Optimal use of MRI in clinical trials, clinical care and clinical registries of patients with rheumatoid arthritis

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ABSTRACT

Magnetic resonance imaging (MRI) clearly is more sensitive than clinical examination and conventional radiography (x-ray) for detection of inflammation (synovitis, bone marrow oedema (osteitis) and tenosynovitis) and damage (bone erosion and cartilage loss/joint space narrowing) in patients with rheumatoid arthritis (RA). The question is when and how MRI should be used. The present article reviews our knowledge about, and provides suggestions for, the use of MRI in clinical trials, clinical care and clinical registries.

In clinical trials, the OMERACT RA MRI scoring system (RAMRIS) is a thoroughly validated method which in less time and with fewer patients than x-ray can discriminate between different therapies regarding structural damage progression, and which on top of this offers detailed assessment of upstream inflammatory drivers of damage.

In routine clinical care, MRI can contribute to an earlier diagnosis of RA, can reveal subclinical disease activity, e.g. in the synovium (synovitis) and bone (osteitis), and can provide information of strong prognostic significance for the subsequent disease course, which may be useful when deciding the treatment strategy. Future studies will clarify the benefits of including MRI in treat-to-target strategies.

The benefits of incorporating MRI into clinical registries are not yet known, but may include improved knowledge about the real-life advantages of MRI, as well as opportunities to develop better clinical and laboratory composite measures to monitor and predict the disease course in RA. In conclusion, MRI has well-documented relevance in several settings in clinical trials and care, but not yet in clinical registries.

Introduction

Magnetic resonance imaging (MRI) provides multiplanar tomographic imaging with unprecedented soft tissue contrast and allows assessment of all structures involved in rheumatic joint diseases, the prototype of which is rheumatoid arthritis (RA). Findings include synovitis, tenosynovitis, bone marrow oedema (osteitis), enthesitis, bone erosion and cartilage damage. It is widely accepted that MRI is more sensitive than clinical examination and x-ray for detection of inflammation and damage (1). The questions include when and how this exciting technology should be used in clinical trials and in clinical care (clinical practice) and whether it is worthwhile to spend resources on inclusion of MRI data in clinical registries? This article will briefly outline the current status on our knowledge for using MRI in these three settings.

Use in clinical trials

The validity of MRI depiction of inflammation (synovitis, osteitis and tenosynovitis) (2-7) and damage (bone erosion and cartilage loss/joint space narrowing) (8-11) in RA has been documented through numerous methodological and observational studies. First of all, MRI has been repeatedly shown to be more sensitive than conventional radiography (x-ray) for detecting structural joint damage in RA (8, 9, 12-16). Furthermore, MRI also can visualise the upstream inflammatory drivers of bone erosion and cartilage loss, namely synovitis and osteitis, as well as other important features of the disease, such as tenosynovitis (4-6, 17-20). The Outcome Measures in Rheumatology (OMERACT) Rheumatoid Arthritis MRI scoring method (RAMRIS), evaluating bone erosion, bone oedema (osteitis) and synovitis, and, most recently, joint space narrowing, has been extensively validated and a set of standard reference images are available (21-27). The RAMRIS is the standard MRI method in RA trials. Several randomised controlled trials

have demonstrated that it is possible with small numbers of patients to discriminate therapeutic efficacy of different structure-modifying therapies with MRI in <6 months, and in some studies even <3 months (28-33). It has been documented that MRI of just unilateral wrist and MCP joints requires less than half the number of patients and less than half the follow-up time of radiography of both hands, wrists and forefeet using the best possible method (Sharp-van der Heijde score) to detect a difference in structural damage progression between 2 treatment groups in early RA patients (30). Given this evidence and the ethical imperative to limit the time that patients are exposed to ineffective treatment in randomised controlled trials, MRI is a logical key outcome measure in clinical trials. Accordingly, it is appropriate that regulatory authorities now consider the use of MRI data as an alternative to radiographic data in support of claims of inhibition of progression of structural damage (34).

Use in clinical care

Diagnosis of RA

Early diagnosis is considered very important in RA, in order to quickly initiate appropriate therapy (35-37). Besides a positive effect on signs and symptoms of the disease, this approach has in RA also been shown to markedly improve long-term outcomes, such as pain, disability and structural damage (35-37).

Conventional clinical and biochemical examinations are often not sufficiently sensitive, neither to determine with certainty whether the patient suffers from an inflammatory arthritis or non-inflammatory arthralgia, nor to determine what the specific diagnosis is in case an inflammatory arthritis is present. Certain imaging modalities can assist in such processes, and may consequently be clinically useful. A 2009 systematic literature review (SLR) concluded that MRI bone oedema and the combined synovitis and erosion pattern seem useful in predicting development of RA from undifferentiated peripheral inflammatory arthritis, but that additional studies were needed (38). The SLR highlights 2 studies in pure undifferentiated arthritis; one showed that the combined synovitis and erosion pattern was related to development of RA or not (39), whereas the other demonstrated that presence of bone oedema had a positive predictive value of ~86% for subsequent development of RA according to the ACR 1987 criteria (40).

Subsequently, a large follow-up study of undifferentiated arthritis has documented MRI as predictor of the diagnosis of RA (41). In 116 undifferentiated patients bone oedema in wrist and MTP joints was an independent predictor of 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 (41).

In 2010, MRI (and ultrasonography (US)) was incorporated in international criteria for RA. The older American College of Rheumatology (ACR) 1987 criteria for RA were not very sensitive in early RA, and with the aim to improve performance in early disease, newly developed classification criteria for RA (the ACR/EULAR 2010 criteria for RA) were published in 2010 (42). In these, classification as definite RA is based on presence of definite clinical synovitis (swelling at clinical examination) in ≥1 joint, 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 4 domains. MRI and ultrasound are acceptable for the 'joint involvement' domain of these criteria, and thereby can provide up to 5 of the 6 points needed for a classification as RA. In other words, MRI can be used to determine the extent of joint involvement (42-44). The fact that MRI is now officially accepted for this purpose by the European and American rheumatological communities is an important step in the recognition of the utility of MRI in the diagnosis and management of inflammatory arthritides. Preliminary data have also demonstrated that substituting clinical assessment of joint involvement with MRI synovitis in 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 (45), supporting that modern imaging is of benefit for diagnosing RA in clinical care.

In agreement with the above, the EULAR recommendations on the use of imaging in RA clinical care, based on a systematic literature review of published evidence and expert opinion, state that MRI "can be used to improve the certainty of an RA diagnosis", as well as "to predict progression from undifferentiated inflammatory arthritis to clinical RA" (1).

Management of RA in clinical care

There is strong evidence, *e.g.* from clinical trials (see above), that MRI allows sensitive monitoring of inflammation as well as damage. This is illustrated in the EULAR recommendations which state "US and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for more accurate assessment of inflammation" (1). Thus, MRI can be used in clinical care to document improvement/worsening of disease activity. The question is when such imaging is needed, and/or when it is cost-effective to do? There is a lack of studies to document exactly how MRI should be used for this purpose. For instance, there is no need to do imaging to assess disease activity if the patient has obvious clinical signs of active RA and requires treatment intensification. Another important consideration is that the selection of method for providing more detailed information on the disease in the clinic depends on which expertise is present at that specific treatment center. For instance, US can replace MRI for assessment of synovitis, if a properly trained ultrasonographer is present. For assessment of inflammation in the bone (osteitis), MRI is, however, the only available modality, and it is also the best method, except for computed tomography (CT), for monitoring of progression of erosions (5, 6, 8, 9, 11, 13, 46).

Two areas are currently the most obvious for use of MRI in clinical care: 1) to obtain prognostic information in early RA for stratification of patients to different treatment approaches;

2) to assess if patients in clinical remission have disease activity which could not be detected by clinical assessment ("subclinical" disease activity).
To these could be added others, *e.g.* using MRI when activity and/or progression is doubtful after clinical assessment. However, below we will put emphasis on the 2 first-mentioned topics.

Prognostication in early RA / selecting patients for a more aggressive treatment strategy
Several studies have demonstrated a predictive value of MRI pathology in wrist and/or MCP joints to radiographic progression. In particular bone marrow oedema (osteitis) is now established as a strong independent predictor of subsequent radiographic progression in early RA (17, 47, 48). Regression analyses in three-year and 5-year follow-up in 2 of the cohorts have documented that MRI-bone oedema is a predictor of long-term radiographic progression (18, 19). Small studies have indicated a relationship of baseline MRI findings with long-term functional disability (49) and tendon rupture at 6 years (20). Recent data, moreover, have documented that early changes in osteitis after treatment initiation predict the course of radiographic damage (48). In other words, MRI is in early RA a very useful method to predict the severity of the disease, which may assist the clinician in the choice of treatment strategy. In agreement with this, the 2013 EULAR recommendations for the use of imaging of the joints in the clinical management of RA states "MRI bone oedema is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic indicator" (1).

MRI in clinical remission and the potential role of MRI in future treat-to-target strategies
The potential importance of MRI (and US) in defining and monitoring remission have attracted much interest in recent years (50). In 2006 Brown *et al.* demonstrated that MRI and/or ultrasonographic findings of inflammation are common in patients in clinical remission, and in 2008 that these findings are related to subsequent progression of structural joint damage (51, 52). Subsequently, it has been confirmed that MRI-detected subclinical inflammation independently predicts progression of structural joint damage (53, 54). Accordingly, the 2013 EULAR recommendations specifically refer to patients in clinical remission: "MRI and ultrasound can detect inflammation that predicts subsequent joint damage, even when clinical remission is present" (1). Thus, the available data indicate that imaging should be part of future remission criteria. However, it needs to be mentioned that no studies have yet addressed whether subclinical inflammation detected by imaging can be improved by treatment and whether an imaging-guided treatment strategy (where treatment is intensified in the presence of certain subclinical MRI-detected (or US-detected) signs of inflammation) improves key outcomes over and above what is achieved by a treat-to-target therapy based on conventional clinical and biochemical examinations. However a randomised controlled trial addressing if patients in clinical remission will benefit from MRI is ongoing in Denmark (the IMAGINE-RA study), in which the target is absence of MRI-detected osteitis and the primary endpoints are clinical remission and absence of radiographic progression after 2 years of follow-up (55).
Thus, increasing amounts of data support the use of MRI in clinical care for the assessment of patients with RA who are in clinical remission, to identify those who will show progression of structural joint damage. Ongoing studies will provide evidence concerning the value of an MRI-based treat-to-target strategy.

Use in clinical registries

Studies of the utility of including MRI (or US) into clinical registries are lacking. However, incorporating registration of MRI assessments into RA registries would provide a more detailed characterization of the inflammatory and damage status of the patient, and would strengthen the opportunities to learn more about the true real-life benefits of MRI in monitoring and predicting the course of RA. Such incorporation should be systematic, *i.e.* contain systematic structured MRI assessments, *e.g.* presence/absence of various features in each area/joint/site, *e.g.* synovitis, osteitis, tenosynovitis and bone erosion. It could also be potentially valuable to include semiquantitative assessments to provide data that could be analysed systematically. If a scoring system were applied, the OMERACT RAMRIS is the best available option (21), since it is the by far most validated method, and an atlas exist for comparison with standard reference images (25-27). However, overall there is no doubt that feasibility issues are the main obstacle to widespread use of MRI in clinical registries. Thus, a less detailed and less time consuming assessment system may increase feasibility. MRI without the use of contrast injection (56, 57), or dynamic contrast-enhanced MRI may be options, but are less validated (58-61).
Incorporation of MRI in clinical registries would also potentially allow developing new and better clinical tools, since it would allow testing of which clinical and biochemical parameters and combinations thereof that show the closest correlation with the best possible imaging modality. Thereby, it may be possible to optimise the clinical tools so they better predict the future disease course. As an interesting example of this potential, a recent study from a clinical trial setting demonstrated that a modification the 28-joint Disease activity score (DAS28), modified so that it best reflected MRI synovitis, more accurately predicts radiographic progression than the original DAS28 (62).
Finally, it should be mentioned that future registries should optimally not only include clinical and imaging data, but also a biobank, so that also novel soluble biomarker development could be improved by comparison with sensitive imaging modalities such as MRI.

Conclusion

MRI has well-documented relevance in several settings in clinical trials and practice, but not yet in clinical registries. In clinical trials, the OMERACT RA

MRI scoring system (RAMRIS) is a thoroughly validated method which in less time and with fewer patients than conventional radiography can discriminate between different therapies regarding structural damage progression, and which on top of this offers detailed assessment of upstream inflammatory drivers of damage.

In routine clinical care, MRI can contribute to an earlier diagnosis of RA, can reveal subclinical disease activity, *e.g.* in synovium (synovitis) and bone (osteitis), and can provide information of strong prognostic significance for the subsequent disease course, which may be useful when deciding the treatment strategy. Future studies will clarify the benefits of including MRI in future treat-to-target strategies.

Since no publications on MRI as part of clinical registries are available, the benefits of incorporating MRI are not yet known. These may include increased knowledge of the temporal and spatial course of the disease process in patients treated in routine care, and about the real-life advantages of MRI. Furthermore, incorporation of MRI may provide opportunities to develop optimal clinical and laboratory composite measures to monitor and predict the disease course in RA.

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