The Journal of Rheumatology Volume 28, no. 5

Measurements of rheumatoid arthritis disease activity and damage using magnetic resonance imaging. Truth and discrimination: does MRI make the grade?

M N Lassere and P Bird

J Rheumatol 2001;28;1151-1157
http://www.jrheum.org/content/28/5/1151

Measurement of Rheumatoid Arthritis Disease Activity and Damage Using Magnetic Resonance Imaging. Truth and Discrimination: Does MRI Make the Grade?

MARISSA N.D. LASSERE and PAUL BIRD

ABSTRACT. Magnetic resonance imaging (MRI) is a tool with unprecedented capabilities. Rheumatoid arthritis (RA) abnormalities that can be measured with MRI include erosions, articular cartilage thickness, synovial membrane volume, and pannus. However, as access to MRI increases, there is a risk that its use will not be evaluated using rigorous scientific measurement principles. We reviewed published MRI measurement methods for RA and investigated whether the methods were systematically evaluated for reliability, validity, and responsiveness to change — components of the OMERACT filter. Medline and Embase databases were searched from 1966 to 1999. Titles and abstracts were scanned to identify publications on MRI methods used to assess either disease activity or damage in RA. A data extraction template was developed and 68 peer reviewed publications from 40 research groups were appraised; 40 addressed RA disease activity, 4 RA damage, and 24 both activity and damage. Joints most frequently assessed were knee (32 publications) and wrist (31 publications). Ninety-one percent of publications evaluated either reliability or validity or responsiveness to change. Thirteen percent evaluated all 3 and only 9% evaluated none of these measurement properties. Validity was evaluated in 85%, responsiveness to change in 37%, and reliability in 35% of publications. Only 12% of publications evaluated both intra and inter-reliability. Few publications of MRI measures of disease activity or damage in RA met the OMERACT filter for all measurement properties. It would be regrettable if MRI measures are developed ad hoc, with little regard to considerations of scaling, reliability, validity, and responsiveness to change, because this will severely limit their ability to confidently assess treatment efficacy and prognostic indicators. (J Rheumatol 2001;28:1151–7)

Key Indexing Terms:
MAGNETIC RESONANCE IMAGING RHEUMATOID ARTHRITIS SYNOVITIS
MEASUREMENT RELIABILITY RESPONSIVENESS

Radiographs: the good, the bad, and the ugly

The good. Traditionally, the radiograph has measured damage in rheumatoid arthritis (RA), and most disease modifying therapies in RA are judged by their ability to prevent or retard radiological damage. Radiographs reflect several elements of structural damage of joints, including joint space narrowing (due to articular cartilage loss), bone cysts and erosions (due to discrete bone resorption), osteophytes, and malalignment. Serial radiographs can be used to evaluate the progression of damage over time. Radiographs and the scoring methods are relatively easy to perform, are relatively cheap, and provide a permanent record allowing repeat scoring.

The bad. Radiographs have clear limitations. Although they offer spatial resolution for bony detail, they present technical problems that limit their role as a disease measure. The radiographic technique projects a 3 dimensional structure onto a 2 dimensional film, and in the process distorts the geometry. This is particularly problematic when comparison of serial films is important. Further, because of superimposition inherent in the projection, certain structures such as erosions may be minimized or obscured entirely. The fundamental limitation of the radiograph is that it cannot directly visualize those important structures such as cartilage, synovium, periarticular soft tissues, and bone marrow that reflect disease activity effects; and in early disease they are relatively insensitive for even osseous structures.

The ugly. The above limitations of the content validity of radiographs are reasonably well recognized. Most work in radiographic scoring methods in the last quarter century has focused on what features to include (i.e., erosions, joint space narrowing, osteoporosis, soft tissue swelling), which joints to include, and what measurement system to adopt (i.e., grading, scoring, counting, measuring area). However, there has been relatively little systematic evaluation of many of the disease activity and damage measures in RA

From the Department of Rheumatology, St. Georges Hospital, Sydney, Australia.

M. Lassere, MB, BS Hons, Grad Dip Epi, PhD, FAFPHM FRACP, Staff Specialist in Rheumatology; P. Bird, BMed Hons, FRACP, Research Scholar.

Address reprint requests to Dr. M.N.D. Lassere, Department of Rheumatology, St. George Hospital, Kogarah, NSW 2217, Australia. E-mail: lasserem@sesahs.nsw.gov.au

including that of radiographs regarding the important measurement issues of reliability and responsiveness[1]. This is partly due to the complexity of measurement methodology.

Therefore, despite decades of development and testing (and numerous peer reviewed publications), current radiographic scoring methods require further evaluation of the basic elements of scaling, discriminatory performance (reliability and responsiveness to change), and truth (validity). This evaluation must be grounded in data and systematic experiment and is fundamental to our understanding of what is a minimal clinically important difference (a recurrent theme of OMERACT 4 and OMERACT 5[2]).

Magnetic resonance imaging (MRI)

MRI may be able to overcome many of the limitations of radiographs noted above. First, from the point of view of the patient, it does not employ ionizing radiation. Being a cross sectional technique, it does not suffer from projectional distortion or superimposition, as does the radiograph. It has the ability to image in any plane, which can help to visualize curved surfaces, and the imaging variables can be manipulated to accentuate a particular process of interest. MRI can also acquire 3 dimensional data allowing volumetric calculations of joint components. Gadolinium, a paramagnetic medium, enhances synovium and can be used to measure synovial volume. Its rate of enhancement can be used to measure inflammatory activity. Therefore, MRI noninvasively provides simultaneous assessment of osseous (including bone marrow) and soft tissue structures (both intra- and extraarticular), and can differentiate between synovium and cartilage. Abnormalities that could be measured include erosions, articular cartilage thickness, and synovial membrane volume and pannus activity.

Foreseeable problems. However, we run the risk of being seduced and bamboozled by this technique — by the anatomic detail, the panorama of tissues, sliced sagitally, coronally and transversely; by the hardware — superconducting magnets, volume coils; and particularly by the impressive and endless jargon — T1 weighted, T2 weighted, spin-echo, fast spin-echo, gradient-echo, GRASS, STIR, FLASH, FISP, gadolinium-DTPA, voxels, pixels, flip angles, magnetization transfer, proton precession, and radiofrequency pulse. Indeed, are we being lured, wooed, and beguiled by the marvels of quantum physics?

Furthermore, as noted above, measurement — and its jargon — are also difficult. Scale construction requires consideration of levels of measurement (nominal, ordinal, interval, and ratio), weighting (implicit, explicit), and aggregation. It requires thought whether to use a discrete or a continuous measure, and whether to grade, score, count, or calculate areas or volume. Once a scale has been constructed, all sources of variability and concomitant reliability (including the smallest detectable difference), validity (face, content, construct, criterion), and responsiveness to change (also with multiple facets) have to be determined.

Given these problems there is a risk that as access to MRI increases its use will not be evaluated using rigorous scientific measurement principles. Therefore the goal of this paper was to systematically survey published MRI methods in RA for evaluation of the OMERACT filter components: truth (validity) and discrimination (reliability and responsiveness to change)[3].

METHODS

Medline and Embase databases were searched using the medical subject headings: "MRI (or magnetic resonance imaging) AND [rheumatoid arthritis OR synovitis OR synovial membrane]" from 1966 to 1999 (121 publications). Titles and abstracts were scanned and the following were excluded: letters, non-English publications, review articles, non-human magnetic resonance, and publications not related to measurement systems of RA disease activity or damage of the knee, wrist, metacarpophalangeal (MCP) joint, proximal interphalangeal (PIP) joint or foot, thus leaving 68 publications. Although 49 published conference proceedings were identified in *Arthritis and Rheumatism* and *British Journal of Rheumatology* (1991-1999), they are not included in this review.

A data extraction template was developed. Studies were evaluated (yes, no, unclear) for the following: description of MRI sequences and variables (e.g., machine, magnet, sequences, views, slice thickness, gaps, field of view, scan times); description of clinical or laboratory or radiographic or histopathological assessment; description of MRI rheumatoid disease activity or damage measurement system; source (and number) of patients and normal controls; assessment of machine reliability; intraobserver/method reliability; interobserver/method reliability; construct validity; criterion validity[4]; and responsiveness of the MRI measure to change.

RESULTS

Sixty-eight peer reviewed publications were identified from 40 research groups (Table 1). Forty publications (59%) assessed RA disease activity alone, 4 assessed damage alone, 20 assessed both activity and damage (29%), and the remaining 4 assessed activity and damage in combination. Seventy-four percent of the reports were published since 1994. Joints most frequently assessed were the knee (32 publications) and wrist (31 publications), then the MCP, PIP, metatarsophalangeal, and tarsal joints, respectively (17, 8, 3, and one publications). All but one publication clearly described the MRI sequences and variables. Fewer publications clearly described any clinical assessment or the MRI measurement system they were evaluating (Table 2).

The MRI measurement system used was qualitative (either purely descriptive or grading of individual MRI features) in 27 publications, semiquantitative (gradings aggregated into an interval-like score) in 19 publications, and quantitative (a true interval or ratio scale, e.g., synovial membrane volume in milliliters, rate of synovial enhancement) in 32 publications. Eight publications developed more than one MRI measurement system. Ninety-one percent of publications evaluated either reliability or validity or responsiveness to change. Thirteen percent evaluated all 3 and only 9% evaluated none of these measurement proper-

Table 1. Study design and MRI measurement system evaluation of reviewed publications.

Year	Author	Joint Region	No. of RA Patients	Activity or Damage	Normal Subjects Included	Machine Reliability	Intrareliability	Interreliability	Construct Validity	Criterion Validity	Responsiveness to Change	Scaling* of MRI Measure
1988`	Gilkeson[5]	Wrist	10	A & D	No	No	No	No	Yes	No	No	1
1989	Heuck[6]	Knee	12	A	No	No	No	Yes	Yes	Yes	No	3
1990	Bjorkengren[7]	Knee	9	A	No	No	No	No	Yes	No	No	1
1990	Konig[8]	Knee	20	A	Yes	No	No	No	No	Yes	No	1
1990	Kursunoglu-Brahme[9]	Knee	14	A	Yes	No	No	No	Yes	Yes	Yes	1
1990	Meske[10]	Wrist		A, D	Yes	Yes	Yes	Yes	Yes	Yes	Yes	1
1991	Adam[11]	Knee	23	A	Yes	No	No	No	No	No	No	1
1991	Foley-Nolan[12]	Wrist	11	D	Yes	No	No	No	Yes	No	No	1
1992	Corvetta[13]	Wrist MCP PIP	31	A, D	No	No	No	No	Yes	No	No	2
1992	Singson[14]	Knee	10 of 1051	A	uncl	No	No	No	uncl	No	No	1
1993	Gubler[15]	Wrist MCP tarsal MTP	9	A	No	No	No	No	Yes	No	No	1
1993	Jevtic[16]	Wrist MCP PIP	45	A	No	No	No	No	Yes	No	No	2
1993	Jevtic[17]	Wrist MCP	65	A	No	No	No	No	Yes	No	Yes	2
1993	Jorgensen[18]	Wrist	15	A, D	Yes	No	No	No	Yes	No	Yes	1
1993	Rominger[19]	Wrist MCP	30	A, D	Yes	No	No	No	uncl	No	uncl	1
1993	Schweitzer[20]	Knee	6	A	Yes	No	No	Yes	No	Yes	No	3
1993	Yamato[21]	Knee	13	A	No	No	No	No	Yes	No	No	3
1993	Yanagawa[22]	Wrist	49	A	Yes	No	No	No	Yes	No	No	1
1994	Ostergaard[23]	Knee	12	A	Yes	Yes	No	Yes	Yes	No	No	3
1994	Ostergaard[24]	Knee	15	A	Yes	No	No	No	Yes	No	No	3
1994	Poleksic[25]	Knee	33	A, D	No	No	No	No	No	No	Yes	1
1994	Tamai[26]	Knee	9	A	No	No	No	No	Yes	No	No	3
1995	Gaffney[27]	Knee	21	A	No	No	Yes	No	Yes	Yes	No	3
1995	Giovagnoni[28]	Wrist MCP PIP	18	A & D	No	No	No	No	No	No	No	1
1995	Jetvic[29]	Wrist MCP	1	A & D	No	No	No	No	No	No	Yes	1
1995	Jetvic[30]	MCP PIP	16	A & D	No	No	No	No	No	No	No	1
1995	Ostergaard[31]	Knee	17	A, D	Yes	No	No	No	Yes	No	Yes	2, 3
1995	Ostergaard[32]	Knee	10	A	No	No	No	No	No	Yes	Yes	3
1995	Ostergaard[33]	Wrist	16	A	Yes	No	No	No	Yes	No	No	2
1995	Ostergaard[34]	Knee	10	A, D	Yes	No	No	No	Yes	No	No	3
1995	Palmer[35]	Wrist	12	A	No	No	Yes	No	Yes	No	Yes	3
1995	Peterfy[36]	MCP	1	D	Yes	No	Yes	Yes	No	Yes	No	3
1995	Polisson[37]	Wrist	2	A	No	No	No	No	Yes	No	Yes	2
1996	Jetvic[38]	Wrist	15	A	No	No	No	No	Yes	No	Yes	2
1996	Leitch[39]	Knee	6	A	No	No	No	No	No	No	Yes	1, 3
1998	Nakahara[40]	Wrist	27	A	Yes	No	No	No	Yes	No	Yes	3
1996	Oliver[41]	Knee	21	A	No	No	No	No	Yes	No	Yes	3
1996	Ostergaard[42]	Knee	15	A, D	No	Yes	Yes	No	No	No	Yes	2, 3
1996	Ostergaard[43]	Wrist	26	A	No	No	No	No	Yes	No	No	2, 3
1996	Ostergaard[44]	Knee	22	A	No	Yes	No	Yes	Yes	No	Yes	3
1996	Poleksic[45]	Knee	43	A, D	No	No	No	No	No	No	No	1

Table 1. Continued.

Year	Author	Joint Region	No. of RA Patients	Activity or Damage	Normal Subjects Included	Machine Reliability	Intrareliability	Interreliability	Construct Validity	Criterion Validity	Responsiveness to Change	Scaling* of MRI Measure
1996	Sugimoto[46]	Wrist MCP PIP	20	A	No	No	No	No	Yes	No	No	1
1996	Tonolli-Serabian[47]	Wrist	22	A. D	Yes	No	No	No	Yes	No	No	1
1997	Clunie[48]	Knee	18	A	No	No	Yes	Yes	Yes	No	Yes	3
1997	Creamer[49]	Knee	16	A	No	No	Yes	No	Yes	Yes	Yes	3
1997	Forslind[50]	Knee MTP	30	A, D	No	No	No	No	Yes	No	No	2
1997	Jetvic[51]	MCP PIP Wrist	31	A	No	No	No	No	Yes	No	No	3
1997	Kalden-Nemeth[52]	Wrist	18	A	Yes	No	No	No	Yes	No	Yes	3
1997	Ostergaard[53]	Knee Wrist	26 knee 17 wrist	A	No	Yes	No	No	No	Yes	No	3
1997	Ostergaard[54]	Knee	37	A	No	No	No	No	Yes	No	No	3
1997	Pierre-Jerome[55]	Wrist	33	D	Yes	No	No	No	Yes	No	No	1
1998	Gaffney[56]	Knee	31	A	No	Yes	Yes	No	Yes	Yes	No	3
1998	McQueen[57]	Wrist	42	A, D	No	No	Yes	Yes	Yes	No	No	2
1998	Ostergaard[58]	Knee	17	A	No	No	No	No	Yes	No	No	3
1998	Sugimoto[59]	Wrist MCP PIP	11	A	No	No	No	No	Yes	No	Yes	3
1998	Takeuchi[60]	Knee	86	A, D	Yes	No	No	No	Yes	No	No	1, 2
1998	Uhl[61]	MCP MTP	20 jts	D	No	No	No	No	Yes	No	No	1
1999	Backhaus[62]	MCP PIP DIP	60	A, D	No	No	Yes	No	Yes	No	No	2
1999	Huh[63]	Wrist	16	A, D	Yes	No	Yes	Yes	Yes	No	Yes	2
1999	Klarlund[64]	MCP	37	A	Yes	No	Yes	Yes	Yes	No	No	2, 3
1999	Klarlund[65]	Wrist MCP	33	A, D	Yes	No	No		Yes	No	No	2
1999	Lee[66]	Wrist	10	A, D	No	No	No	No	No	No	Yes	1, 2, 3
1999	McGonagle[67]	MCP		A	Yes	No	No	Yes	Yes	No	No	1
1999	McQueen[68]	Wrist	42	A, D	No	No	Yes	Yes	Yes	Yes	Yes	2
1999	Ostergaard[69]	Wrist	26	A, D	No	No	Yes	No	Yes	No	Yes	3
1999	Pirich[70]	Knee	13	A, D	No	No	Yes	Yes	Yes	No	Yes	1, 2, 3
1999	Rand[71]	Knee	20	A	No	No	No	Yes	No	No	No	1
1999	Veale[72]	Knee	12	A	Yes	No	No	No	Yes	Yes	Yes	3

*1: qualitative; 2: semi-quantitative; 3: quantitative. MCP: metacarpophalangeal; PIP: proximal interphalangeal; DIP: distal interphalangeal; MTP: metatarsophalangeal.

Table 2. Reporting of study methods and MRI measurement system evaluation.

Study Methods and MRI Measurement System	No. of Publications		
	Yes	No	Unclear
Description MRI sequences and variables?	67	0	1
Description patient clinical assessment?	50	12	6
Description MRI measurement system?	51	13	4
Evaluation of MRI machine reliability?	6	62	0
Evaluation of MRI intraobserver/method reliability?	15	53	0
Evaluation of MRI interobserver/method reliability?	15	53	0
Evaluation of MRI measurement system construct validity?	51	15	2
Evaluation of MRI measurement system criterion validity?	13	55	0
Evaluation of MRI measurement system responsiveness to change?	18	49	1

ties. Validity was evaluated in 85%, responsiveness to change in 37%, and reliability in 35% of publications. Only 12% of publications evaluated both intra and inter-reliability. Construct validity (reported in 75% of publications) was ascertained using clinical constructs (joint swelling or tenderness) in 39 publications, radiographs in 27 publications, other imaging in 2 publications (PET and ultrasound), and histology in 7 publications. Criterion validity (reported in 19% of publications) was ascertained using several innovative methods including direct estimation of synovial effusion volume by arthrocentesis, and histopathological examination of joints following joint replacement surgery. Responsiveness to change (reported in 37% of publications) was generally ascertained in a longitudinal before–after treatment study design.

DISCUSSION

An important endpoint of therapeutic assessment in RA is damage prevention, as reflected in structure. Currently, this is done via the radiograph and appears to take a minimum of 12–18 months. To accelerate testing of the ability of new therapies to control damage, it is critical that we develop new techniques that are both superior in sensitivity and have more stringent metrological properties than the standard radiograph. MRI has the potential to serve this purpose.

A foreseeable problem is that increased access to new technology will lead to neglect of rigorous evaluation of measurement fundamentals. In this review of published MRI methods of RA activity and damage evaluation, few met all OMERACT filter components of truth (validity) and discrimination (reliability and responsiveness to change).

All new clinical tools should be developed and tested in a systematic and meticulous manner, and MRI, in particular, would benefit from a confluence of clinicians, radiologists, technicians, and measurement experts. The OMERACT 5 Working Party on MRI Evaluation of RA[73] is one example of how the interaction of experts can facilitate the development and testing of new clinical tools that efficiently and accurately demonstrate prognostic indicators and therapeutic effects.

REFERENCES

1. Lassere M, van der Heijde DM, Johnson K, Boers M, Edmonds J. The reliability of measures of disease activity and disease damage in rheumatoid arthritis: implications for the smallest detectable difference, the minimal clinically important difference and the analysis of treatment effects in randomized controlled trials. J Rheumatol 2001;28:892-903.
2. Lassere M, van der Heijde DM, Johnson K. Foundations of the minimal clinically important difference for imaging. J Rheumatol 2001;28:890-1.
3. Boers M, Brooks P, Strand V, Tugwell P. The OMERACT filter for outcome measures in rheumatology. J Rheumatol 1998;25:198-9.
4. Last J. A dictionary of epidemiology. New York: Oxford University Press; 1988.
5. Gilkeson G, Polisson R, Sinclair H, et al. Early detection of carpal erosions in patients with rheumatoid arthritis: a pilot study of magnetic resonance imaging. J Rheumatol 1988;15:1361-6.
6. Heuck A, Steiger P, Stoller D, Gluer C, Genant H. Quantification of knee joint fluid by MR imaging and CT using three-dimensional data processing. J Comput Assist Tomogr 1989;13:287-93.
7. Bjorkengren AG, Geborek P, Rydholm U, Holtas S, Petterson H. MR imaging of the knee in acute rheumatoid arthritis: synovial uptake of gadolinium-DPTA. AJR Am J Roentgenol 1990; 155:329-32.
8. Konig H, Sieper J, Wolf KJ. Rheumatoid arthritis: evaluation of hypervascular and fibrous pannus with dynamic MR imaging enhanced with Gd-DTPA. Radiology 1990;176:473-7.
9. Kursunoglu-Brahme S, Riccio T, Weisman MH, et al. Rheumatoid knee: role of gadopentetate-enhanced MR imaging. Radiology 1990;176:831-5.
10. Meske S, Friedburg H, Hennig J, Reinbold W, Stappert K, Schumichen C. Rheumatoid arthritis lesions of the wrist examined by rapid gradient-echo magnetic resonance imaging. Scand J Rheumatol 1990;19:235-8.
11. Adam G, Dammer M, Bohndorf K, Christoph R, Fenke F, Gunther RW. Rheumatoid arthritis of the knee: value of gadopentetate dimeglumine-enhanced MR imaging. AJR Am J Roentgenol 1991;156:125-9.
12. Foley-Nolan D, Stack JP, Ryan M, et al. Magnetic resonance imaging in the assessment of rheumatoid arthritis — a comparison with plain film radiographs. Br J Rheumatol 1991;30:101-6.
13. Corvetta A, Giovagnoni A, Baldelli S, et al. MR imaging of rheumatoid hand lesions: comparison with conventional radiology in 31 patients. Clin Exp Rheumatol 1992;10:217-22.
14. Singson RD, Zalduondo F. Value of unenhanced spin echo MR imaging in distinguishing between synovitis and effusion of the knee. AJR Am J Roentgenol 1992;159:569-71.
15. Gubler FM, Algra PR, Maas M, Dijkstra PF, Falke TH. Gadolinium-DTPA enhanced magnetic resonance imaging of bone cysts in patients with rheumatoid arthritis. Ann Rheum Dis 1993;52:716-9.
16. Jevtic V, Watt I, Rozman B, et al. Precontrast and postcontrast (Gd-DTPA) magnetic resonance imaging of hand joints in patients with rheumatoid arthritis. Clin Radiol 1993;48:176-81.
17. Jevtic V, Watt I, Rozman B, Kos-Kolja M, Prapotnik S. The value of contrast enhanced MRI in evaluation of drug therapy in rheumatoid arthritis — prospective study on hand joints in 65 patients. Acta Pharm 1993;43:267-76.
18. Jorgensen C, Cyteval C, Anaya JM, Baron MP, Lamarque JL, Sany J. Sensitivity of magnetic resonance imaging of the wrist in very early rheumatoid arthritis. Clin Exp Rheumatol 1993;11:163-8.
19. Rominger MB, Bernreuter WK, Kenney PJ, Morgan SL, Blackburn WD, Alarcon GS. MR imaging of the hands in early rheumatoid arthritis: preliminary results. Radiographics 1993;13:37-46.
20. Schweitzer ME, Falk A, Pathria M, Brahme S, Hodler J, Resnick D. MR imaging of the knee: can changes in the intracapsular fat pads be used as a sign of synovial proliferation in the presence of an effusion? AJR Am J Roentgenol 1993;160:823-6.
21. Yamato M, Tamai K, Yamaguchi T, Ohno W. MRI of the knee in rheumatoid arthritis: Gd-DTPA perfusion dynamics. J Comput Assist Tomogr 1993;17:781-5.
22. Yanagawa A, Takano K, Nishioka K, Shimada J, Mizushima Y, Ashida H. Clinical staging and gadolinium-DTPA enhanced images of the wrist in rheumatoid arthritis. J Rheumatol 1993;20:781-4.
23. Ostergaard M, Gideon P, Henriksen O, Lorenzen I. Synovial volume — a marker of disease severity in rheumatoid arthritis? Quantification by MRI. Scand J Rheumatol 1994;23:197-202.
24. Ostergaard M, Lorenzen I, Henriksen O. Dynamic gadolinium-enhanced MR imaging in active and inactive immunoinflammatory gonarthritis. Acta Radiol 1994;35:275-81.

25. Poleksic L, Zdravkovic D, Musikic P, Campion G, Bacic G. Rheumatoid knee: the role of Gd-DTPA enhanced MRI in assessment of synovial and bony changes in therapeutic trials. Acta Pharm 1994;44:197-203.
26. Tamai K, Yamato M, Yamaguchi T, Ohno W. Dynamic magnetic resonance imaging for the evaluation of synovitis in patients with rheumatoid arthritis. Arthritis Rheum 1994;37:1151-7.
27. Gaffney K, Cookson J, Blake D, Coumbe A, Blades S. Quantification of rheumatoid synovitis by magnetic resonance imaging. Arthritis Rheum 1995;38:1610-7.
28. Giovagnoni A, Grassi W, Terilli F, Blasetti P, Paci E. Magnetic resonance imaging of the hand in psoriatic arthritis and rheumatoid arthritis. European Radiology 1995;5:590-5.
29. Jevtic V, Rozman B, Watt I, Presetnik M. Use of contrast enhanced MRI in the assessment of therapeutic response to a disease-modifying antirheumatic drug. Case study of a patient with rheumatoid arthritis — 6- and 24-month follow up. Br J Rheumatol 1995;34:956-9.
30. Jevtic V, Watt I, Rozman B, Kos-Golja M, Demsar F, Jarh O. Distinctive radiological features of small hand joints in rheumatoid arthritis and seronegative spondyloarthritis demonstrated by contrast-enhanced (Gd-DTPA) magnetic resonance imaging. Skeletal Radiol 1995;24:351-5.
31. Ostergaard M, Stoltenberg M, Gideon P. Effects of intraarticular osmic acid on synovial membrane volume and inflammation determined by magnetic resonance imaging. Scand J Rheumatol 1995;24:5-12.
32. Ostergaard M, Stoltenberg M, Henriksen O, Lorenzen I. The accuracy of MRI-determined synovial membrane and joint effusion volumes in arthritis. A comparison of pre- and post-aspiration volumes. Scand J Rheumatol 1995;24:305-11.
33. Ostergaard M, Gideon P, Sorensen K, et al. Scoring of synovial membrane hypertrophy and bone erosions by MR imaging in clinically active and inactive rheumatoid arthritis of the wrist. Scand J Rheumatol 1995;24:212-8.
34. Ostergaard M, Court-Payen M, Gideon P, et al. Ultrasonography in arthritis of the knee. A comparison with MR imaging. Acta Radiol 1995;36:19-26.
35. Palmer WE, Rosenthal DI, Schoenberg OI, et al. Quantification of inflammation in the wrist with gadolinium-enhanced MR imaging and PET with 2-[F-18]-fluoro-2-deoxy-D-glucose. Radiology 1995;196:647-55.
36. Peterfy CG, van Dijke CF, Lu Y, et al. Quantification of the volume of articular cartilage in the metacarpophalangeal joints of the hand: accuracy and precision of three-dimensional MR imaging. AJR Am J Roentgenol 1995;165:371-5.
37. Polisson RP, Schoenberg OI, Fischman A, et al. Use of magnetic resonance imaging and positron emission tomography in the assessment of synovial volume and glucose metabolism in patients with rheumatoid arthritis. Arthritis Rheum 1995;38:819-25.
38. Jevtic V, Watt I, Rozman B, et al. Prognostic value of contrast enhanced Gd-DTPA MRI for development of bone erosive changes in rheumatoid arthritis. Br J Rheumatol 1996:35 Suppl 3:26-30.
39. Leitch R, Walker SE, Hillard AE. The rheumatoid knee before and after arthrocentesis and prednisolone injection: evaluation by Gd-enhanced MRI. Clin Rheumatol 1996;15:358-66.
40. Nakahara N, Uetani M, Hayashi K, Kawahara Y, Matsumoto T, Oda J. Gadolinium-enhanced MR imaging of the wrist in rheumatoid arthritis: value of fat suppression pulse sequences. Skeletal Radiol 1996;25:639-47.
41. Oliver C, Speake S, Watt I, Dieppe P, Ratcliffe G. Advantages of an increased dose of MRI contrast agent for enhancing inflammatory synovium. Clin Radiol 1996;51:487-93.
42. Ostergaard M, Stoltenberg M, Gideon P, Sorensen K, Henriksen O, Lorenzen I. Changes in synovial membrane and joint effusion volumes after intraarticular methylprednisolone. Quantitative assessment of inflammatory and destructive changes in arthritis by MRI. J Rheumatol 1996;23:1151-61.
43. Ostergaard M, Hansen M, Stoltenberg M, Lorenzen I. Quantitative assessment of the synovial membrane in the rheumatoid wrist: an easily obtained MRI score reflects the synovial volume. Br J Rheumatol 1996;35:965-71.
44. Ostergaard M, Stoltenberg M, Henriksen O, Lorenzen I. Quantitative assessment of synovial inflammation by dynamic gadolinium-enhanced magnetic resonance imaging. A study of the effect of intra-articular methylprednisolone on the rate of early synovial enhancement. Br J Rheumatol 1996;35:50-9.
45. Poleksic L, Musikic P, Zdravkovic D, Watt I, Bacic G. MRI evaluation of the knee in rheumatoid arthritis. Br J Rheumatol 1996;35 Suppl 3:36-9.
46. Sugimoto H, Takeda A, Masuyama J, Furuse M. Early-stage rheumatoid arthritis: diagnostic accuracy of MR imaging. Radiology 1996;198:185-92.
47. Tonolli-Serabian I, Poet JL, Dufour M, Carasset S, Mattei JP, Roux H. Magnetic resonance imaging of the wrist in rheumatoid arthritis: comparison with other inflammatory joint diseases and control subjects. Clin Rheumatol 1996;15:137-42.
48. Clunie G, Hall-Craggs M, Paley M, et al. Measurement of synovial lining volume by MRI of the knee in chronic synovitis. Ann Rheum Dis 1997;56:526-34.
49. Creamer P, Keen M, Zananiri F, et al. Quantitative magnetic resonance imaging of the knee: a method of measuring response to intra-articular treatments. Ann Rheum Dis 1997;56:378-81.
50. Forslind K, Larsson EM, Johansson A, Svensson B. Detection of joint pathology by magnetic resonance imaging in patients with early rheumatoid arthritis. Br J Rheumatol 1997;36:683-8.
51. Jevtic V, Watt I, Rozman B, et al. Contrast enhanced Gd-DTPA magnetic resonance imaging in the evaluation of rheumatoid arthritis during a clinical trial with DMARDs. A prospective two-year follow-up study on hand joints in 31 patients. Clin Exp Rheumatol 1997;15:151-6.
52. Kalden-Nemeth D, Grebmeier J, Antoni C, Manger B, Wolf F, Kalden JR. NMR monitoring of rheumatoid arthritis patients receiving anti-TNF-alpha monoclonal antibody therapy. Rheumatol Int 1997;16:249-55.
53. Ostergaard M. Different approaches to synovial membrane volume determination by magnetic resonance imaging: manual versus automated segmentation. Br J Rheumatol 1997;36:1166-77.
54. Ostergaard M, Stoltenberg M, Lovgreen-Nielsen P, Volck B, Jensen CH, Lorenzen I. Magnetic resonance imaging-determined synovial membrane and joint effusion volumes in rheumatoid arthritis and osteoarthritis: comparison with the macroscopic and microscopic appearance of the synovium. Arthritis Rheum 1997;40:1856-67.
55. Pierre-Jerome C, Bekkelund SI, Mellgren SI, Torbergsen T, Husby G, Nordstrom R. The rheumatoid wrist: bilateral MR analysis of the distribution of rheumatoid lesions in axial plan in a female population. Clin Rheumatol 1997;16:80-6.
56. Gaffney K, Cookson J, Blades S, Coumbe A, Blake D. Quantitative assessment of the rheumatoid synovial microvascular bed by gadolinium-DTPA enhanced magnetic resonance imaging. Ann Rheum Dis 1998;57:152-7.
57. McQueen FM, Stewart N, Crabbe J, et al. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals a high prevalence of erosions at four months after symptom onset. Ann Rheum Dis 1998;57:350-6.
58. Ostergaard M, Stoltenberg M, Lovgreen-Nielsen P, Volck B, Sonne-Holm S, Lorenzen I. Quantification of synovitis by MRI: correlation between dynamic and static gadolinium-enhanced magnetic resonance imaging and microscopic and macroscopic signs of synovial inflammation. Magn Reson Imaging 1998; 16:743-54.

59. Sugimoto H, Takeda A, Kano S. Assessment of disease activity in rheumatoid arthritis using magnetic resonance imaging: quantification of pannus volume in the hands. Br J Rheumatol 1998;37:854-61.
60. Takeuchi K, Inoue H, Yokoyama Y, et al. Evaluation of rheumatoid arthritis using a scoring system devised from magnetic resonance imaging of rheumatoid knees. Acta Med Okayama 1998;52:211-24.
61. Uhl M, Allmann KH, Ihling C, Hauer MP, Conca W, Langer M. Cartilage destruction in small joints by rheumatoid arthritis: assessment of fat-suppressed three-dimensional gradient-echo MR pulse sequences in vitro. Skeletal Radiol 1998;27:677-82.
62. Backhaus M, Kamradt T, Sandrock D, et al. Arthritis of the finger joints: a comprehensive approach comparing conventional radiography, scintigraphy, ultrasound, and contrast-enhanced magnetic resonance imaging. Arthritis Rheum 1999;42:1232-45.
63. Huh YM, Suh JS, Jeong EK, et al. Role of the inflamed synovial volume of the wrist in defining remission of rheumatoid arthritis with gadolinium-enhanced 3D-SPGR MR imaging. J Magn Reson Imaging 1999;10:202-8.
64. Klarlund M, Ostergaard M, Lorenzen I. Finger joint synovitis in rheumatoid arthritis: quantitative assessment by magnetic resonance imaging. Br J Rheumatol 1999;38:66-72.
65. Klarlund M, Ostergaard M, Gideon P, Sorensen K, Jensen KE, Lorenzen I. Wrist and finger joint MR imaging in rheumatoid arthritis. Acta Radiol 1999;40:400-9.
66. Lee J, Lee SK, Suh JS, Yoon M, Song JH, Lee CH. Magnetic resonance imaging of the wrist in defining remission of rheumatoid arthritis. J Rheumatol 1997;24:1303-8.
67. McGonagle D, Conaghan PG, O'Connor P, et al. The relationship between synovitis and bone changes in early untreated rheumatoid arthritis: a controlled magnetic resonance imaging study. Arthritis Rheum 1999;42:1706-11.
68. McQueen FM, Stewart N, Crabbe J, et al. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals progression of erosions despite clinical improvement. Ann Rheum Dis 1999;58:156-63.
69. Ostergaard M, Hansen M, Stoltenberg M, et al. Magnetic resonance imaging-determined synovial membrane volume as a marker of disease activity and a predictor of progressive joint destruction in the wrists of patients with rheumatoid arthritis. Arthritis Rheum 1999;42:918-29.
70. Pirich C, Schwameis E, Bernecker P, et al. Influence of radiation synovectomy on articular cartilage, synovial thickness and enhancement as evidenced by MRI in patients with chronic synovitis. J Nucl Med 1999;40:1277-84.
71. Rand T, Imhof H, Czerny C, et al. Discrimination between fluid, synovium, and cartilage in patients with rheumatoid arthritis: contrast enhanced spin echo versus non-contrast-enhanced fat-suppressed gradient echo MR imaging. Clin Radiol 1999; 54:107-10.
72. Veale DJ, Reece RJ, Parsons W, et al. Intra-articular primatised anti-CD4: efficacy in resistant rheumatoid knees. A study of combined arthroscopy, magnetic resonance imaging, and histology. Ann Rheum Dis 1999;58:342-9.
73. Conaghan P, Edmonds J, Emery P, et al. Magnetic resonance imaging in rheumatoid arthritis: summary of OMERACT activities, current status and plans. J Rheumatol 2001;28:1158-61.