Ultrasound *versus* high-field magnetic resonance imaging in rheumatoid arthritis

Y.K. Tan[1], M. Østergaard[2], P. Bird[3], P.G. Conaghan[4]

[1]Department of Rheumatology and Immunology, Singapore General Hospital, Singapore; [2]Copenhagen Center for Arthritis Research, Copenhagen Center for Rheumatology and Spinal Diseases, Copenhagen, and Dept. of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark; [3]University of NSW, Sydney, Australia; [4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, United Kingdom.

York Kiat Tan, MBBS, MRCP, MMED
Mikkel Østergaard, MD, PhD, DMSc
Paul Bird, BMed (Hons), FRACP, PhD, Grad Dip MRI
Philip G. Conaghan, MBBS, PhD, FRACP, FRCP

Please address correspondence to:
Prof. Philip G. Conaghan,
Leeds Institute of Rheumatic and Musculoskeletal Medicine,
Chapel Allerton Hospital,
Chapeltown Road,
Leeds LS7 4SA, United Kingdom.
E-mail: p.conaghan@leeds.ac.uk

Received on August 26, 2013; accepted in revised form on October 11, 2013.

Clin Exp Rheumatol 2014; 32 (Suppl. 80): S99-S105.

Key words: rheumatoid arthritis, ultrasound, MRI, erosion, synovitis

Competing interests: none declared.

ABSTRACT

Over the past decade there have been significant advances in the field of musculoskeletal imaging, especially in the application of ultrasound (US) and magnetic resonance imaging (MRI) to the management of rheumatoid arthritis (RA). Both modalities offer significant advantages over the previous standards of clinical examination and radiography, and allow direct visualisation of both joint inflammation and structural damage. Although measuring similar pathology, each of these imaging tools has its own benefits and limitations; understanding these will help researchers and clinicians to determine the appropriate role for these tools in RA joint assessment. This review article seeks to compare the usefulness of US and MRI in RA diagnosis, prognosis and outcome assessment.

Introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory joint disease with a worldwide prevalence of about 1%. It usually manifests between 35–50 years of age and if undetected and/or not treated early, can lead to considerable morbidity and increased mortality. Early aggressive therapy with disease-modifying anti-rheumatic drugs (DMARDs) is associated with better treatment outcomes (1). Traditionally, rheumatologists rely on clinical examination and conventional radiography (CR) in RA joint assessment in their daily practice. Modern imaging tools such as ultrasound (US) and magnetic resonance imaging (MRI) offer superiority over clinical examination (2) and have greater sensitivity than CR in detecting joint erosion especially in early disease (3). They allow direct visualisation of both inflamed and damaged joint structures. In the clinical setting, they can be useful to support the presence or absence of joint inflammation and/or damage findings especially if conventional methods of assessment yield uncertainty. They are also excellent research tools, for example, in the evaluation of therapeutic response in RA. Being highly sensitive, they can be used in RA studies with a smaller number of subjects and shorter follow-up period (4). This is attractive in both early and late phase RA trials (5).

Although they can measure similar pathologies in RA, there are important differences in the two imaging modalities, with each having its unique strengths and weaknesses. For example, ultrasound is well suited for dynamic, multiple joint area assessments but does not visualise beyond the bony cortex (precluding bone marrow oedema (BME) assessment) and certain joint sites (*e.g.* mid-carpal/tarsal) can have restricted acoustic windows. MRI is ideal for single joint site assessment and allows an in-depth study of anatomical structures (including the bone marrow) but high-resolution scanning of multiple joint sites can be time-consuming and the MR machine is generally not located in the rheumatology clinic.

The European League against Rheumatism (EULAR) and Outcome Measures in Rheumatology (OMERACT) US and MRI workgroups have provided important consensus definitions of joint inflammatory and damage pathologies visualised by these clinical tools (6, 7). To date, there are validated, reliable, semi-quantitative scoring methods for use in both modalities (7, 8). This allows standardisation in interpretation and comparison of findings across clinical studies – especially useful in the research setting. Recently, a EULAR task force has also published a set of recommendations for clinical use of these advances imaging tools in RA diagnosis, prognosis and monitoring (9). This was derived from data

from 199 studies and expert opinion. In several of the clinical scenarios, both US and/or MRI have both been recommended with no specific mention as to tool preference, related in part to the recognition of availability and feasibility issues for individual clinicians.

As these imaging tools become increasingly available for use in modern clinical practice, the issue of which imaging modality would be more appropriate in specific clinical scenario(s) or research setting(s) becomes important. This review will focus on relevant RA imaging studies with the aim to understand the usefulness of US *versus* MRI in RA diagnosis, prognosis and outcome assessment.

RA diagnosis:
which is a better tool?

The EULAR Task Force has included in its recent set of recommendations that US or MRI can be used to improve diagnostic certainty in RA above the clinical criteria – importantly this is in cases where there is a diagnostic doubt (based on clinical history, examination and routine laboratory testing) (9). MRI and US were recently incorporated in the international criteria for RA. In the recent ACR/EULAR 2010 criteria for RA, classification as definite RA is based on the presence of definite clinical synovitis (swelling at clinical examination) in one joint or more, absence of an alternative diagnosis that better explains the synovitis, and achievement of a total score ≥6 (of a possible 10) from the individual scores in four domains. In the joint involvement domain, which can provide up to 5 of the 6 points needed for an RA diagnosis, MRI and US synovitis count. In other words, MRI and US can be used to determine the joint involvement (10-12). The fact that MRI and US are now officially accepted for this purpose by the European and American rheumatologic communities is an important step in the recognition of the utility of MRI and US in the diagnosis and management of inflammatory arthritides. Furthermore, The American College of Rheumatology (ACR) has also recently described the reasonable use of musculoskeletal US in clinical practice, and included the diagnosis in a patient who presents with joint symptoms without definitive diagnosis on clinical examination (13).

US has the advantage of allowing multi-joint scanning in the same sitting and may be well suited for evaluation in those who present with oligo- or polyarticular joint symptoms. In this context, choosing a subset of representative joints for assessment will be important as extended joint scanning can be time-consuming (14) and hence reduces feasibility. This area is therefore an important focus of research.

These imaging tools have been shown to add value to routine clinical assessment, in the diagnostic evaluation of patients who presents with undifferentiated arthritis, in a few recent studies. Filer *et al*. determined (using logistic regression modelling) that the minimal set of joints to scan should include the metacarpophalangeal joints (MCPJs), wrists and metatarsophalangeal joints (MTPJs) (15) in order to provide the optimal information for RA prediction. The findings from this study were derived from 38-joint US scanning, which was shown to modestly improve the diagnostic performance when used along with the 2010 RA classification criteria in patients who presented within 3 months of their inflammatory joint symptoms. A separate study evaluated the use of a 20-joint (all MCPJs/ proximal interphalangeal joints (PIPJs)) power Doppler ultrasound (PDUS) screening method in 50 patients with undifferentiated polyarthralgia (of which 50% developed RA). This study reported high sensitivity (92%), specificity (91%) and positive likelihood ratio in RA prediction (16). The study by Nakagomi *et al*. demonstrated that US inflammatory findings can improve the accuracy of the 2010 ACR/EULAR classification criteria for predicting RA patients requiring MTX treatment within one year (17). Specifically, without ultrasound, the 2010 criteria had a sensitivity and specificity of 58.5% and 79.4%. The use of US grey-scale (GS) imaging score ≥1 increased the sensitivity to 78.0% (specificity was retained) while the use of GS ≥2/ power Doppler (PD) ≥1 increased the specificity to 93.7% although mildly compromising the sensitivity to 56.1%.

Several studies have described the diagnostic utility of MRI in inflammatory arthritis. A systematic literature review (SLR) up to 2009 (18) concluded that MRI bone oedema and the combined synovitis and erosion pattern seemed useful in predicting the development of RA from undifferentiated peripheral inflammatory arthritis, but that additional studies were needed. This was particularly based on 2 studies in undifferentiated arthritis; one showed that the combined synovitis and erosion pattern was related to the development of RA (19) whereas the other demonstrated that the presence of bone oedema had a positive predictive value of 86.1% for the subsequent development of RA according to the ACR 1987 criteria (20). After the SLR, a large follow-up study of undifferentiated arthritis documented MRI as a predictor of the diagnosis of RA (21). In 116 undifferentiated patients, bone oedema in the wrist and metatarsophalangeal (MTP) joints was an independent predictor of the subsequent development of RA according to the ACR 1987 criteria. A prediction model, including clinical hand arthritis, morning stiffness, positive rheumatoid factor (RF), and MRI bone oedema score, in MTP and wrist joints correctly identified the development of RA or non-RA in 82% of patients. Finally, recently presented data showed that substituting clinical assessment of joint involvement with MRI synovitis in the joints of one hand increased the sensitivity, specificity and positive and negative predictive value of the ACR/EULAR 2010 criteria in undifferentiated arthritis for predicting development of RA according to the original ACR 1987 criteria (22), further supporting the benefits of modern imaging in clinical practice.

To date, there is no prospective RA study that systematically compares the diagnostic use of these two imaging modalities. The clinical presentation of RA patients can vary and we do not know how these imaging tools will fare relative to the other in various clinical contexts: *e.g*. polyarticular *versus* oligo/mono-articular involvement,

Table I. US *versus* high-field MRI as prognostic tools in RA studies.

Reference	No of RA patients	RA duration/ follow-up period (months)	Joint site(s) imaged		Baseline US/MRI finding(s) with prognostic value	Corresponding odds ratio or correlation coefficient for structural progression
			US	MRI		
						radiographic progression
Brown (25)	102	<12/12	*MCPJs Wrist	MCPJs Wrist	1) US Synovial hypertrophy score 2) US **PD score 3) Positive PD signal on US 4) MRI synovitis score	^OR 2.3 OR 4 OR 12.2 OR 2.98
						radiographic progression
Kamishima (28)	29	8(median)/12	MCPJs	Wrist	1) MRI erosion (time-integrated) MRI erosive progression 2) #PDUS score (time-integrated)	^^CR 0.65 CR 0.56
						MRI erosive progression
Boyeson (29)	84	<12/12	Wrist	Wrist	1) ##GSUS inflammation 2) MRI ***BME	OR 2.01 OR 1.28

*MCPJs: metacarpophalangeal joints; **PD: power Doppler; ***BME: bone marrow oedema; #PDUS, power Doppler ultrasound; ##GSUS: grey-scale ultrasound; ^OR: odds ratio; ^^CR: correlation coefficient.

smaller *versus* larger joint involvement and seropositivity *versus* seronegativity. Clearly, well-designed studies incorporating both US and MRI in the diagnostic workup of RA patients are needed.

RA prognosis: predicting structural progression

The recent EULAR recommendations included that (a) MRI BME could be used as a prognostic indicator since it can predict subsequent radiographic progression in early RA while (b) both synovitis and joint damage seen on MRI or US can be considered for prediction of further joint damage (9). The stronger wording for MRI BME is justified by the fact that MRI in early RA in multivariate analyses have been demonstrated to be a strong independent predictor of subsequent radiographic progression, up to 5 years after MRI (23-24), while similar data were not available for US. Table I summarises RA studies that compare US and high-field MRI as prognostic tools. Inflammatory findings such as US synovitis (both GS and PD) and MRI synovitis/BME at the MCPJs and/or wrist joint have both been shown to some extent to predict structural progression in people with short disease duration (<12 months). PDUS looks rather promising in the study by Brown *et al*. (25) which reported positive PD signals to have the highest predictive value for CR progression in early RA when compared to various US and MRI inflammatory findings, although multivariate analyses were not performed. MRI is substantially more costly than US although it has the advantage of visualising BME, a unique pathology on imaging that corresponds to area of osteitis (26) on histopathology and to sites of subsequent bone erosions (27). We need further studies to understand the cost-effectiveness of these imaging tools when used for RA prognosis, and to understand the timing of their application in the patient treatment pathway.

RA assessment and monitoring: inflammation and damage

i) Synovitis assessment

US and MRI can both assess synovitis. Both modalities are superior to clinical examination in this regard and EULAR has included in its recommendation that both can be considered for more accurate inflammatory assessment and may be useful in monitoring disease activity (9). Takase *et al*. recently compared synovitis detected on PDUS and contrast-enhanced high-field (1.5 Tesla) MRI with histopathology at the knee joint in 20 patients (15 of which were diagnosed with RA and the remaining with osteoarthritis (OA)) underwent total knee replacement (30). The main pathological findings studied were inflammatory cell infiltration, synovial cell proliferation and neo-angiogenesis while US (both GS and PD) and MRI scored synovitis semi-quantitatively using a 0–3 scale and according to RA MRI score (RAMRIS) (7) respectively. Although PDUS correlated significantly with contrast-enhanced MRI synovitis score (correlation coefficient (CR) 0.53), higher grade (2-3) findings were found in 9 and 17 patients for PDUS and MRI, respectively. Among the three imaging parameters, PDUS correlated best with total pathology synovitis score (CR of 0.84) although both GSUS and MRI had significant correlation with the latter (both CR of 0.48). Looking at individual pathologies, significant correlations were seen by all three imaging parameters with inflammatory cell infiltrate, two imaging parameters (GSUS and PDUS) with vascularity and one imaging parameter (PDUS) with synovial lining thickness. Using histopathology findings as a reference, MRI was found to be more sensitive (75–83%) compared to PDUS (67–100%) while PDUS was more specific (69–88%) than MRI (8–13%). While this study could not conclusively decide if one imaging modality is superior to the other in the chronic disease under study, it does highlight the point that there exist important differences between modalities when used for inflammatory assessment. This needs to be further explored. Table II shows the RA studies that compare PDUS and high-field contrast-enhanced MRI in synovitis assessment. It is difficult to make comparison across studies given the heterogeneity in patient baseline characteristics (*e.g*. disease duration), different joint sites assessed and variety of scoring methods.

Table II. PDUS *versus* high-field contrast-enhanced MRI for synovitis assessment in RA studies.

Reference	No of RA patients	RA duration (years)	Joint site(s)	Scoring method	Reliability (synovitis)	Comparative analysis (synovitis detection)	
						At patient level	At joint level (by regions)
Wamser (31)	24	6.3 (median)	Shoulder	*PDUS: **Semi-quant (1-4) MRI: Semi-quant (1-4)	PDUS: nil MRI: nil	PDUS: 8/24(33%) MRI: 22/24 (92%)	PDUS: 14/96(15%): MRI: 69/96 (72%)
Hoving (32)	46	less than 2	Wrist ^MCPJs ^^PIPJs	PDUS used, vascularity not scored MRI: Semi-quant (1-4	PDUS: nil MRI: #Intra-RR: ICC 0.90 ##Inter-RR ICC 0.89	US: 25/46(54.3%)-baseline MRI: 33/46(71%)-baseline	nil
Brown (33)	107	7 (median	Wrist MCPJs	PDUS: Semi-quant (0-3) MRI: Semi-quant (***RAMRIS)	PDUS: Intra-RR: ICC 0.38 MRI: Intra-RR: ICC 0.83	PDUS: 64(60.4%) MRI : 87(92.6%)	PDUS:118/354(33%) sites with synovial hypertophy MRI: 327/741(52%)
						Predictive values	
Bruyn (34)	9 1(normal)	2 (median)	Shoulder	PDUS: present/absent MRI: present/absent	PDUS: axillary/posterior recess Intra-observer Kappa: 0.77/0.91 Inter-observer maximum Kappa: 0.07/0.97 MRI: nil	Note: MRI used as reference standard (sensitivity/specificity/@PPV/@@NPV) US Axillary recess:0.60/0.88/0.88/0.43 US Posterior recess:0.93/0.49/0.36/0.97	
Takase (30)	15 RA 5 OA	6 (median)	Knee	PDUS: Semi-quant 0-3 MRI: Semi-quant(RAMRIS)	PDUS (former study): intra-observer Kappa 0.92 MRI: inter-observer Kappa 0.85	Note: Histopathology used as reference standard (sensitivity range/specificity range) PDUS:67-100%/69-88%, MRI: 75-83%/8-13%	

*PDUS: power Doppler ultrasound; **Semi-quant: semi-quantitative; ***RAMRIS: RA MRI Score; ^MCPJs: metacarpophalangeal joints; ^^proximal interphalangeal joints; #Intra-R: intra-rater reliability; ##Inter-RR: inter-rater reliability; @PPV: positive predictive value; @@NPV: negative predictive value.

ii) Bony erosion assessment

CR is often used as the initial imaging modality of choice to look for erosive changes in RA. The EULAR set of recommendations has included US and/or MRI as additional imaging modalities that could be considered for use if CR does not show damage; US and/or MRI may be used to detect damage at an earlier time point than CR (9). Although computer tomography (CT) is often considered the gold standard for evaluating bony erosions, its main disadvantage is the exposure to ionising radiation. Two RA studies comparing US and MRI to CT will be elaborated. The first study compares grey-scale ultrasound (GSUS) and contrast-enhanced MRI (1.0 Tesla) at the shoulder joint in 26 RA patients (35). Humeral head erosions were scored as either none, small, superficial or large for all 3 modalities. MRI detected erosions in 25 out of 26 shoulders (96%), US detected 24 out of 26 shoulders (92%) while CT in 20 out of 26 shoulders (77%). At the greater tuberosity and anteromedial region, the congruency between US and MRI was quite good, although MRI detected more erosions than US posterolaterally. In this study, MRI detected more erosions than US although the authors raised the concern whether these are true erosions or may be pre-erosive oedematous change in the subchondral bone. The second study by Dohn *et al*. also compared US and MRI erosive findings to CT (as reference standard) at the MCPJs of 17 RA patients (although MRI used was intermediate field strength at 0.6 Tesla) (36). When compared to CT, US and MRI had a high specificity in detecting erosion (91% and 96% respectively), even in radiographically normal joints (corresponding specificity of 92% and 96%). This suggests that erosions seen on US and MRI are sites of cortical destruction representing 'true' erosions. The sensitivity of MRI was 68%, US 42% and radiography 19%. Similar results were found in a larger material of 52 patients (37). A recent systematic review included 21 studies (913 patients) which aimed to compare US and MRI in detection of bony erosions (38). This analysis revealed similar efficacies of both US and MRI at both the patient (OR of 1.76, p=0.22 with 338 patients) and the joint levels (OR is 1.19, p=0.45 with 869 joints) in early RA, but the studies generally included no gold standard reference, except for the studies by Døhn *et al*. mentioned above. The inter-observer reliability of US was found to be comparable to MRI (despite the former being described as a more operator dependent modality). However, it is important to acknowledge that reproducibility data on the most variable part of the examination, US image acquisition (as opposed to scoring previously recorded US images) is generally lacking.

iii) Inflammatory assessment in clinical remission

Both US and MRI inflammatory findings are common in RA clinical remission and low disease activity states (25, 33, 39). The EULAR recommendations suggest that both US and MRI can be use for inflammatory assessment that predicts subsequent joint damage even in states of clinical remission (9). In states of clinical remission, active PD findings on US have been demonstrated to predict subsequent disease flare in two RA studies (40, 41) while a separate study including 102 RA patients reported that an increased PD signal, scores for GS synovial hypertrophy,

PD and MRI synovitis were all predictive of subsequent radiographic progression at 12 months (OR (95% CI): 12.21 (3.34, 44.73), 2.31 (1.06, 5.52), 4.00 (1.98, 8.08) and 2.98 (1.49, 5.97), respectively) (25).

iv) Monitoring joint inflammation and structural progression

Again the EULAR recommendations suggest that US and MRI may be useful in monitoring disease activity as both can more sensitively detect inflammation when compared to clinical examination (9). There are now increasing numbers of randomised controlled therapeutic trials in RA that have utilised MRI as an outcome measurement tool (4, 5, 42). In comparison, the use of US as a monitoring tool in randomised controlled drug trials has been limited, although there are several longitudinal observation studies evaluating drug therapy and a number of large trials underway (4, 43). MRI has in place an internationally recognised, reliable and validated scoring system (RAMRIS) for inflammatory assessment at the wrist and MCPJs (7). The sensitivity to change at the wrist has been evaluated in a multi-reader validation study with MRI performed at baseline and one year (44). The minimal detectable change for synovitis change score (26.5%) was greater than the corresponding value for BME change score (8.17%) which implies that the latter is more sensitive to change when compared to the former. A recent systematic review conducted by the ACR RA clinical trials task force identified 9 randomised controlled trials (RCTs) (5 of which examined FDA-approved disease modifying anti-rheumatic drugs [DMARDs]) in which MRI was use as outcome measurement tool. These 9 RCTs all utilised RAMRIS for scoring pathology. From these studies, MRI inflammatory and structural joint damage findings were shown to be of high value in discriminating therapeutic effects in RA (42).

For US, although there is a semi-quantitative (0-3) scoring system available (8), there is lack of consensus on the minimal joint sites to select for US scanning (45). A recent study on 20 RA patients reported equal response to adalimumab treatment using various US joint combination (7- to 78- joint US score) (46). Specifically, the reduced joint scores all had high correlation with the extended 78-joint score and the sum of their GS and PD scores all improved significantly over time. A separate study by Haavardsholm et al which included 36 RA subjects on anti-TNFs reported standardised response mean (SRM) as a measurement of responsiveness of both GSUS and contrast-enhanced MRI findings at the wrist joint over time (at 3,6 and 12 month time-points) (47). MRI showed a greater responsiveness as the SRM for MRI total inflammation score was greater than the US total inflammation score which ranged between -1.05 to -1.24 and -0.37 to -0.54 respectively although this study did not utilise PDUS. It is currently difficult to conclude whether US or MRI is the better tool for outcome measurement based on the limited available data, and clearly this may be dependent on the clinical setting (trials *vs*. practice). While the EULAR recommendations state that CR should be considered for use for periodic assessment of joint damage, MRI (and possibly US), being more sensitive to such damage, can also be used to monitor disease progression (9). The study by Haavardsholm *et al*. (47) revealed that MRI and CR annual progression rates were similar although MRI was more responsive than CR for erosive changes at both 3 and 6 months time-points. There was no comparative data with US for detection of erosions.

Summary

The application of musculoskeletal US and MRI in the context of RA joint assessment has undergone extensive development over the last decade. Recently, EULAR has published a set of recommendations for the use of imaging tools spanning across RA diagnosis, prognosis and disease monitoring. Use of US and MRI are frequently included together in these recommendations, but it was impossible from the evidence review to provide clear guidance on which is the more appropriate tool to use in clinical practice settings. This is not surprising, given that there are no studies comparing both US and MRI in RA diagnosis and limited studies comparing their use in RA prognosis and monitoring. In face of diagnostic uncertainty, both US and MRI can be useful adjunctive tools and their application should be further explored and compared in various clinical scenarios (*e.g*. seropositivity status, distribution and number of joints involved). Both US and MRI can provide prognostic information on RA structural progression. MRI has the added advantage of visualising BME while PDUS has been shown to predict future disease flares in RA clinical remission states. Both US and MRI have superiority over clinical examination in inflammatory assessment and CR in detection of erosions. Hence they are well suited for monitoring RA disease activity and structural progression. The technologies associated with these modalities are constantly improving, and the use of whole-body MRI or quantitative US may well change their roles as discussed here. Local service considerations and the needs of individual studies will determine which modality is best placed to optimally provide the enhanced clinical information that they can both provide.

References

1. SMOLEN JS, LANDEWÉ R, BREEDVELD FC *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010; 69: 964-75.
2. WAKEFIELD RJ, FREESTON JE, O'CONNOR P *et al*.: The optimal assessment of the rheumatoid arthritis hindfoot: a comparative study of clinical examination, ultrasound and high field MRI. *Ann Rheum Dis* 2008; 67: 1678-82.
3. RAHMANI M, CHEGINI H, NAJAFIZADEH SR *et al*.: Detection of bone erosion in early rheumatoid arthritis: ultrasonography and conventional radiography versus non-contrast magnetic resonance imaging. *Clin Rheumatol* 2010; 29: 883-91.
4. TAN YK, CONAGHAN PG: Imaging in rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2011; 25: 569-84.
5. PETERFY C, ØSTERGAARD M, CONAGHAN PG *et al*.: MRI comes of age in RA clinical trials. *Ann Rheum Dis* 2013; 72: 794-6.
6. WAKEFIELD RJ, BALINT PV, SZKUDLAREK M *et al*.: Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32: 2485-7.

7. ØSTERGAARD M, PETERFY C, CONAGHAN P *et al*.: OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. *J Rheumatol* 2003; 30: 1385-6
8. D'AGOSTINO MA, CONAGHAN PG, NAREDO E *et al*.: The OMERACT ultrasound task force – Advances and priorities. *J Rheumatol* 2009; 36: 1829-32.
9. COLEBATCH AN, EDWARDS CJ, OSTERGAARD M *et al*.: EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis* 2013 ; 72: 804-14.
10. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69: 1580-8.
11. ØSTERGAARD M: Clarification of the role of ultrasonography, magnetic resonance imaging and conventional radiography in the ACR/EULAR 2010 rheumatoid arthritis classification criteria - comment to the article by Aletaha *et al*. *Ann Rheum Dis* 2010; e-letter [Epub Dec 2, 2010].
12. ALETAHA D, HAWKER G, NEOGI T, SILMAN A: Re: Clarification of the role of ultrasonography, magnetic resonance imaging and conventional radiography in the ACR/EULAR 2010 rheumatoid arthritis classification criteria - Reply to comment to the article by Aletaha *et al*. *Ann Rheum Dis*, e-letter [Epub Jan 11, 2011].
13. MCALINDON T, KISSIN E, NAZARIAN L *et al*.: American College of Rheumatology report on reasonable use of musculoskeletal ultrasonography in rheumatology clinical practice *Arthritis Care Res* (Hoboken) 2012; 64: 1625-40.
14. NAREDO E, GAMERO F, BONILLA G *et al*.: Ultrasonographic assessment of inflammatory activity in rheumatoid arthritis: Comparison of extended versus reduced joint evaluation. *Clin Exp Rheumatol* 2005; 23: 881-4.
15. FILER A, DE PABLO P, ALLEN G *et al*.: Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. *Ann Rheum Dis* 2011; 70: 500-7.
16. FUKAE J, SHIMIZU M, KON Y *et al*.: Screening for rheumatoid arthritis with finger joint power Doppler ultrasonography: quantification of conventional power Doppler ultrasonographic scoring. *Mod Rheumatol* 2009; 19: 502-6.
17. NAKAGOMI D, IKEDA K, OKUBO A *et al*.: Ultrasound can improve the accuracy of the 2010 American College of Rheumatology/ European League against rheumatism classification criteria for rheumatoid arthritis to predict the requirement for methotrexate treatment. *Arthritis Rheum* 2013; 65: 890-8.
18. MACHADO PM, KOEVOETS R, BOMBARDIER C, VAN DER HEIJDE DM: The value of magnetic resonance imaging and ultrasound in undifferentiated arthritis: a systematic review. *J Rheumatol* 2011; 87 (Suppl.): 31-7.
19. DUER A, ØSTERGAARD M, VALLØ J, HØRSLEV-PETERSEN K: Value of magnetic resonance imaging and bone scintigraphy in the differential diagnosis of unclassified polyarthritis. *Arthritis Rheum* 2005; 52: S1842.
20. TAMAI M, KAWAKAMI A, UETANI M *et al*.: A prediction rule for disease outcome in patients with undifferentiated arthritis using magnetic resonance imaging of the wrists and finger joints and serologic autoantibodies. *Arthritis Rheum* 2009; 61: 772-8.
21. DUER-JENSEN A, HORSLEV-PETERSEN K, HETLAND ML *et al*.: Bone edema on magnetic resonance imaging is an independent predictor of rheumatoid arthritis development in patients with early undifferentiated arthritis. *Arthritis Rheum* 2011; 63: 2192-202.
22. DUER-JENSEN A, HØRSLEV-PETERSEN K, BAK L *et al*.: Using MRI synovitis to count involved joints in the ACR/EULAR 2010 RA criteria increases their sensitivity and specificity. *Ann Rheum Dis* 2012; 71 (Suppl.): S601.
23. HETLAND ML, EJBJERG B, HORSLEV-PETERSEN K *et al*.: MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomised controlled trial (CIMESTRA). *Ann Rheum Dis* 2009; 68: 384-90.
24. HETLAND ML, STENGAARD-PEDERSEN K, JUNKER P *et al*.: Radiographic progression and remission rates in early rheumatoid arthritis - MRI bone oedema and anti-CCP predicted radiographic progression in the 5-year extension of the double-blind randomised CIMESTRA trial. *Ann Rheum Dis* 2010; 69: 1789-95.
25. BROWN AK, CONAGHAN PG, KARIM Z *et al*.: An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. *Arthritis Rheum* 2008; 58: 2958-67.
26. MCQUEEN FM, GAO A, OSTERGAARD M *et al*.: High-grade MRI bone oedema is common within the surgical field in rheumatoid arthritis patients undergoing joint replacement and is associated with osteitis in subchondral bone. *Ann Rheum Dis* 2007; 66: 1581-7.
27. HAAVARDSHOLM EA, BØYESEN P, ØSTERGAARD M *et al*.: Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression. *Ann Rheum Dis* 2008; 67: 794-800.
28. KAMISHIMA T, TANIMURA K, SHIMIZU M *et al*.: Monitoring anti-interleukin 6 receptor antibody treatment for rheumatoid arthritis by quantitative magnetic resonance imaging of the hand and power Doppler ultrasonography of the finger. *Skeletal Radiol* 2011; 40: 745-55.
29. BØYESEN P, HAAVARDSHOLM EA, VAN DER HEIJDE D *et al*.: Prediction of MRI erosive progression: a comparison of modern imaging modalities in early rheumatoid arthritis patients. *Ann Rheum Dis* 2011; 70: 176-9.
30. TAKASE K, OHNO S, TAKENO M *et al*.: Simultaneous evaluation of long-lasting knee synovitis in patients undergoing arthroplasty by power Doppler ultrasonography and contrast-enhanced MRI in comparison with histopathology. *Clin Exp Rheumatol* 2012; 30: 85-92.
31. WAMSER G, BOHNDORF K, VOLLERT K, BÜCKLEIN W, SCHALM J: Power Doppler sonography with and without echo-enhancing contrast agent and contrast-enhanced MRI for the evaluation of rheumatoid arthritis of the shoulder joint: differentiation between synovitis and joint effusion. *Skeletal Radiol* 2003; 32: 351-9.
32. HOVING JL, BUCHBINDER R, HALL S *et al*.: A comparison of magnetic resonance imaging, sonography, and radiography of the hand in patients with early rheumatoid arthritis. *J Rheumatol* 2004; 31: 663-75.
33. BROWN AK, QUINN MA, KARIM Z *et al*.: Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. *Arthritis Rheum* 2006; 54: 3761-73.
34. BRUYN GA, PINEDA C, HERNANDEZ-DIAZ C *et al*.: Validity of ultrasonography and measures of adult shoulder function and reliability of ultrasonography in detecting shoulder synovitis in patients with rheumatoid arthritis using magnetic resonance imaging as a gold standard. *Arthritis Care Res* (Hoboken) 2010; 62: 1079-86.
35. ALASAARELA E, SURAMO I, TERVONEN O, LÄHDE S, TAKALO R, HAKALA M: Evaluation of humeral head erosions in rheumatoid arthritis: a comparison of ultrasonography, magnetic resonance imaging, computed tomography and plain radiography. *Br J Rheumatol* 1998; 37: 1152-6.
36. DØHN UM, EJBJERG BJ, COURT-PAYEN *et al*.: Are bone erosions detected by magnetic resonance imaging and ultrasonography true erosions? A comparison with computed tomography in rheumatoid arthritis metacarpophalangeal joints. *Arthritis Res Ther* 2006; 8: R110.
37. DØHN UM, EJBJERG B, BOONEN A *et al*.: No overall progression and occasional repair of erosions despite persistent inflammation in adalimumab-treated rheumatoid arthritis patients: results from a longitudinal comparative MRI, ultrasonography, CT and radiography study. *Ann Rheum Dis* 2011; 70: 252-8.
38. BAILLET A, GAUJOUX-VIALA C, MOUTERDE G *et al*.: Comparison of the efficacy of sonography, magnetic resonance imaging and conventional radiography for the detection of bone erosions in rheumatoid arthritis patients: a systematic review and meta-analysis. *Rheumatology* (Oxford) 2011; 50: 1137-47
39. GANDJBAKHCH F, CONAGHAN PG, EJBJERG B *et al*.: Synovitis and osteitis are very frequent in rheumatoid arthritis clinical remission: results from an MRI study of 294 patients in clinical remission or low disease activity state. *J Rheumatology* 2011; 38: 2039-44.
40. SCIRÈ CA, MONTECUCCO C, CODULLO V *et al*.: Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. *Rheumatology* (Oxford) 2009; 48: 1092-7.
41. PELUSO G, MICHELUTTI A, BOSELLO S *et al*.: Clinical and ultrasonographic remission

determines different chances of relapse in early and long standing rheumatoid arthritis. *Ann Rheum Dis* 2011; 70: 172-5.

42. RANGANATH VK, STRAND V, PETERFY CG *et al*.: The utility of magnetic resonance imaging for assessing structural damage in randomized controlled trials in rheumatoid arthritis: Report from the imaging group of the American College of Rheumatology RA clinical trials task force. *Arthritis Rheum* 2013 [in press].
43. WAKEFIELD RJ, D'AGOSTINO MA, NAREDO E *et al*.: After treat-to-target: can a targeted ultrasound initiative improve RA outcomes? *Ann Rheum Dis* 2012; 71: 799-803.
44. HAAVARDSHOLM EA, OSTERGAARD M, EJBJERG BJ *et al*.: Reliability and sensitivity to change of the OMERACT rheumatoid arthritis magnetic resonance imaging score in a multireader, longitudinal setting. *Arthritis Rheum* 2005; 52: 3860-7.
45. MANDL P, NAREDO E, WAKEFIELD RJ, CONAGHAN PG, D'AGOSTINO MA: A systematic literature review analysis of ultrasound joint count and scoring systems to assess synovitis in rheumatoid arthritis according to the OMERACT filter. *J Rheumatology* 2011;38: 2055-62.
46. HAMMER HB, KVIEN TK: Comparisons of 7- to 78-joint ultrasonography scores: all different joint combinations show equal response to adalimumab treatment in patients with rheumatoid arthritis. *Arthritis Res Ther* 2011; 13: R78.
47. HAAVARDSHOLM EA, ØSTERGAARD M, HAMMER HB *et al*.: Monitoring anti-TNF-alpha treatment in rheumatoid arthritis: responsiveness of magnetic resonance imaging and ultrasonography of the dominant wrist joint compared with conventional measures of disease activity and structural damage. *Ann Rheum Dis* 2009; 68: 1572-9.