cartilage sensitive sequences, there are still limitations regarding visualization of the early and subtle degenerative or traumatically induced cartilage alterations, as supported by a thorough review from Radiology in 2003 stating that: "Except for full-thickness lesions, the role of MR imaging in detecting articular cartilage defects has not been well established. Especially for lesions that are limited to half of the cartilage thickness, the diagnostic accuracy of MR imaging seems poor. We performed a MEDLINE search of articles on MR imaging of knee cartilage, but among the articles that we found, we considered the patient population, grading systems, definition of disease, and regions studied as too heterogeneous to justify a meta-analysis. Thus there is a need for new imaging techniques visualizing the molecular processes within the cartilage (169). Several molecular imaging methods have been suggested like "magic angle" effect of T2 (Xia Y 2002 MRM) and "diffusion tensor imaging"(170) Assuming these methods mostly reflect the collagen architecture and breakdown, T2-diffusion and magnetization transfer that seem to be sensitive to the molecular structure and concentration of both collagen and the glucoseamino- glycan (GAG) content, but all of these techniques that may play a role in the future are not used often due to technical limitations and reproducibility issues. The most used technique for cartilage composition measures in OA are "T2 mapping" (171), "T1-rho mapping"(172) and "dGEMRIC"(23). T2 mapping is a promising and obvious candidate for measuring cartilage composition, since the T2 value is sensitive to many of the interesting aspects of the cartilage such as tissue architecture and hydration as well as molecular structure and concentration, but this novel parameter is not fully understood, and the clinical value is still debated since the T2 value in longitudinal studies have shown little or no change over time. More importantly, the T2 value seems to differ only a little between the OA and control groups, and one study could not find T2 value differences in the different stages of OA (173).

The newest parameter suggested for cartilage composition imaging is the T1-rho mapping technique that seems to reflect and correlate to the GAG and the collagen concentration, but which might be most affected by the collagen concentration. Even though this parameter is regarded as a sensitive marker for cartilage disease, understanding it is challenging, as many components within the cartilage affect the

measured values, which makes interpretation difficult. Other aspects in T1-rho measurements are the hardware requirements, the long examination times and radiofrequency power deposition, which all together limit the clinical use.

dGEMRIC

The most promising technique to date, although time-consuming, is the dGEMRIC method of intravenous (indirect) delayed MR arthrography and T1-relaxation mapping of the cartilage. The technique has been shown to indirectly image the content of GAG within the cartilage, and has already been investigated in several in-vitro as well as in-vivo studies(18-21;174;175). The technique is based on the fact that the GAGs are negatively charged, therefore, if a charged MRI contrast agent such as GdDTPA^{2-} (Magnevist®, Schering) is given time to passively distribute in the cartilage, it will distribute in inverse relationship to the GAG concentration. Because the GdDTPA^{2-} distribution in cartilage is reflected in the MRI parameter of T1, T1 imaging in the presence of GdDTPA^{2-} can be used as an index of GAG concentration (174;175). Evidence supporting this assumption comes from an in vitro study showing that delayed Gadolinium-enhanced MRI of cartilage can be used to follow GAG replenishment over time in degraded cartilage in culture(174). Several in vivo clinical studies have shown the clinical feasibility of the technique on 1.5T(19-21;165). The only problem with the technique on 1.5 Tesla, is the fact that it is time- consuming with relatively long patient- time in the MR scanner, and that it also requires a time- consuming post- processing step in a separate computer with a dedicated software program. Thus clinical applications of the method are currently being tested on 3T MR scanners, with promising preliminary results regarding reduction in imaging time, along with increased signal to noise ratios and joint coverage.(176;177).

In a study of patients with hip dysplasia, the GAG concentration in cartilage was significantly lower in the symptomatic hips than the asymptomatic, even though the cartilage thickness was the same on both sides, which was interpreted as an immaturity of the cartilage in the dysplastic hip, and which could be a possible explanation of the early development of hip OA in these patients (20).

The technique behind dGEMRIC relies as mentioned on the passive diffusion of Gadolinium into the cartilage driven by a concentration gradient from outside the cartilage, which is counteracted by the negative charge in the cartilage. In other words Gadolinium will diffuse into the cartilage over time and thus also have a delayed washout from the cartilage. In theory this can be used to selectively increase the signal to noise ratio within the cartilage, which can be detected and visualized by a T1-w sequences such as the newly developed 3D T1-w spoiled gradient echo cartilage sensitive sequences. We tested this hypothesis in study III in order to investigate whether clinically delayed cartilage imaging, using either an i.v. injection (as most groups do) or an IA injection, can overcome the problem of low sensitivity for macroscopic changes and low signal to noise ratios in the very thin cartilage of the hip joint. Our hypothesis was supported by a recent in-vitro experiment (178) showing that dGEMRIC increases the detection threshold of early cartilage lesions in the patellar cartilage. To our knowledge no data have been published prior to our study III of the in-vivo use of the dGEMRIC method for better cartilage delineation in the hip joint.

Future studies will hopefully determine the place of all these interesting parameters, and because several tissues are involved in the OA disease entity, most of these measurements might be needed. Thus the future challenge will be to develop imaging protocols that can retrieve the different parameters in the same session within a reasonable scan time.

Material and methods

Patients

All patients in the three studies were recruited from the outpatient clinic, Department of Rheumatology, Frederiksberg Hospital. The patients in all studies (I, II and III) were unselected representing the standard patient group and the treatments were standard in the department, apart from the extra imaging investigations.

The 25 RA patients included in study I were the subgroup with wrist joint involvement from a larger randomized controlled double-blinded trial of the clinical effect of IA etanercept compared with methylprednisolone(49). These patients had a therapy resistant wrist joint, which in the opinion of their

treating physician demanded an IA injection. The injections were all given guided by ultrasound to ensure the correct IA placement of the drug in the wrist. The needle was placed in the proximal radio-carpal row according to published standards (figure 3)(179). Demographics and baseline characteristics are given in study I (appendix I).

In study II, another group of 17 patients with active RA according to the ACR criteria were enrolled. As in study I, these patients had wrist arthritis resistant to the systemic treatment, and the clinician referred them to an ultrasound guided IA injection of methylprednisolone, which is a standard within the Department of Rheumatology. Demographics and baseline characteristics are given in study II (appendix II). In study II, the wrist joint was defined according to published standards for MRI studies (92) (figure 1). In study III, 5 male and 5 female patients, otherwise unselected, were studied. All 10 patients had radiographical signs of hip OA in slight to moderate degree (grade 2-3) according to the K &-L score(158) and presence of hip pain. These patients were all participants in an ongoing study of hip IA injection therapy (154).

Clinical evaluation:

In the beginning and in the end of study I the following clinical observations were recorded:

All patients described the degree of wrist pain on a 100mm VAS and filled in the HAQ questionnaire. The same independent clinician, blinded to the treatment, evaluated the number of tender and swollen joints (28-joint count), which were furthermore graded 0-3 with 0 = no activity and 3=most prominent activity. The physician also filled in a subjective disease activity VAS. The DAS 28 was calculated and biochemical blood tests, including IgM and CRP concentrations, were performed.

In study II the patients were seen after 2 weeks and possible adverse events were recorded after clinical inspection of the wrist area.

In study III the ten patients recruited were participants in a larger clinically randomized study of hip OA. The clinical details of these patients were not used in our study and are described elsewhere (154).

MRI:

All MRI examinations in study I-II were performed using a 0.2 T musculoskeletal dedicated extremity scanner (E-scan®, Esaote Biomedica, Genoa, Italy). To select the most appropriate image protocol for study I and II, a pilot experiment was carried out at the Parker Institute where the potential useful standard sequences for joint assessment were first tested on a porchine phantom (a ribcage) to evaluate how the different sequences performed regarding fat/muscle/bone contrast, fluid detection, SNR, time consumption and number of acquisitions in terms of image quality. Later on, four of the sequences that proved best in the pilot experiment (3D Turbo T1-w gradient-echo, T1-w spin-echo (SE), Turbo multi-echo and T2-w contrast enhancement (CE) gradient echo) were tested on patients to evaluate the best protocol for detecting the usual pathology in RA of the wrist, such as bonemarrow oedema, synovitis, erosions, effusion and tenosynovitis. We chose the standard sequences delivered with the MRI scanner as we were not capable of writing new sequences, and based on the experiences from the pilot study, we initially used both axial and coronal T1-w spin-echo (SE) and 3D turbo T1-w gradient-echo images before and after intravenous injection of Gadolinium. When our preliminary results were analysed (data not shown) and we noted a better and more sensitive detection of the small erosions using the 3D Turbo T1-w gradient echo sequence compared to the T1-w SE sequence (figure 2), we abandoned the SE sequence from the protocol in April 2004. The main reason for choosing the 3D turbo T1-w gradient-echo sequence was that this sequence could give us sub-millimetre in-plane resolution (0.8 x 0.8) and a slice thickness of 1-1.2mm which was necessary to see the post contrast enhancement within the erosions even though there was a substantial chemical shift artefact (figure 2). The other sequences tested along with the T1-w SE all had a slice thickness of 2-3mm making visual evaluation of contrast enhancement within the small erosions difficult due to partial volume artefacts (figure 2). Testing the different sequences also revealed that multiplanar reconstruction of the 3D dataset in the orthogonal plane gave a visual insufficient image resolution regarding detection of the small erosions, because the used standard 3D T1-w turbo sequence was not entirely isotropic.

STIR   SE T1   3D T1 Turbo
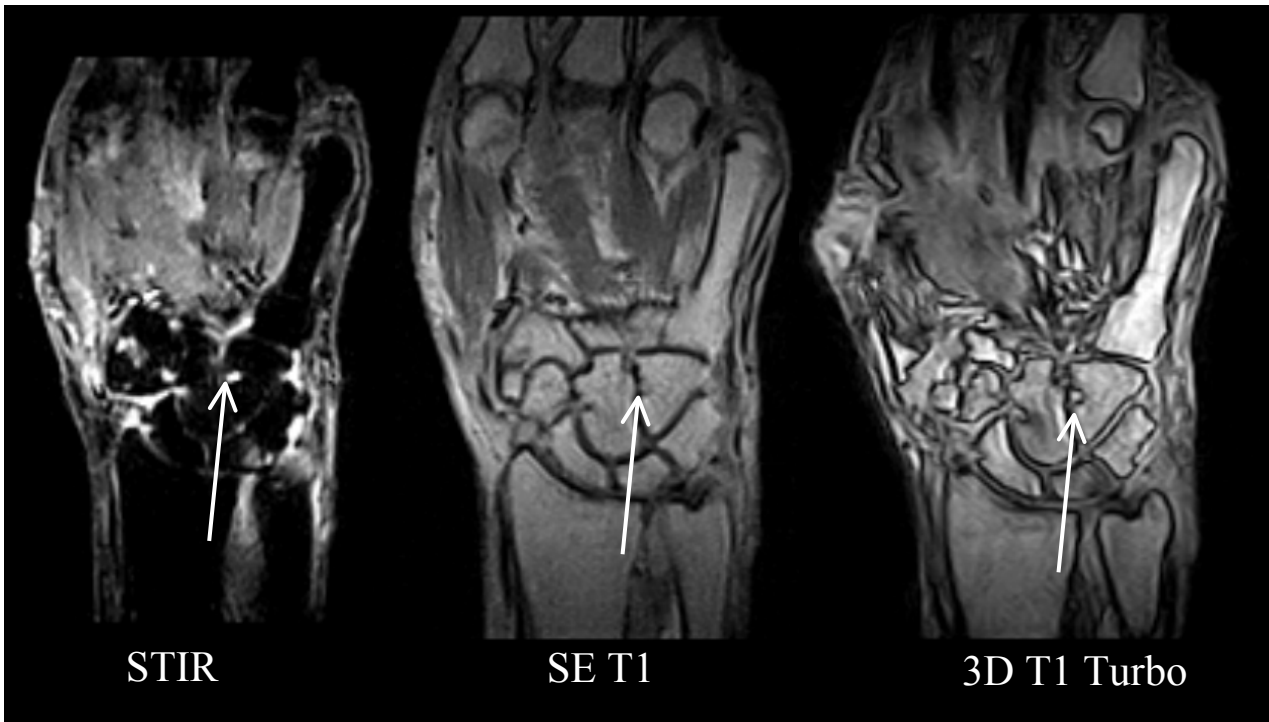
Figure 2: Sequence selection on the low-field MR scanner:
For optimal image contrast regarding synovitis and erosion detection the 3D T1 Turbo gradient echo sequence is superior to the Spin Echo (SE) T1. Note the arrow pointing at an erosion in the hamate bone visible on the STIR but best seen on the coronal 3D T1 Turbo sequence. Both T1 images are after Gadolinium contrast, note how easy contrast enhancent is detected within the erosion on the 3D T1 Turbo sequence compared to the T1 SE sequence (arrow).

Therefore we decided to continue the protocol, scanning with both a 3D T1-w turbo sequence in the axial- and in the coronal plane before and after contrast, and we used the 3D Turbo T1-w sequences for the MRI scoring in study I and II. Our findings corresponded with the observations of similar low-field MRI datasets from wrist joints in RA patients published by Ejbjerg et al in 2005(12) who found, that the 3D T1-w sequence performed much better than the T1-w SE sequence when scoring erosions. Thus we could not publish these observations, but only mention them in the article describing study I, which was accepted for publication in November 2007 in Journal of Rheumatology. Our findings are also in concordance with earlier published data regarding sequence selection(11;12;113), except that Ejbjerg et al, Taouli et al and Schirmer et al, all scanned in only one image plane with subsequent reconstruction in the orthogonal planes. In addition Taouli et al did not use i.v. Gadolinium in their study for synovitis scoring, and Schirmer et al did not use the OMERACT RAMRIS score for erosions.

Our patients were examined in supine position with the hand alongside the body. For signal collection, receiver-only cylindrical solenoid wrist coil was used. The following pulse sequences were applied:

gradient-echo scout, coronal T1-w spin-echo (TR/TE: 600/18 ms, FOV/matrix: 180 x 180 mm / 192 x 192, slice thickness 2,0 mm), coronal STIR (TR/TE/TI: 1310/24/85, FOV/matrix: 200 x 170 mm / 192 x 163, slice thickness 3,0 mm) and axial/coronal turbo 3D T1-w gradient echo (TR/TE: 38/16, FOV/matrix: 180 x 180 x 100 mm / 192 x 160 x 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. Following the Gadolinium injection, the coronal and axial T1-w 3D pulse sequences mentioned above, was repeated. Total scan time was 45 minutes. All images were evaluated on the scanner-processing console using the standard Esaote® software. The MRI data were paired and evaluated by the same independent observer in chronological order as recommended by Van der Heide et al(180) for longitudinal x-ray studies, and suggested by Haavardsholm et al(181) for longitudinal MRI studies of the wrist. The MRI observer (MB) had general MRI research experience since 2001, and dedicated low-field MRI research experience of joint pathologies since 2003. Furthermore, the MRI reader was supervised at all time during the initial reading experience by a senior expert in musculoskeletal radiology (KEJ). KEJ also performed the OMERACT RAMRIS scoring of 10 randomly chosen wrist joints before and after treatment, which were used to calculate the Intra Class correlation Coefficient (ICC) of the inter-observer variation score (see below). The disease activity was scored according to the OMERACT RAMRIS evaluation standard for synovitis, bone marrow oedema and erosions (115)and in cases of doubt, the OMERACT reference atlas was used (92). The MRI observers were blinded to the clinical, biochemical, and US data.

In study II, following the same baseline MRI examination as mentioned above, all patients had an US guided IA drug injection into the space between the central part of the radius and the lunate bone in the wrist (figure 3).

The drug solution contained 1ml Depo-Medrole® (40mg/ml), 0.5ml Lidocaine® (5mg/ml) and 0.1-0.15 ml Gadolinium (Omniscan® 0.5mmol/ml).
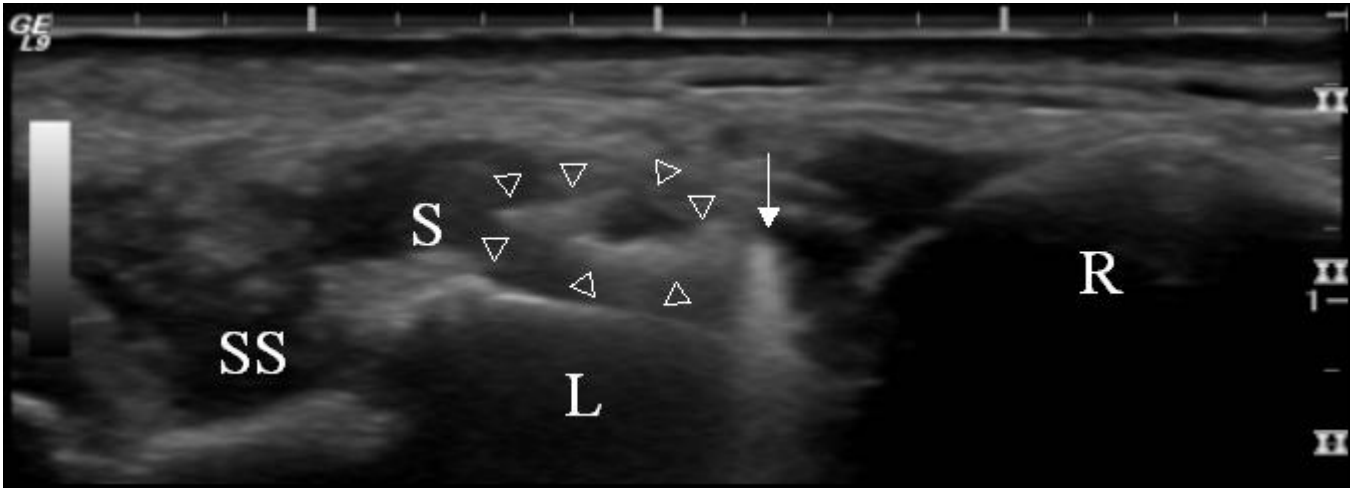
Figure 3: Ultrasound guided injection.

It is a longitudinal image with proximal oriented left. The needle tip (arrow) is seen with comet tail artefact between radius (R) and lunate (L). The injected fluid is seen as a hyperechoic cloud (arrowheads) spreading distally from the needle tip into the synovial duplication of the radiocarpal joint (S). On ultrasound, the fluid does not continue into the synovial duplication of the intercarpal joint cavity (SS). General Electric, Logiq 9 with a 14 MHz linear array matrix transducer.

Gadolinium dose:

The Gadolinium dose was chosen after a minor in-vitro pilot experiment testing different doses (0.1,

0.15, 0.2, 0.3ml Omniscan 0.5mmol/ml) of the Gadolinium compound added to 2 ml saline.

In addition we tried to use a pre-diluted Gadolinium solution of 2mmol/l (Magnevist®, Schering,

Germany) but adding 0.15 ml of this solution to the injected methylprednisolone was too low a dose to

be recognized on the subsequent MR images on both high and low field (data not shown).

The chosen dose of Gadolinium ranged from 0.1 to 0.15ml taken from a standard Gadolinium solution

(Omniscan 0.5mmol/ml), which gave good enhancement in a pilot examination and was easy to apply to

the drug solution for the clinician performing the US guided injection without prior dilution. This gave a

Gadolinium concentration of approximately 45-50mmol/l in the injected solution which is approximately

ten times higher than the recommended MR arthrography solution on low field scanners according to a

recent publication(182). The high concentration did leave room for further dilution after injection

without loosing signal, as we suspected a dilution of the injected Gadolinium due to possible existing

effusion as well as washout from the joint cavity. There was a delay of 20-30 minutes between the US

guided injection and the subsequent MRI using the 3D T1-w turbo sequence in the axial and coronal plane, in order to trace the distribution pattern of the injected drug solution. The first 5 patients were also scanned after the IA injection on a high-field MR-scanner (Philips Intera® 1.5T, Philips, Eindhoven Nederland) in order to evaluate whether low-field MRI had equal sensitivity compared to high-field MRI in tracing the distribution pattern of the injected drug. The following sequences were applied in the high-field scanner: gradient echo scout, 3D coronal and axial Gradient echo T1-w FFE SPIR with SENSE (TR/TE : 39/5.2, FOV/matrix : 150x150x100mm / 512x256x166 , slice thickness 1.5mm).

In study III the idea to use the dGEMRIC technique to obtain better cartilage images in the hip joint using the dGEMRIC technique, was developed in a case of an elderly patient referred to MRI of the hip prior to hip replacement surgery. The patient had a baseline standard MR protocol of the hip, revealing a destructed femoral head with severe cystic changes, joint space narrowing and the impression of severe cartilage breakdown (figure 4A).
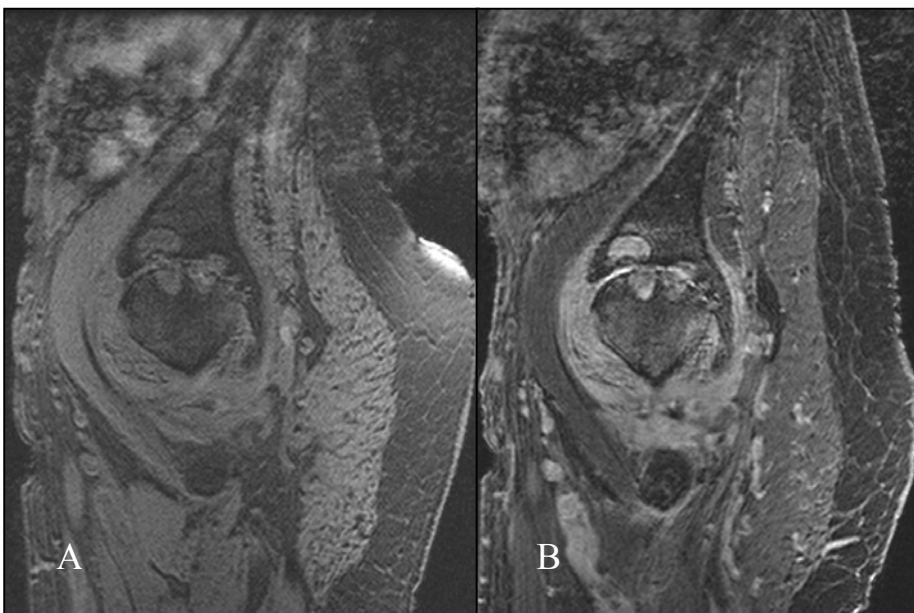
Figure 4: Hip joint imaging

Sagittal 3D SPGR T1-w cartilage sequnece before A)
And 90 min after i.v Gd-GDTPA B).

Note the profound enhancement in the remaining cartilage of the hip joint in B that is not visible in image A)

She also had a massive synovitis that seemed to displace the iliopsoas muscle. After i.v. Gadolinium the patient could not lie still due to hip pain and we had to wait approximately 90 minutes for pain relief before the post contrast images could be taken. The delayed post contrast images showed an enhancement of the remaining cartilage in the hip joint that was not visualized in the baseline images, thus confirming our hypothesis that a delayed increase in cartilage signal was possible (figure 4B).

The use of the dGEMRIC technique and subsequent scanning with a clinical 3D T1-w cartilage sensitive sequence has not been suggested before, as all previous publications using the dGEMRIC technique have been done in order to calculate T1 maps of the cartilage, and thus get an estimate of the relative GAG content within the imaged cartilage(18;19;21-23). Additionally the dGEMRIC technique in the published literature is performed using an i.v. approach based on the pioneer work by Bashir et al in Radiology 1997(175). The group developed the dGEMRIC technique when testing a double i.v. dose to a 4mmol/l IA dose in the knee joint of two patients and found no differences in performance regarding the subsequent T1 maps. Bashir et al thus concluded that a double i.v. dose should be used due to feasibility reasons.

In study III we had the opportunity to test whether an i.v. or an IA approach would perform best regarding cartilage enhancement using the fore mentioned 3D T1-w cartilage sensitive sequence. We used a standard clinical 1.5 Tesla MR scanner (Signa Exite, General Electric Cooperation, Milwaukee, Wisc, USA) for all patient examinations, applying a dedicated receive-only phase array body coil. The baseline MRI protocol used is generally accepted in the clinical setting and consisted of a conventional coronal STIR imaging (slice-thickness 5mm, TR: 4000ms, TI:150ms, TE:38ms, FOV: 380x380mm) as well as a coronal T1-w fat-saturated spin echo sequence (slice thickness of 5 mm, TR:690ms/TE:9ms, FOV 380x380mm). Following these conventional sequences, both hip joints were scanned using a standard clinical T1-w spoiled gradient echo (SPGR) cartilage imaging sequence in the sagittal plane (slice thickness of 2mm, TR:38ms/TE:6,9ms, FOV: 250x250mm, matrix: 512x512, giving a pixel size of 0.48x0.48mm) . All patients were placed in the supine position (feet first). Images were obtained using the phase-array body-coil, placed with the symphysis in the centre of the coil. All subjects were examined twice within a one-week interval and all scan parameters as well as image planes were identical throughout the study. In the first examination (the indirect MR arthrography), MRI was initially performed without contrast administration. Thereafter 0.3mmol/kg body weight (triple routine dose(183)), of the Gadolinium contrast agent Gd-DTPA (Magnevist®, 0.5mmol/ml, Schering AG, Berlin, Germany) were administered i.v.

Following i.v. Gd-DTPA the patient was asked to perform light stair walking as recommended for approximately 15 minutes within the outpatient clinic and 90-180 minutes after the i.v. Gd-DTPA injection, the T1-w MRI sequences of each hip joint were repeated.

At the second MRI examination (direct MR arthrography), MRI was preceded by injection of 2.2 ml mixture of Gd-DTPA (4mmol/l) and a drug guided by US(184). Again, the patient was asked to walk for 15 min. in the outpatient clinic and the final MRI was performed 90-180 minutes after injection.

Ultrasound

An Acuson Sequoia ® was used for all studies. This equipment was regarded as the best in its field at the time of investigations. In study I and II, the ultrasound examinations were performed according to published standards (43;184) and all examinations performed by specialists trained in musculoskeletal US. The US in study I was performed immediately prior to and on the same day as the MRI examinations, while in study II, the US was done in between the two MRIs.

The patients in study I and II were placed opposite the operator in the upright position with the hand of interest placed on a cushion, fully pronated (figure 5). The wrist was scanned on the dorsal side from side to side in the longitudinal plane and from superior to inferior in the transverse plane.
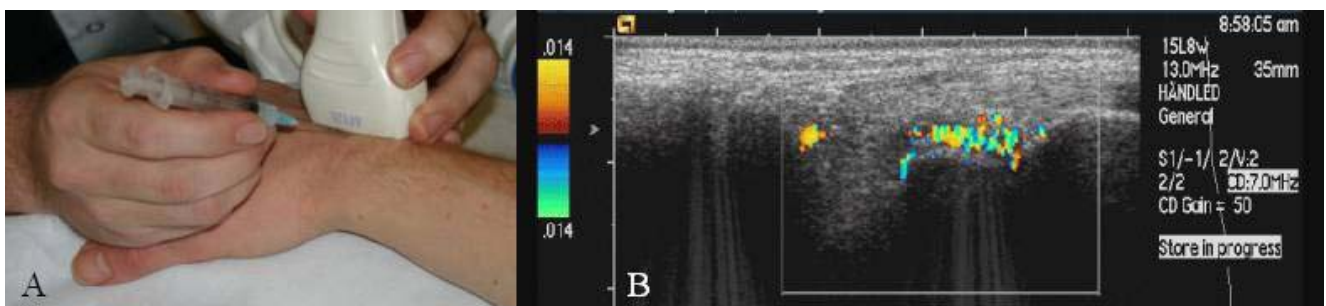
Figure 5
The US injection technique, the patient position (A) and the corresponding US image (B) illustrating how the injection is performed in the central part of the joint. This procedure ensures that the injected drug is placed inside the joint cavity in the area between the central part of the radius end the lunate bone. Note arrow pointing at the needle tip visible in the scan plane.

Quantitative estimation of the vascularisation in the synovial membrane was performed using the colour Doppler image (CDI) with maximum colour activity selected for analysis. The synovium inside the colour box was traced, thereby defining a ROI. By using a colour recognition function, the amount of

coloured pixels was then expressed in relation to the total amount of pixels in the marked ROI – the colour fraction (184).

In study III an experienced physician performed the US examination and the subsequent IA injections with the patient in the supine position and the hip in neutral position. The ultrasound scanning was made on an Acuson Sequoia ® using a 5 cm linear probe with a 14 MHz center frequency. Both depth and focus of the image were adjusted for the position of the hip joint. The joint was scanned in a longitudinal plane slightly angled to the sagittal plane and aligned with the axis of the femoral neck. In the hip joint, Doppler signals are detected very rarely (185), and we found none in the 10 patients of study III.

US guided injection

In rheumatology, a standard approach is recommend when injecting into a joint (179). For the distal radio-ulnar joint the drug injection is performed using a superior approach just medial to the ulnar styloid, or lateral to the extensor pollicis longus tendon. For the radio-carpal joint a superior approach is used entering the triangular space between the distal radius, the lunate and scaphoid bone. For the hip joint the use of imaging control (fluoroscopy or US) is recommended (186) for aspiration and/or injection into the hip, as arthrocentesis of the hip joint is technically difficult, and unless fluid is aspirated, the needle cannot be confirmed in the joint space without the use of imaging. In all cases the needle is in the correct position if it can be pushed easily to the required depth and the injection can be made with little resistance.

The US guided injections in study I and II were performed according to recommended standard from 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. The needle was inserted 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

In study III the needle (gauge 21, 0.8 x 80 mm) was inserted anteriorly 8-10 cm under the inguinal ligament towards the anterior/inferior capsule below the femoral head. By ultrasound the needle could be traced, in real time, from 1 cm below the skin surface all the way to the joint. The injection consisting of 1 ml lidocaine 1% along with the drug, 0.5-1.0 ml air and 0.2 ml saline diluted Gd-DTPA was injected

into the joint(125) The total volume of the injected solution was 2.2 ml containing a concentration of 4 mmol/L Gd-DTPA. A movie clip along with still ultrasound images of the aspiration and the injection of air, as well as the injection of the drug, was recorded as evidence of the placement.

Statistics:

The statistical analyses in all studies I-III were performed using the statistical analysis software program, SPSS® version 13 for Windows®. P-values < 0.05 were considered significant.

In study I, differences in treatment response between baseline and follow up in all the patients were tested by using Spearman's two-tailed correlation. Results are presented in table 2. The treatment effect between the two treatment groups was tested by using simple general linear models with values at 4 weeks as dependent variable, treatment as a factor (two levels), and baseline values as a covariate. Estimated marginal means derived from these models are presented in table 2. By using these models we eliminate minor differences in baseline values, allowing a difference in estimated marginal means to be an estimate of the true difference between the two groups.

As recommended by the OMERACT group in clinical treatment trials the intra-reader and the inter-reader reliability of the different OMERACT MRI scores (synovitis, erosions and bonemarrow edema) in our study were evaluated in 10 randomly chosen patients and calculated by means of the two-way mixed model, single measure intraclass correlation coefficient (ICC) for absolute values, and was calculated for both the baseline and the follow-up scores as recommended by Haavardsholm et al(181) (table 3A+3B). Scores above 0.8 is considered very good correlation as the ICC coefficient can be regarded as a kappa value.

Sensitivity to change was calculated for the intra-reader results as the smallest detectable difference (SDD) described by Bland and Altman (187) and recommended as an outcome measure in longitudinal trials with MRI scores of the wrist in rheumatology (188). The SDD represent the smallest detectable change score that within a 95% confidence interval represent a "true" change and not a measurement error (table 3A).

SDD was calculated according to the following formula:

SDD = 2 x SD ((observation $A_{followup}$ – observation $A_{baseline}$) – (observation $B_{followup}$ – observation $B_{baseline}$)

where SD = standard deviation ; observation A = score at first reading and observation B = score at second reading.

Finally the minimum detectable change (MDC) was calculated for the intra-reader results to express the SDD as a percentage of the maximum score (181)(table 3A). P values <0.05 were considered significant. For the inter reader

In the 17 patients with RA included in study II, the MR images were evaluated by two trained viewers in musculoskeletal MRI (Mikael Boesen and Marco Cimmino) using qualitative comparison between the T1-w MR images before and after IA injection, in order to detect the distribution pattern. The distribution pattern of each patient was recorded regarding distribution to the radio-ulnar joint, radio-carpal joint, the inter-carpal joints and the carpo-metacarpal joints. Spread to the tendon sheaths was also recorded. A full distribution in one joint compartment was given the value 1, partial distribution to a single joint compartment was given the value 0.5 and no distribution was given the number 0 (Table 5). A sum of the total distribution count for all 4 compartments was calculated and the relationships between the distribution sum for all 4 compartments and the OMERACT score, duration of disease, RF status and CRP concentration was calculated using Spearman's two-tailed correlation.

In study III the distribution of the results was tested, and as it was not different from a normal distribution, parametric tests were used. Baseline results were compared to i.v. and IA results using Student t-test. I.v. and IA results were standardized by dividing the ROI values with the standard deviation of the mean (SD) in each ROI, and tested using the Student t-test. Our null-hypothesis (H_0) was that there were no differences in signal intensity of cartilage between the two methods. SNR was calculated using the formula S1: N, where S1 corresponds to the mean signal of the drawn cartilage ROI and N corresponds to the mean signal intensity of the drawn ROI in the background noise. CNR was calculated using the formula (S1 - S2)/N, where S2 correspond to the mean signal intensity of the bone marrow ROI in the femoral head. For a given joint and between patients, the ROIs of the bone marrow and the background noise were identical in shape and size and were placed at the same location in all

images analyzed. SD for each drawn ROI was calculated by the Philips View Forum® software. An example of a drawn ROI surrounding the hip joint cartilage are given in figure 6.
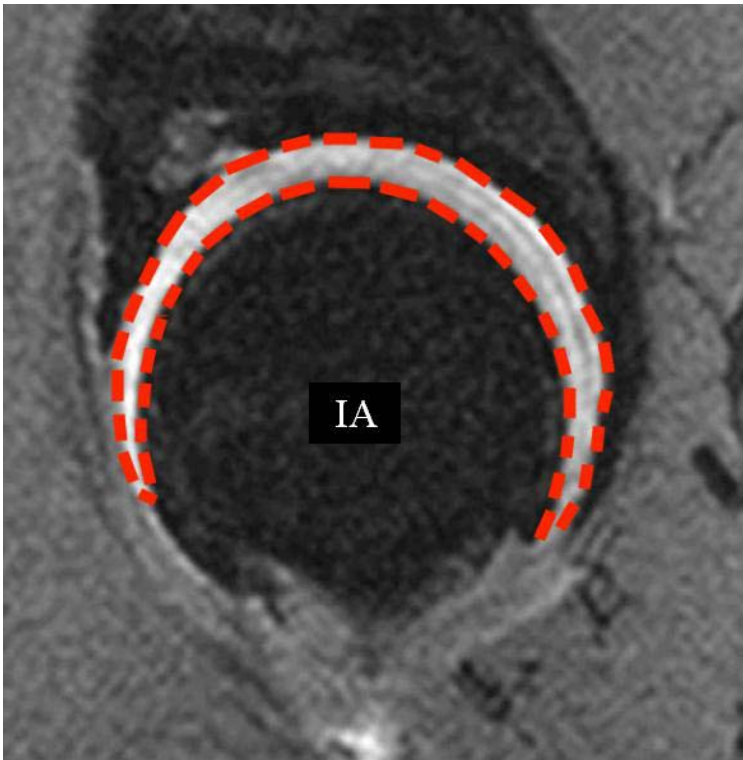
Figure 6
Example of a drawn ROI surrounding the hip joint cartilage after the IA dGEMRIC method

Results

Study 1

At baseline, the patient in the two treatment arms (Methylprednisolone and Etanercept) did not differ in demographics regarding the distribution of gender (males/females 3/22), mean age (55 years, range 22-80), mean duration of RA (7.7 years, range 1.9-30), IgM-RF positive (n=18), mean DAS 28 (4.2, range 2.1-6.6).

MRI:

According to the OMERACT reference atlas for wrist joint pathologies in RA(92), the patients had in general a mean total erosion-, and bone edema score at a rather low level and a mean total synovitis score in the midrange (table 2). No significant differences were observed for MRI scores between the two groups at baseline.

The global MRI synovitis score did not differ between the treatment groups at 4 weeks (estimated marginal mean: methylprednisolone 4.91 vs. etanercept 5.24, p = 0.4) nor did the overall response score differ from baseline to 4 weeks (p=0.52)(figure 7 and table 2).

The overall MRI bone marrow edema score was also unchanged after 4 weeks (p=0.13)(table 2) and neither were any group differences found (estimated marginal mean between groups (p = 0.1). The global erosion score increased significantly at 4 weeks in both groups (p<0.001) (table 2).

Table 2
Clinical parameters*, MRI Total OMERACT score and Ultrasound (US) score at baseline and 4 weeks follow-up in the total patient group

Mean (SD)	Baseline	4 week	P
Swollen target joint*	1.6 (0.6)	0.9 (0.8)	P < 0.001
Tender target joint*	1.72 (0.9)	0.8 (1.0)	P < 0.001
Physician VAS*	36.3 (25.1)	15.2 (15.7)	P < 0.001
Patient VAS*	43.3 (24.7)	32.2 (28.6)	P = 0.09
MRI erosion score	17.88 (8.5)	18.25 (8.6)	P < 0.001
MRI bone oedema score	4.46 (7.2)	3.71 (6.6)	P = 0.13
MRI synovitis score	5.08 (2.0)	4.96 (1.9)	P = 0.52
US color pixel fraction	0.25 (0.18)	0.19 (0.14)	P = 0.07
US resistive index	0.75 (0.13)	0.77 (0.10)	P = 0.36
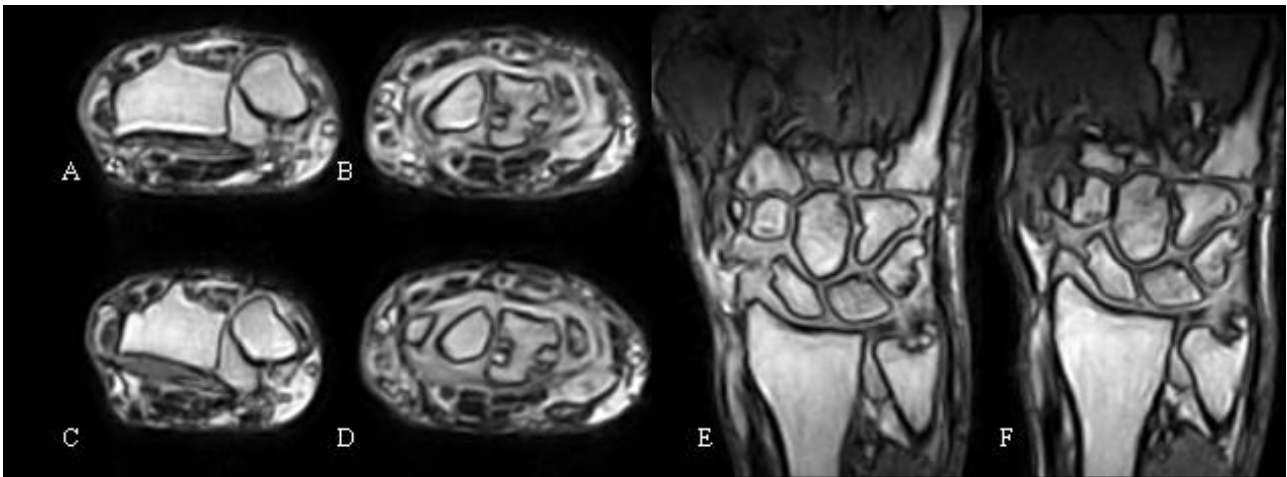
Figure 7:
MRI images of the wrist at baseline (A,B,E) and 4 weeks after (C,D,F) i.a injection of steroid. All images are post-Gadolinium. Note that the synovitis score and visible erosions are unchanged. A,C: Axial 3D Turbo T1 gradient echo image of the distal radio-ulnar joint. B,D: Axial 3D Turbo T1 gradient echo image of the intercarpal joint; E,F: Coronal 3D Turbo T1 gradient echo image of the wrist.

The ICC, SDD and the MDC for the intra-reader agreement of the different MRI scores are presented in table 3A, and the ICC for the inter-reader agreement of the MRI scores are presented in table 3B. The number of patients that showed a regression or a progression in the MRI scores before and after correction by the intra-reader SDD are presented in table 4.

Table 3A:
Intra-reader agreement of the different OMERACT MRI scores determined by a two-way mixed effect model single measures with absolute values

MRI	ICC Baseline	ICC Follow-up	SDD	MDC in %
Erosion score	0.96	0.95	1.89	4.75
Bone oedema score	0.89	0.81	2.08	9.56
Synovitis score	0.89	0.95	0.86	9.56

Table 3B
Inter-reader agreement of the different OMERACT MRI scores
determined by a two-way mixed effect model single measures
with absolute values

MRI	ICC Baseline	ICC Follow-up	ICC Change score
Erosion score	0.87	0.86	0.83
Bone oedema score	0.95	0.96	0.97
Synovitis score	0.69	0.89	0.77

Table 4:
MRI Total OMERACT score and the number of subjects with increased or decreased values at baseline
and 4 weeks before and after correction of the SDD from the intra-observer results.

MRI Mean (SD)	Baseline	4 week	No. of progressors	No. of regressors	SDD	No. of definite progressors corrected by the SDD	No. of definite regressors corrected by the SDD
MRI erosion score	17.88 (8.5)	18.25 (8.6)	8	0	1.9	1	0
MRI bone oedema 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

An example of a patient with progression in total OMERACT erosion score higher than the SDD and

with a likely erosive progression in the hamate bone is shown in figure 8A+8B.
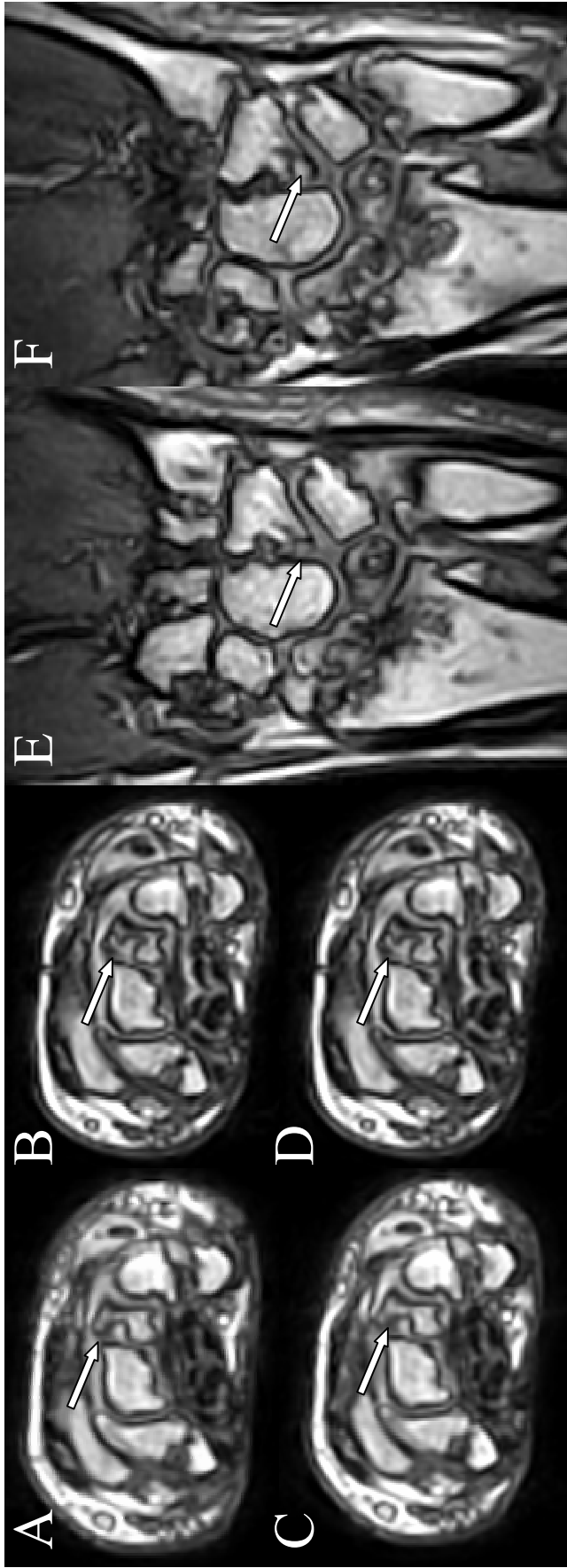
Figure 8A:

MRI images of the wrist at baseline (A,E) and 4 weeks (B,F) after i.a injection of etanercept. All images are post Gadolinium. A,B: Axial 3D Turbo T1 image of the midcarpal region. Note the arrow pointing at 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. The arrows are pointing at the same erosion in the proximal part of the Hamate bone as seen in image A and B. The synovitis score is unchanged.

Reconstructed
baseline image
taken from
figure 8A

Prox

Dist

Baseline   4 weeks follow-up
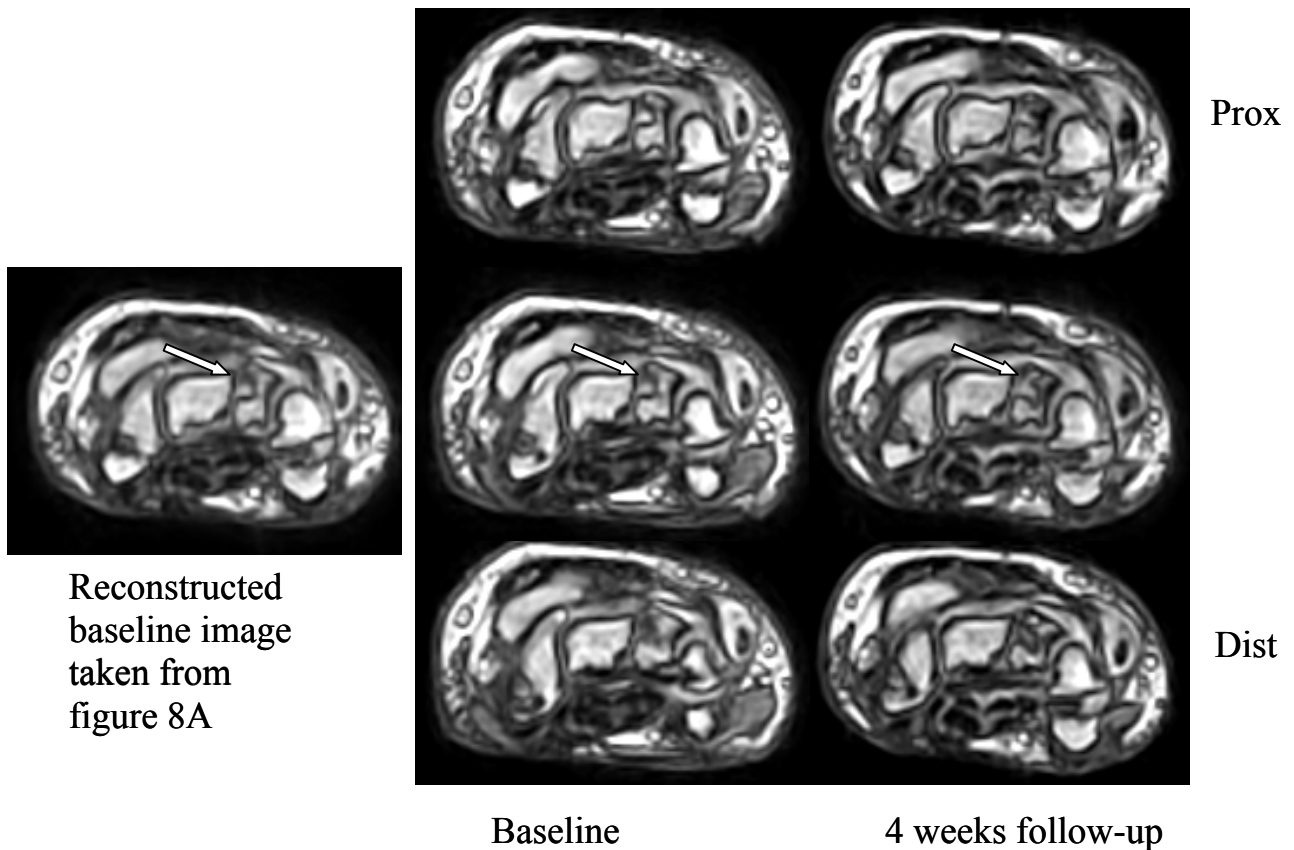
Figure 8B
This figure shows that we see a configuration change in the original data at follow-up of the erosion outlined by the arrow, which is also seen in the images above and below the scan plane presented in figure 8A We conclude that this configuration change is not likely to be either a scan plane partial volume artifact nor a chemical shift artifact as this erosion at baseline does not change configuration after reconstruction, and the fact that the configuration change is visible above and below the imageplane presented in figure 8A

Ultrasonography.

All patients had moderate to high activity on US Doppler at baseline. In general, the activity was distributed throughout the joint. In table 1 the mean colour pixel fraction and RI values of the wrists are given. There were no significant differences between the baseline measures in the two groups of patients. The US Doppler was calculated as colour 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 4 weeks follow-up (p=0.07). In addition, no significant changes were seen in resistive index (RI), which were 0.76 at baseline in both groups and 0.77 at 4 weeks (p=0.36) (figure 9 and table 2)
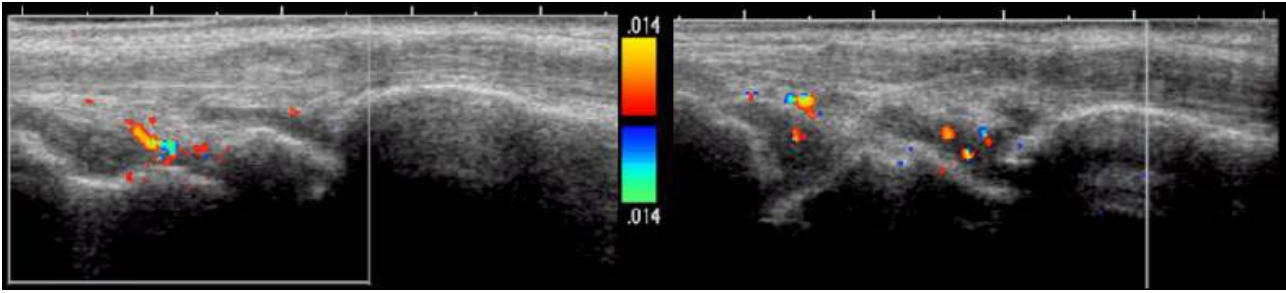
Figure 9:
Ultrasound colour Doppler image of the radial part of the wrist joint from the same patient as shown in figure 7. Note that the colour fraction is basically unchanged from baseline 0.2 (A) to 4 weeks follow-up 0.19 (B)

Clinical data:

Both groups showed a significant improvement in the clinical parameters 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 2)

Clinical vs. imaging data:

Within the two groups, the clinical- and imaging scores showed no significant correlations in the etanercept group at 4 weeks follow up, while 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 parameters (IgM, CRP, HAQ DAS 28 and VAS) did not correlate with any imaging data (MRI and US) at baseline, nor at 4 weeks follow-up.

Study II

The results from the patient evaluated treatment response, the OMERACT MRI scores and the distribution count for each patient in study II are listed in table 5.There were no differences in sensitivity, between the 5 patients examined on both high- and low-field MRI regarding the detection of the drug distribution (mean distribution score 2.4 on both modalities). We were not able to compare the OMERACT scores from the different MRI modalities, because the high-field protocol was not designed

for this purpose, as we could not give the patient i.v. Gadolinium contrast two times within the same

day.

Table 5
The OMERACT MRI scores and the distribution count for each patient

Table 1.										
The OMERACT MRI scores and the distribution count for each patient.										
Patient No.	Sum MRI Erosion	Sum MRI Oedema	Sum MRI Synovitis	D_RU	D_1	D_2	D_3	D_Flex	D_Ext	Sum Distibution
1	25	12	3	0.5	0	0	0	0	0	0.5
2	9	5	3	0	0.5	0	0	0	0	0.5
3	11	11	6	0	0.5	0	0	0	1	1.5
4	9	7	6	1	1	1	1	0	0	4
5	16	0	4	1	1	1	0	0	0	3
6	16	5	8	1	1	1	0	0	0	3
7	14	35	9	1	1	1	1	0	0	4
8	7	1	4	1	1	1	0	0	0	3
9	20	32	8	1	1	1	0	0	0	3
10	22	4	4	1	1	0	0.5	0	0	2.5
11	4	2	3	0	1	0.5	0	0	0	1.5
12	17	7	3	0	1	1	0.5	0	0	2.5
13	10	13	4	0	1	1	0.5	1	0	2.5
14	12	8	5	0	1	1	0	0	0	2
15	20	7	5	0	1	1	1	0	0	3
16	22	6	5	0	1	1	0.5	0	0	2.5
17	18	10	4	0	1	0	0	0	0	1
Mean	14.2	9.6	5.1	0.4	0.9	0.7	0.3	0.06	0.06	2.4
Minimum	4.0	0.0	3.0	0.0	0.5	0.0	0.0	0.0	0,0	0.5
Maximum	22.0	35.0	9.0	1.0	1.0	1.0	1.0	1,0	1.0	4.0
MRI : OMERACT MRI score										
D_RU : Distribution to the Radio-ulnar joint				0 = No distribution to the joint space						
D_1 : Distribution to the Radio-carpal joint				0.5 = Partial distribution to the joint space						
D_2 : Distribution to the Inter-carpal joint				1 = Full distribution						
D_3 : Distribution to the Carpo-metacarpal joint										
D_Flex : Distribution to the flexor tendons										
D_Ext : Distribution to the extensor tendons										

No universal pattern was seen in the distribution of the contrast. Only 2 patients had a full spread of

contrast to all 4 joint compartments, and the mean distribution count for all patients was 2.4 (range 0.5-

4). One patient only had contrast in the radio-ulnar joint, three patients had full or partial spread of

contrast to the proximal carpal row and 10 patients had full or partial spread of contrast to both the

proximal and intercarpal rows (figure 10-12)(Table 5).
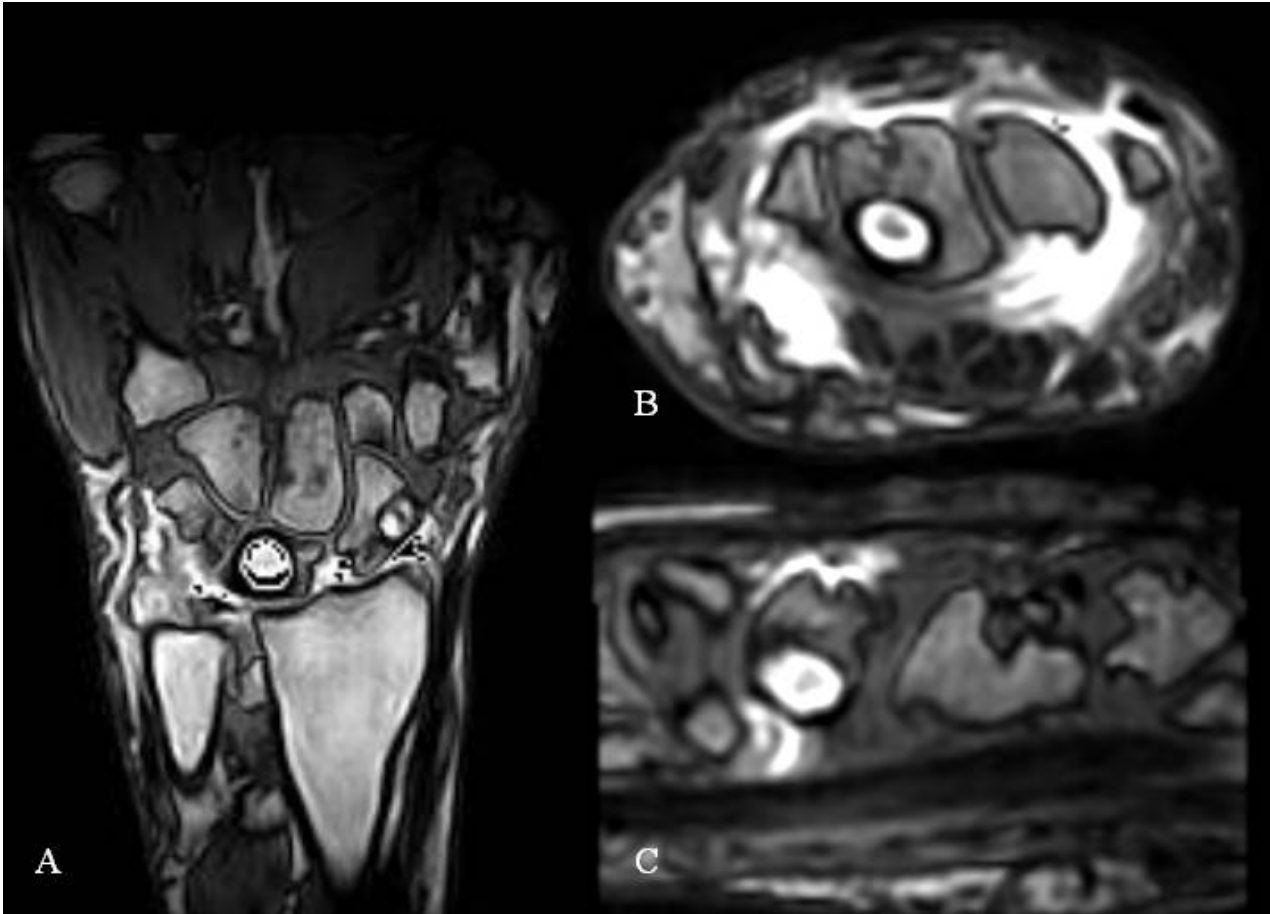
Figure 10: Distribution to the radio-carpal and radio-ulnar joint compartments

Coronal (A) and axial (B) and reconstructed sagittal (C) Turbo 3D T1 gradient echo images after IA treatment. This patient is an example of distribution to the radio-ulnar joint and the radio-carpal joint. Note that pannus tissue seems to block further spread of the Gadolinium contrast to the more distal parts of the wrist joint. Note that the large erosion in the lunate bone is well-filled with the contrast agent giving a possible T2 effect in the image.
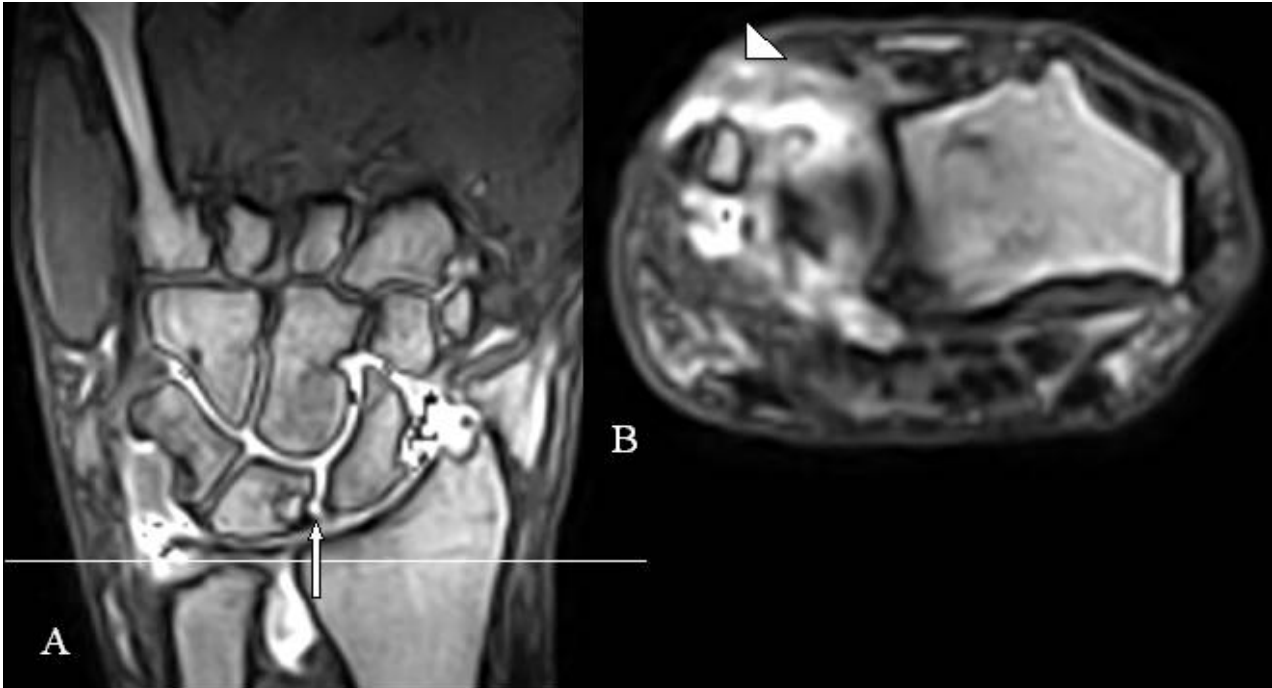
Figure 11: Distribution to the radio-ulnar joint, the radio-carpal joint and the inter-carpal joints.

Coronal (A) and axial (B) Turbo 3D T1 gradient echo images after i.a. treatment. This patient is an example of distribution to the radio-ulnar joint, the radio-carpal joint and the inter-carpal joints. Note the arrow in (A) pointing at a disrupted intrinsic carpal ligament between the lunate and the scaphoid bones, compared to an intact ligament between the lunate and the triquetrum. The line in (A) indicates the image level in (B), where the arrowhead points at the skin penetration of the ultrasound guided injection.
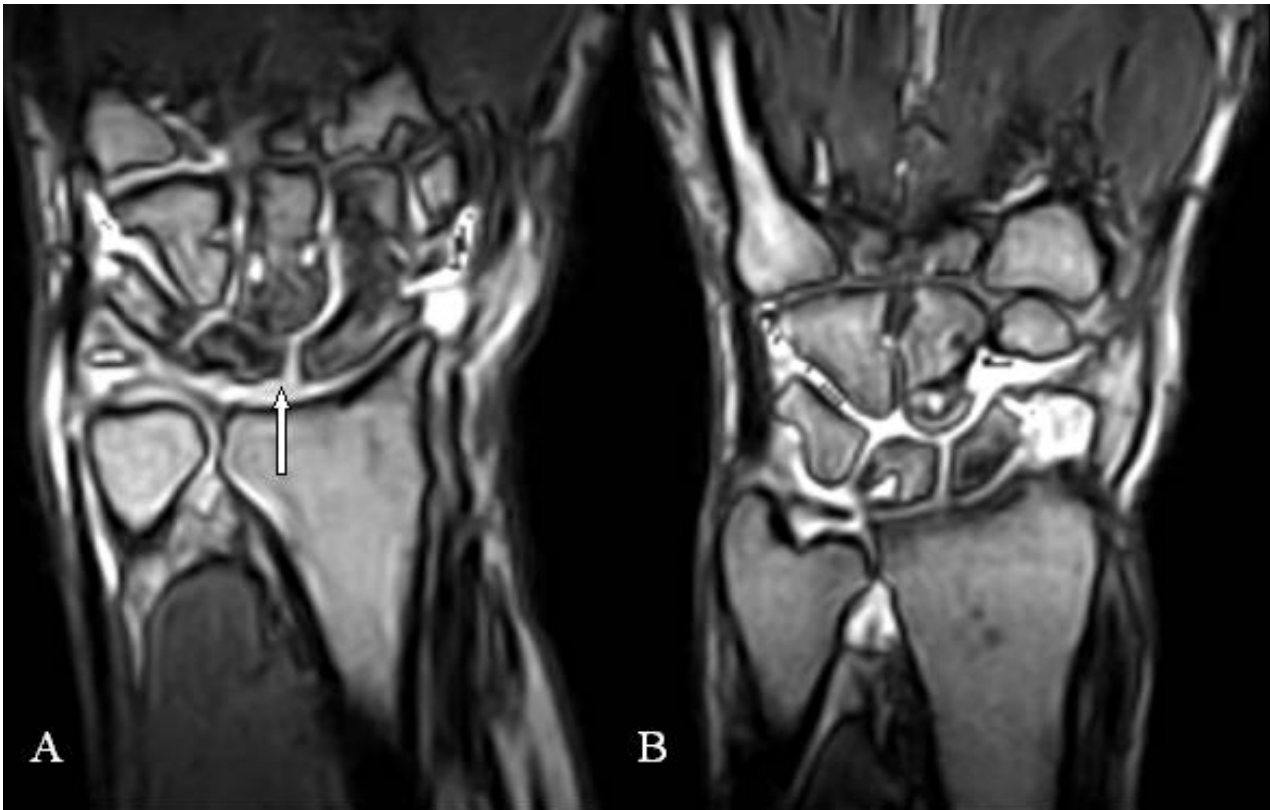
Figure 12: Distribution to all wrist joint compartments.

Coronal Turbo 3D T1 gradient echo images after i.a treatment in two patients (A) and (B). Both patients are examples of distribution to all compartments (n=3) of the wrist including the radio-ulnar joint. Note the arrow in (A) pointing at a disrupted intrinsic carpal ligament between the lunate and the scaphoid bones compared to an intact ligament between the lunate and the triquetrum.

The OMERACT synovitis score correlated with the distribution count (r=0.60, p=0.014), while no association was found between the distribution pattern and the erosion score (p=0.70) or the bone marrow oedema score (p=0.35). There was no correlation between the MRI distribution pattern of the drug and the following parameters: Age, disease duration, IgM RF status, and CRP value.

We saw evidence of a communication between the wrist compartment and inflamed tendon sheaths in some patients (n=2). In one case distribution to the extensor tendons was seen, and in one patient a signal enhancement was seen in the flexor tendons.

In 5 patients an additional MRI the following day (18-26 hours after injection) found no trace of Gadolinium. Clinical inspection at baseline and at 2 weeks follow-up revealed no side effects after the injection.

Study III

Pre-contrast SNR and CNR values did not differ between the first and second MRI examination (data not shown).

All images obtained after i.v. and IA Gd-DTPA showed a marked signal intensity increase within the cartilage compared to non-enhanced baseline images. This was noted both in the qualitative image evaluation (figure 13A-C) as well as by a marked increase in SNR ($p<0.002$) and CNR ($p<0.0001$) of the cartilage (table 6).

Table 6: Signal to noise and contrast to noise ratios in the ROIs of the hip- joint cartilage, on images without Gd-DTPA, after indirect i.v. Gd-DTPA and after direct IA Gd-DTPA.

Patients	Signal to noise ratio			Contrast to noise ratio		
	Without Gd-DTPA	After i.v Gd-DTPA	After IA Gd-DTPA	Without Gd-DTPA	After i.v Gd-DTPA	After IA Gd-DTPA
1	4.12	7.20	6.90	3.71	9.04	7.17
2	4.18	6.50	8.97	3.42	7.10	9.18
3	4.56	5.09	5.62	4.79	8.50	6.00
4	4.13	9.26	5.68	4.21	11.80	7.63
5	5.21	4.20	6.54	4.64	10.52	8.26
6	4.82	7.87	9.94	5.44	10.35	11.14
7	4.23	6.16	6.56	4.12	5.23	6.85
8	5.36	7.72	10.03	5.66	10.94	11.84
9	3.56	8.05	4.44	3.44	7.89	4.48
10	4.40	8.32	7.85	4.86	11.22	11.22
Median	4.31	7.46	6.73	4.42	9.69	7.95
Mean	4.46	7.04	7.25	4.43	9.26	8.38

T-test SNR mean baseline vs i.v $p<0.001$	T-test CNR mean baseline vs i.v. $p<0.001$
T-test SNR mean baseline vs IA $p<0.001$	T-test CNR mean baseline vs IA $p<0.001$
T-test SNR mean i.v vs IA	T-test CNR mean i.v vs IA
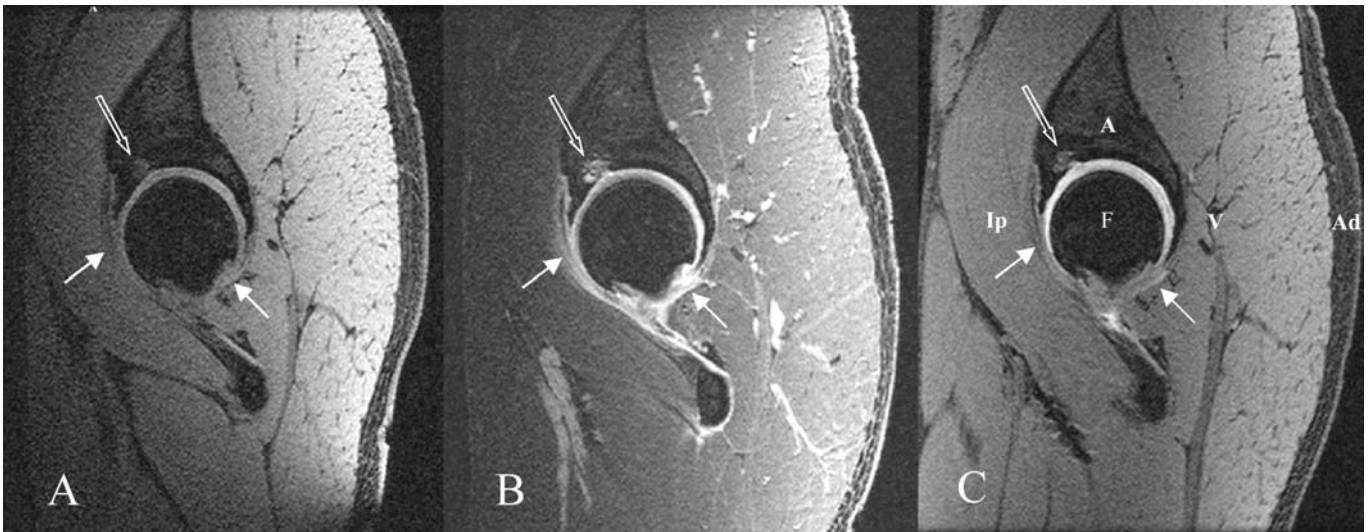
Figure 13:
Sagittal T1-weighted 3D SPGR cartilage images of the hip joint without Gd-DTPA (A), 140 min after indirect i.v. Gd-DTPA (B) and 140 min after direct i.a. Gd-DTPA (C).
Note the better cartilage contrast in images B and C compared to image A. The closed arrow points at the synovial lining of the joint, note that there is a marked synovial enhancement after the i.v. Gd-DTPA (B) making it difficult to separate the cartilage and synovial border. The arrowhead points toward the subchondral border. Note the better delineation of the subchondral border after i.a Gd-DTPA (C).
The open arrow marks the synovial enhancement in subchondral cyst best seen in (B). Femoral Head (F), acetabulum (A), musculus iliopsoas (Ip), blood vessels (V), adipose tissue (Ad).

In all patients the IA images showed a clear delineation of the cartilage in areas with synovial lining as well as a better delineation of the subchondral border than the i.v. images (Fig. 13C). The i.v. method showed CNR problems at the subchondral border, as well as difficulties in distinguishing between contrast-enhanced synovium and cartilage (Fig. 13B).

The impression of a more pronounced cartilage enhancement after the IA injection compared to i.v., was confirmed statistically by comparing the SD-corrected SNR values ($p<0.01$) and CNR values ($p<0.01$) (Table 7 and figure 14).

No patients experienced adverse events following either i.v. Gd-DTPA or ultrasound guided IA Gd-DTPA injection.

Table 7: Signal to noise and contrast to noise ratios in the ROIs of the hip joint cartilage after SD-correction of values observed after i.v Gd-DTPA and after IA Gd-DTPA.

Patients	Signal to noise ratio		Contrast to noise ratio	
	After i.v. Gd-DTPA	After IA Gd-DTPA	After i.v. Gd-DTPA	After IA Gd-DTPA
1	1.63	1.60	0.53	0.57
2	1.18	1.99	0.18	1.06
3	1.38	1.67	0.36	0.69
4	1.14	1.29	0.17	0.35
5	0.80	2.32	0.06	1.54
6	1.41	1.77	0.40	0.78
7	1.19	1.59	0.26	0.55
8	1.30	1.77	0.29	1.25
9	1.13	1.29	0.12	0.31
10	1.34	2.04	0.38	1.14
Median	1.24	1.72	0.27	0.73
Mean	1.25	1.73	0.24	0.82

T-test SNR SD-corrected mean i.v. vs IA p <0.001
T-test CNR SD-corrected mean i.v. vs IA p<0.001

Figure 14
Signal to noise ratio (A) and contrast to noise ratio (B) after indirect i.v. and direct IA Gd-DTPA using SD-corrected values of the drawn ROIs. Note that IA Gd-DTPA has the best signal to noise and

Discussion

Study 1: Treatment effect after US guided IA injection in the wrist joint of patients with RA

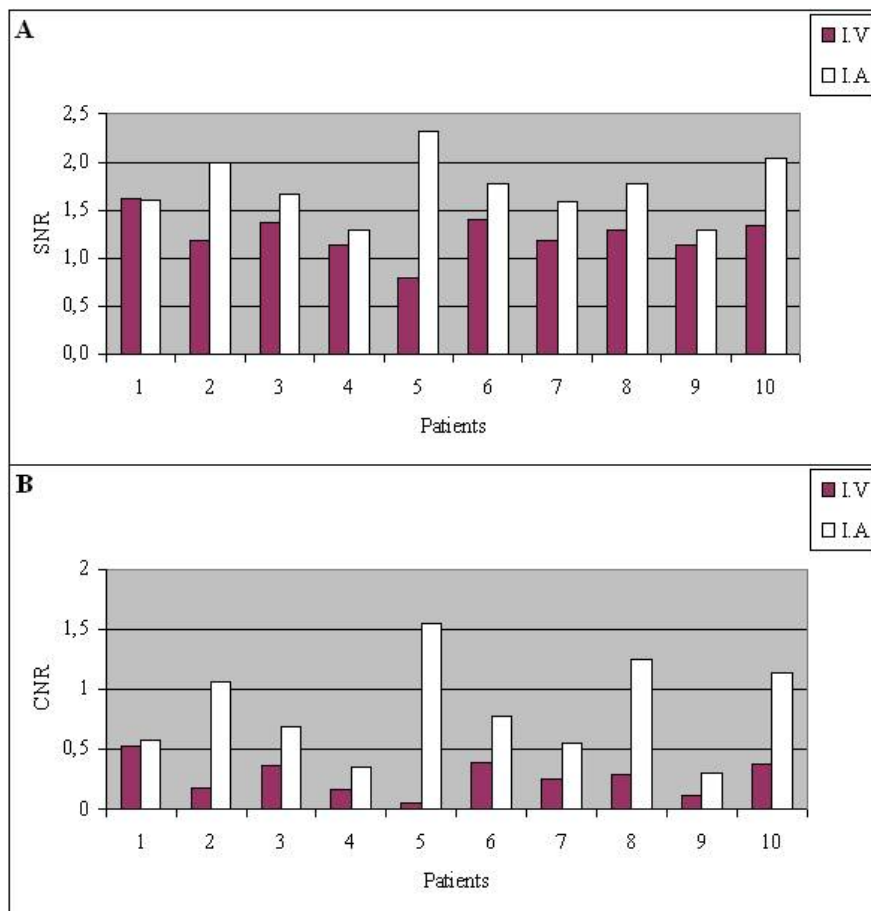Overall, study I provided new evidence regarding the imaging monitored short-term treatment response after IA injection in the wrist joint of patients with RA. This double blinded clinical controlled study attempted to assess the efficacy of a single IA injection of either etanercept or glucocorticoid after 4 weeks, which have both shown significant clinical effect within the first month (43;48;189). Surprisingly, the clinical response was not confirmed by imaging, as neither MRI nor US-Doppler could demonstrate a benefit of one such injection at the 4-weeks follow-up. All parameters tested with the two methods proved negative, including synovitis and bone marrow oedema on MRI, and colour-fraction-index or RI-index on US, which represent very sensitive signs of inflammation (190). The clinical observer in our study was blinded to the therapy and phase in therapy of the patients, however, a discrepancy between clinical and imaging efficiency may be explained to some extend by bias of the patient wanting to experience a positive effect. A definite source of concern was our finding of a significantly higher erosion score at 4 weeks follow-up, indicating that joints with active disease may deteriorate within a period as short as 1 month due to insufficient response to the injection regardless of therapy. The erosions may be in a state of progress, which cannot be arrested by a single injection of medication. However, due to the SDD of the erosion score presented in table 3A this result should be regarded with some reservation, and the risk of a TYPE 2 error is definitely present. This is supported by the results from table 4, where only one of the patients who had an increase in the OMERACT erosion score exceeding the SDD, and the results from table . This patient had however imaging evidence of progression in the hamate bone as can be seen in figure 8. To our best knowledge we are the first to show MRI documentation of an erosive progression within 4 weeks.

The intra-observer agreement values that we present in table 3 are all above 0.8 indicating a very good correlation, which is in agreement with previously published results on both high-field and low-field equipment (181;188). The seemingly higher erosive progression in the etanercept group compared to the methylprednisolone group is based on small changes in few patients from a small sample size that are all below the measured SDD from this cohort (table 3A), and should thus be regarded with

reservation, again due to a high risk of a type 2 error. The inter-reader agreement presented in Table 3B
show high level of agreement between observers both in the cross sectional score as well as in the
change scores which are all above 0.74.

Table 8 : Interreader correlation coefficient (ICC) from previous studies compared to study I

	MRI Synovitis	MRI Bone Erosions	MRI Bonemarrow Oedema	Field Strength
Østergaard et al*				
Baseline	0.58	0.65	NA	High
Lassere et al				
Baseline	0.74	0.72	0.78	High
Conaghan et al (Ref)				
Baseline	0.74	0.15	0.08	High
Follow-up	0.68	0.45	0.56	High
Change	0.46	0.55	0.45	High
Haavardsholm et al***				
Baseline	0.69	0.83	0.79	High
Follow-up	0.78	0.73	0.95	High
Change	0.74	0.67	0.95	High
Schirmer et al*				
Baseline	0.86	0.84	NA	Low
Conaghan et al**				
Change	0.78	0.72	0.09	Low
Boesen et al (Study 1)				
Baseline	**0.87**	**0.75**	**0.95**	Low
Follow-up	**0.86**	**0.89**	**0.96**	Low
Change	**0.79**	**0.77**	**0.93**	Low
* Østergaard et al and Schirmer et al did not use the RAMRIS score (0-10) for erosions but a score between 0-3				
** Conaghan et al used a 10 year old lowfield MRI dataset with poor image quality to perform their study				
***The presented results are the average ICC's for 4 readers with various RAMRIS expertice from beginner to expert				

As can be seen in table 8 the inter-observer agreement in the 10 randomly chosen patients is in the high
range compared to previous published studies. We were only 2 observers that through out the phd
period continiusly have been calibrated to the RAMRIS score as the second reader KEJ served as a
reference for MB throught the the study, whereas the presented ICC for the study of Haavardsholm et al
that resembles study I, using highfield data, is a bit lower, mainly due to the various experiences of the
4 readers from beginner to experts in using the RAMRIS score. In addition our study used the
published reference atlas(92)in all cases of doubt which again can contribute to the higher ICC. Taken
the ICC of the change score into account the presented results of a higher erosive progression at 4

weeks follow-up should again be regarded with caution, due to the small sample size with a high risk of a type 2 error. Newer the less we have imaging documentation of a potential erosive progression in the hamate bone after 4 weeks that is most likely a true erosive progression and not a partial volume- or a chemical shift artefact (see below and figure 8A + 8B page 54-55). In conclusion our disappointing one-month results in imaging parameters are in contrast with the clinical impression of the injections in joints, which are commonly regarded as having a dramatic immediate effect. This clinical effect was also experienced, mostly in small joints, by participants in our former studies of injections with etanercept (48;49). However, the imaging parameters can be regarded as more objective evidence that after one month, a single injection in the wrist joint may be efficient in some individuals, but the global effect in the group is nsufficient. By consequence, clinical measures with subjective scores might give a false impression of response if used as the only criteria of success. Our results lend further support to the recently published 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"(1).

Studies of the smaller and single-chambered metacarpophalangeal and the metatarsophalangeal joints have reported a good correlation between MRI and US synovitis evaluations (191;192). Our imaging data were in contrast to these results, which might be explained by the fact that the wrist is a more complicated joint with less strict definitions of region of interest for MRI and US respectively. 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 (190).

Study I is to our knowledge the first to show indications of further bone destruction within a period as short as 4 weeks (figure 8A+B). None of our patients were treated with anti-TNF systemically, while all by DMARDS, suggesting an insufficient protection by the latter compounds on the disease progression.

In clinical practice, flares of arthritis in one of a few joints are commonly treated with a single injection, even though evidence has been presented that the effect of a single injection of methylprednisolone is rather unpredictable, since it has large variations in both clinical and imaging parameters of inflammation (Doppler US and RI) (43). A one-shot strategy must be regarded as delivering a sort of rescue medication and is not an alternative to changes in systemic treatment in case of a generally dissatisfactory treatment of RA. In the meantime, after planning the present study, evidence has been presented of a more sustained effect of repeated injections of steroid into RA joints (80), while not as the only therapeutic measure.

The present 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 or weeks after injection. We have found indications of an earlier clinical and US response to etanercept, when tested one week after IA injection (193).

Treatment failure may also be caused by malplacement of the IA injection due to poor technique (85), but 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.

The present patient group had a long duration of disease, a moderate synovitis score according to the OMERACT RAMRIS score, a moderate DAS score, and might be relatively more resistant to the injections than would be seen in early arthritis. Whatever the reason for the neutral and possibly even negative outcome, our patients were not treated sufficiently and should have been treated more aggressively. Especially 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 the fact that these drugs seem to give patients a higher chance of arrest of erosions than traditional DMARDs (73-75).

Finally, the OMERACT RAMRIS synovitis score could be poorly sensitive to changes in the very short term, and not being the ideal method to follow-up IA injections. In this perspective the effect of IA glucocorticoid injections in the knee has been successfully evaluated by calculation of synovial membrane volume and dynamic MRI (104). On the same note, a new dynamic sequence for the

lowfield scanner has successfully been evaluated for discriminating active disease from inactive disease in RA patients(194).

In conclusion, neither MRI nor US parameters 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, even though we used optimized "state of the art" lowfield MRI and US, as well as internationally recommended scoring systems. Furthermore, we present possible MRI evidence of a progressive erosive disease within 4 weeks in at least one patient, that could not be stopped by a single IA injection which is in clear in contrast to the clinical impression of improvement. By consequence, an injection into a joint does not seem to have a sufficient effect on arthritis and should not be used as only measure against its flares. It may be speculated that a clinically relevant effect of intra-articular treatment requires more than one injection and we suggest considering imaging to monitor IA injections.

Study II: Distribution pattern of US guided injection in the wrist joint of patients with RA

In study II we saw data that challenge the usual assumption in rheumatology as to drug distribution in the wrist joint of RA patients, giving us a potential explanation of treatment failure after IA injection into the joint cavity. In 1984 Mikic et al presented evidence of a compartmentalization of the wrist with various degrees of communication between the compartments (90) and due to this anatomical variance, some authors even suggest a triple injection technique for a whole-joint arthrographic evaluation (195-197). Thus, treatment failure of a wrist injection may be caused by insufficient spread of the medication into all relevant joint compartments. This suspicion of a large diversity regarding the complex anatomy and intercommunication of the multiple joints comprising the wrist joint was confirmed in study II, thus supporting this hypothesis generated after completion of study I. The different distribution patterns presented in table 4 may be due to normal variation or may be caused by arthritic changes.

A higher degree of joint communication could be caused by destruction of the interposed septa as indicated in some patients (fig 11A and 12A). Here, the contrast passes through the intrinsic ligament of the lunate and scaphoid bones as an indication of damage to this structure. If this were the explanation, a larger degree of communication might be expected in long-standing arthritis, which was,

however, not observed in our series. It also could be speculated that passageways between compartments might be blocked by pannus, leading to a lower degree of joint communication as could be seen in the patient in figure 10. Whatever the reason for the different distribution patterns, our study shows that in most cases a drug injection into the radio-carpal joint will be insufficient as treatment for the all the joints of the wrist.

An explanation for non-response in some patients to an IA injection of a potent anti-inflammatory drug such as glucocorticoid, is the fact that injections done without guidance may not hit the joint cavity at all (85). In our series this possibility was, as in study I, overcome by giving all injections guided by US with documentation of the placement of the injected substance into the joint space between the distal radius and the lunate in the proximal wrist compartment. In all cases the placement was confirmed on the subsequent MRI. What the US technique does not, is to ensure a distribution of the drug into all relevant areas of activity, which could be one of the reasons for treatment failure with injections into the wrist. To our knowledge, our study is the first to address this potential problem with the use of MRI to trace the drug distribution, and our results support the conclusion that communication between the various compartments within the wrist joint varies between patients. Our results also showed distribution to the tendon sheaths in two patients, which indicate that there is a direct communication between the pannus of the wrist compartment and the tenosynovitis of the involved tendons in some patients. This distribution could be due to an abnormal capsule communication or a reflux of the injected drug through the injection canal, but this was not seen during the actual process using real-time US. Our standard is to make sure that the extensor tendons and tendon sheaths are seen clearly on the screen and are kept out of range from the needle (figure 3 and 5). Also, in one patient a distribution to the flexor tendons was observed after a dorsal injection far from these tendon sheaths. Accordingly, as only few patients have communication between the tendon sheaths and the wrist joint, tenosynovitis seems not to be treated along with the wrist joint and significant inflammation in the tendon sheaths should be treated separately.

Until now it has been our routine to give IA injections in the wrist in the space between the central part of the distal radius and the lunate bone. Our present series shows that this approach is inadequate, and

we suggest further studies to develop the optimum injection strategy for the wrist joint. One strategy suggested by Koski et al. may overcome this by injecting into both the radio-carpal joint and the inter-carpal joints, which in their study showed a better response than a single injection into the standard site (198). According to our results listed in table 4, the radio-carpal joint was reached to a large extent by one injection in the majority of patients (16 of 17). One patient had contrast enhancement only in the radio-ulnar joint, suggesting that the US guided injection into the radio-carpal joint applied the treatment in this joint space without further distribution to the rest of the wrist. The drug was distributed to the inter-carpal joints in 12 of the 16 patients after injection in the radio-carpal joint; but in 11 of 17 patients, the contrast did not reach the carpo-metacarpal joints, which must be regarded as insufficient treatment. With the use of US Doppler, most active areas in the wrist may be distinguished, and possibly partitioned injections should be guided into these by US to optimize the effect of the steroid. It must be noted that in some cases an injection placed directly in the pannus may give rise to unpleasant tension in the tissue, To avoid this, a small pre-injection of air to ensure the position of the needle tip free in the joint cavity was used(86). Finally we found that high-field MRI and low-field MRI revealed similar sensitivity to the distribution of the IA contrast, which supports the use of dedicated extremity MR-scanners to track the distribution pattern, as this modality is more patient friendly and cheaper (10). A larger study designed to compare the high- and lowfield scanner performance in this perspective is desirable.

 The chosen Gadolinium dose was in the high range (50mmol/l) compared to previously published arthrographic studies in the wrist on both 1,5T(199;200) and 0.2T(201) using up to 8ml of injected solution. As the current study was designed to trace the distribution of the injected drug and not considered to be a diagnostic arthrography of the wrist, no direct comparison can be made. A recent in-vitro publication has shown the optimal Gadolinium dose to be 2-5 mmol/l in the 0.2T low-field scanner when injecting approximately 20 ml into a shoulder joint of cadavers (182). In contrast to that study, we had no problems with tracing the distribution pattern using the 10 times higher concentration, even though one patient revealed a signal drop within a large erosion of the lunate bone that could be due a concentration dependent T2 effect (figure 10). Finally, our observation that the Gadolinium was

not seen in the MR images the following day is in accordance with the previous reports and reviews of the temporal behavior of IA Gadolinium injections concluding that the IA Gadolinum has left the joint cavity within 24 hours(202;203). The small volume injected and the use of a low-field MR scanner may also account for the lack of visible Gadolinium on the one-day follow-up MR scan(202). In retrospect our concentration of Gadolinium was high. However, when we started the data collection of the current pilot study no studies had addressed the optimal Gadolinium dose for the presented arthrographic procedure in wrists using a low-field scanner. Our preliminary results revealed good visualization in the MRI images and as the injected volume was low compared to standard arthrography volumes we continued this pilot experiment with the above mentioned solution. Regarding the safety aspects of the procedure, the total amount rather than the local concentration of Gadolinium in one joint is of importance for possible toxicity(202). The range of concentration optimal for tracing the drug distribution in the wrist on the low-field scanner remains to be determined, as well as the cost effectiveness of the suggested MR arthrography method vs. a more conventional fluoroscopically guided arthrography method.

We choose to use MR arthrography in our study to trace the drug distribution, as many rheumatologists increasingly use MRI to monitor therapy response and we wanted to reduce the lifetime radiation dose of the involved patients to a minimum. Furthermore the low-field MRI scanner has not prior to study II been used for arthrographic investigations in the wrist joint according to MEDLINE (key word: MRI lowfield wrist arthrography).

In conclusion the distribution of contrast on MRI showed patient-specific and random patterns after IA injections in active RA wrist joints. The degree of distribution correlated with the MRI synovitis score, while no association was found with the MRI erosion- and bonemarrow oedema scores or any clinical scores. Therefore, injecting patients with more severe synovitis seems to be associated with a more complete diffusion into the wrist, possibly increasing the infiltration's efficacy. These results also indicate that injection into the proximal central part of the wrist cannot be regarded as sufficient to treat the whole wrist joint. The diversity of distribution patterns among patients could be an explanation of

the variation in treatment responses seen with IA injections(43;49), and based on our results we recommend that patients, who do not respond sufficiently to IA injections into the wrist joint, should have their distribution pattern examined, and that they might benefit from additional injections elsewhere in the joint.

Study III: I.v or IA dGEMRIC for better delineation of hip joint cartilage

In study III we present a different use of the dGEMRIC technique for improved enhancement, SNR, CNR and delineation of the cartilage in the hip joint, which is easy to implement in current clinical practice, and does not require sophisticated sequences and post processing equipment.

The series of hip MRI in study III, using the dGEMRIC technique demonstrated a general superiority of the IA to the i.v. route, regarding the delineation of the subchondral cartilage border (figure 13 and 14). We believe this result was due to CNR problems in the joint cartilage following i.v. Gd-DTPA because of a lower concentration of Gd-DTPA in the cartilage, as well as the fact that we saw subchondral bone marrow enhancement after the i.v injection. The IA Gd-DTPA on the other hand gave a clear delineation of the cartilage in areas with synovial lining, whereas after i.v. administration, it was impossible to distinguish between Gd-DTPA enhanced cartilage and synovial lining in the images (Fig. 13B and 13C, closed arrows).

Our data confirm that in comparison to a conventional T1-w weighted cartilage MRI sequence, the dGEMRIC technique gave a superior cartilage image quality in the hip joint independent of the way of Gd-DTPA administration (figure 13-14 + table 6 and 7). The observation is in agreement with the hypothesis of Gd-DTPA diffusion into the cartilage, and the data are also in agreement with the in-vitro observations of excellent late enhancement of cartilage, and thus better delineation of the patellar cartilage damage after incubation in 2mmol/L Gd-DTPA saline solution when using a clinical T1-w weighted spin echo sequence(178).

The obstacles of low SNR and CNR of the hip joint cartilage (16) apparently can be overcome by the use of the dGEMRIC technique and a T1-w weighted SPGR cartilage sequence. This approach may provide a better platform for developing automatic segmentation algorithms for volume estimation of the hip joint cartilage. In this setting, our data support the use of the IA method for volume calculations

whenever possible, because the IA method optimizes the outlining of the synovial and subchondral cartilage border.

In a previous study by Bashir et al., double i.v. doses of Gd-DTPA was given in volunteers providing excellent cartilage delineation for T1-w-mapping (18). We chose to give triple i.v. dose Gd-DTPA, which in the knee joint has been shown to give an increased signal intensity in the cartilage compared to a double dose(183). .The dose used for IA injection was 4 mmol/L Gd-DTPA, the same concentration as used by Bashir et al in their pioneer work for comparing i.v. with IA gadolinium whilst developing dGEMRIC for T1-w mapping (175). A recent work by Zhai et al.(204), applying a similar 3D-T1-w-SPGR cartilage sequence without Gd-DTPA enhancement, correlated the hip joint cartilage thickness and volume to joint-space narrowing and the OA score on radiographs, and found a modest correlation. It may be speculated that with improved cartilage delineation, using the dGEMRIC approach and IA Gd-DTPA, volume calculations may be more accurate and correlations may be better. Finally the debate regarding nephrotoxicity of certain Gadolinium compounds (205) can be neglected using the IA approach, as the amount of Gadolinium injected IA is several 1000 fold lesser than the double or triple dose i.v. approach.

Further studies with true volume comparisons are needed to shed light to these questions, and future studies will also show whether the present protocol might be of advantage for cartilage diagnostics in other synovial joints such as the knee, ankle, wrist etc. The application of such a clinical protocol could at the same time provide 1) clinical T1-w weighted images for better delineation of cartilage thus giving better volume calculation, 2) T1-w mapping for indirect glycosaminoglycan (GAG) concentration measurement, and 3) better cartilage images for preoperative evaluation.

The hip joint is of special interest for MRI studies due to its relative inaccessibility for other examinations such as arthroscopy and ultrasound. Often the hip joint disease present clinically equivocal signs, which may or may not be explained by imaging findings. The cartilage of the hip joint is thinner than that of the knee, and pushes the demands further for in- and through-plane resolution and increased CNR between cartilage, synovium and bone. Ultrasound-guided medical treatment(184;206;207) is rapidly gaining acceptance, hence ultrasound guidance of injections opens

for a more extensive use of IA MRI contrast agents. The need for detailed cartilage evaluations increases due to the improved options for treatment of early hip OA, by both IA therapies and new surgical procedures such as GANZ osteotomia(208).

Concluding remarks

The studies of this thesis have raised several questions regarding the current clinical and imaging procedures in both RA and OA, and the following conclusions can be drawn:

- Evaluated by MRI and US-Doppler, one ultrasound guided IA injection of either etanercept or methylprednisolone seems not to be enough to arrest flare of wrist arthritis in "standard" RA patients on oral DMARDS fulfilling the clinical criteria of an IA treatment.

- Both methylprednisolone and etanercept gave some clinical relief to the patient while injection of IA methylprednisolone might provide a slightly better disease control

- Within the 25 patients as a group we saw a significant erosive progression at 4 weeks, which was in clear contrast to a significant clinical relief, but this result could in all but one patient be explained by the SDD of the measuring method.

- The one patient with a higher erosive progression score than the SDD revealed MRI documentation likely representing a erosive progression in the hamate bone within the 4-week follow-up, which we, to the best of our knowledge, are the first group to show.

- Injecting drugs ultrasound-guided IA in the recommended standard site of the wrist joint seems to ensure the correct placement of the drug in the joint compartment.

- Distribution of IA injected drugs is apparently varying and patient specific, although there seems to be a correlation between the MRI synovitis score and the spread of the drug within the different compartments of the wrist joint. This could be a potential explanation of the lack of treatment effect in some patients receiving IA injections

- IA injection of Gd-DTPA along with a drug treatment in the hip joint and subsequent delayed MRI of cartilage (dGEMRIC) gave a significantly better SNR, CNR and visual delineation of the cartilage in the hip than the triple dose i.v. dGEMRIC technique. The IA administration

especially improved visualization of the cartilage in the subchondral and the synovial lining areas.

- The suggested dGEMRIC approach is easy to implement in departments equipped with a standard 1.5T MRI scanner having a 3D T1-w GRE cartilage sensitive sequence.

- The amount of Gadolinium injected for dGEMRIC is significantly lower using the IA approach compared to the double or triple i.v. approach. This is of interest as perspectivized in the ongoing debate regarding the nephrotoxicity of certain Gadolinium compounds.

Future perspectives

Clinical evaluation of the treatment response after an IA drug injection in the wrist of patients with RA seems to be insufficient, as many patients respond clinically to the treatments even though imaging parameters are unchanged, and in some cases show signs of progression. Thus we recommend that MRI and US should be used more frequently in the follow-up of the treatment response, and maybe should be applied in even shorter intervals than 4 weeks to follow the response to an IA treatment. A similar conclusion in a recently published study supports this assumption showing imaging progression in a cohort of patients on systemic DMARD treatment in clinical remission.

Studies in smaller joints such as the MCP and MTP joints have shown good correlations between the MRI RAMRIS synovitis score and the US power Doppler score. The wrist joint represents a much more complex situation, which must be solved to facilitate a detailed monitoring of the development of RA in this joint. The OMERACT RAMRIS score for synovitis might not be sensitive enough for verifying changes in the very short term in the wrist joint, and might not serve as good standard method for follow-up IA injections. Data from a larger number of patients (n=100) with US Doppler and MRI RAMRIS scores in the wrist are currently being analyzed at the Parker Institute. Preliminary results (N=41) from this study reveal a disappointing correlation regarding synovitis (r=0.4), indicating that different aspects of the synovitis are being reflected by the two imaging modalities. The best correlate is seen between the colour Doppler and the bone marrow oedema (r=0.6), which theoretically makes sense as it is believed that colour Doppler reflects the degree of local inflammation, and bone marrow

oedema represents true inflammation in the bone, and also can be regarded as an indication of more aggressive disease. Other MRI methods, such as dynamic MRI, might build a better bridge between the US and MRI measures. The effect of steroidal IA injections in the knee has been successfully evaluated in the past by calculation of synovial membrane volume and dynamic MRI (104), and a new dynamic sequence for the low-field scanner has successfully been evaluated for discriminating active disease from inactive disease in RA patients (194). Further development of the evaluation of this dynamic sequence by automatic voxel based segmentation technique is planned and has been published in an international collaboration(209)

Based on the current knowledge, we believe with others that MRI and possibly also US should be mandatory in the disease evaluation of treatment follow-up and that they may even supplement each other. Larger multicenter studies should validate the US-Doppler and dynamic MRI for short-term and conventional MRI with the 3D sequence for long-term follow-up in order to substantiate a true regression in disease activity and erosive arrest. In this perspective the results in study II indicate that injection into the proximal central part of the wrist cannot be regarded as sufficient to treat the whole wrist joint in most patients, consequently we recommend that patients, who do not respond sufficiently on imaging evaluation to IA injections in the wrist joint, should have their distribution pattern examined to clarify whether an effect might be obtained by additional injections elsewhere in the joint, if the distribution of the injected drug is blocked by either anatomical variation or expanding pannus. Furthermore an ongoing study investigates whether it is possible to monitor the regional effect of an IA injection into the wrist with US Doppler and dynamic MRI. We hope that this study will help to clarify if the potential regional response is correlated to the baseline distribution pattern of the injected drug. In addition the optimal Gadolinium concentration needed to trace a drug distribution still needs to be settled to avoid a possible T2 effect and signal drop, since a recent study has indicated that a very high concentration of IA Gadolinium results in a significant signal drop in both high and low-field scanners. The recommended dose from that study was 2-5mmol/l for arthrography, but future studies should test whether this is also the optimal dose to trace the drug distribution. We have experience from one

patient receiving 2mmol/l, which could not be seen in the subsequent MR image of the wrist on both high-field and low-field, possibly due to the relative low volume (1.5ml) injected.

Regarding cartilage imaging the suggested technique with either i.v. or IA Gd-DTPA for late enhancement of cartilage is currently used at Rigshospitalet in patients with hip dysplasia considered for GANZ osteotomia where the baseline MR examination has revealed insufficient SNR for cartilage visualisation. At the moment two patients have been taken off the operation program due to sufficient cartilage coverage visualized with the i.v. dGEMRIC approach.

In the future we need to explore the use of the technique for cartilage imaging in synovial joints such as the knee, ankle, wrist etc, as well as the potential benefits in MR scanners with different field strengths (0.2T through 3.0T). Furthermore we need evidence from larger cohorts on the different field-strengths MR scanners, to see whether the suggested dGEMRIC method in study III is useful in the clinical setting. In this perspective we plan to initiate a large randomized controlled study of the cartilage changes in obese patients (BMI>30) with knee OA (N=150) during a weight loss program where the goal is to examine whether the IA dGEMRIC method suggested in study III along with the conventional dGEMRIC T1 relaxation measures can at the same time improve 1) The clinical T1-w images for better delineation of cartilage thus giving better volume calculation, 2) T1 mapping for indirect glycosaminoglycan (GAG) concentration measurement, 3) Better cartilage images for preoperative evaluation and 4) Arthrographic imaging immediately after the IA injection.

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