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Paper from the OMERACT MRI in Arthritis Working Group

The OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system (RAMRIS) – Updated recommendations by the OMERACT MRI in Arthritis Working Group

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Short Running footline:

Updated OMERACT RAMRIS recommendations

ABSTRACT

Objective:

The outcome measures in Rheumatology (OMERACT) Rheumatoid Arthritis (RA) Magnetic Resonance Imaging (MRI) scoring system (RAMRIS), evaluating bone erosion, bone marrow oedema/osteitis and synovitis, was introduced in 2002, and is now the standard method of objectively quantifying inflammation and damage by MRI in RA trials. The objective of this paper was to identify subsequent advances and, based on these, to provide updated recommendations for the RAMRIS.

Methods:

MRI studies relevant for RAMRIS, and technical and scientific advances were analyzed by the OMERACT MRI in Arthritis Working Group, which used these data to provide updated considerations on image acquisition, RAMRIS definitions and scoring systems for the original and new RA pathologies. Furthermore, a research agenda was outlined.

Results:

Since 2002, longitudinal studies and clinical trials have documented RAMRIS variables to have face, construct and criterion validity, high reliability and sensitivity to change, and the ability to discriminate between therapies. This has enabled RAMRIS to demonstrate inhibition of structural damage progression with fewer patients and shorter follow-up times than has been possible with conventional radiography. Technical improvements, including higher field strengths and improved pulse sequences, allow higher image resolution and contrast-to-noise ratio. These have facilitated development and validation of scoring methods of new pathologies: joint space narrowing and tenosynovitis. These have high reproducibility and moderate sensitivity to change, and can be added to RAMRIS. Combined scores for inflammation respectively joint damage may increase sensitivity to change and discriminative power. However, this needs further research.

Conclusion:

Updated 2016 RAMRIS recommendations and a research agenda were developed.

Introduction

Magnetic resonance imaging (MRI) allows sensitive assessment of disease activity and structural damage in inflammatory arthritides and MRI variables are now frequently used outcome measures in rheumatoid arthritis (RA) clinical trials, providing new insights into disease status and treatment response(1;2). The Outcome Measures in Rheumatology OMERACT RA MRI scoring system (RAMRIS) was developed and validated from 1998-2002 by the OMERACT MRI Working Group (3). A core set of MRI acquisitions, joint pathology definitions, and a scoring system for semiquantitative evaluation of bone erosion, bone marrow oedema (osteitis) and synovitis were provided (3), and this method is now the standard MRI method used in RA clinical trials (1;2). Since 2002, new developments and increased knowledge have become available. These include development of an MRI atlas, new data from clinical trials, technical developments, and development and validation of MRI scoring methods for assessing additional pathologies that are important in RA. These improvements and their implication for the use of RAMRIS have never been systematically described, which is now done here.
Thus, in the present article, the OMERACT MRI in Arthritis Working Group for the first time since the RAMRIS was published in 2003 describe the advances related to the RAMRIS, which include clinical trial data, MRI technical improvements and development of assessment methods for new RA pathologies, and provide updated recommendations on how to use the OMERACT RAMRIS for different purposes in RA clinical trials and observational studies.

Methods

Based on recent developments on MRI in RA in general and the OMERACT RAMRIS in particular, we summarize the important achievements of relevance for RAMRIS, including technical developments, new validated instruments (4), and acquired scientific knowledge. Updated recommendations by the OMERACT MRI in Arthritis Working Group, including an updated list of RAMRIS definitions (Table 1) and scoring systems (Table 2) for RA pathologies are provided. Furthermore, a research agenda is outlined (Table 3).

Results

The performance of the original RAMRIS features

The superior sensitivity of MRI for assessing inflammation and structural damage, as compared to clinical examination and conventional radiography, has been documented in many randomized controlled trials (RCT) of patients with early and established RA (1;5,6,7), also documenting the feasibility of RAMRIS. Compared to radiography, MRI can document statistically significant structural damage inhibition in less than half the time and with fewer than half the patients (8;9). The American College of Rheumatology RA Clinical Trials Task Force Imaging Group and the OMERACT MRI in Arthritis Working Group have, based on a systematic literature review, concluded that MRI best serves the purpose of achieving sensitive ascertainment of structural damage in RCT, and additionally provides objective measures of inflammatory predictors of damage (2). An independent value of early MRI inflammatory changes (synovitis and osteitis) and changes therein, for predicting subsequent structural damage progression has been documented (10,11,12).

MRI osteitis and synovitis have documented criterion validity, by comparison with histology, and MRI erosion has documented construct validity by comparisons with computed tomography (1;2;13,14,15,16). Criterion validity of MRI of articular cartilage has also been demonstrated (17).

Recently, also the relevance of MRI findings (synovitis, osteitis, erosion, tenosynovitis) for important patient-reported outcomes (PRO) of functional disability (Heath Assessment Questionnaire, HAQ) and pain has been documented (18;19). Independent, statistically significant associations of RAMRIS synovitis, erosion and tenosynovitis scores with pain and patient global (synovitis only) and HAQ (all) have been found(18;19). Further, improvements in synovitis and bone erosion were associated with improvements in patient reported outcomes PRO (18). In contrast, radiographic change, assessed by the Sharp-van der Heijde method (SvDH), were not associated with PRO. A significant correlation between HAQ and radiographic joint damage (SvDH) has, however, previously been documented (20), but this required larger studies.

Considerations for image acquisition MRI technical improvements

MRI is undergoing continuous technical innovations and refinements, and important developments have occurred since 2002. Improvements in hardware (magnets, gradients and coils) and software (pulse sequences) have made it possible to acquire images with higher resolution and signal-to-noise ratios. This among other things allowed our group to develop the (JSN) score, which was not originally included in 1998-2002 because of insufficient image quality at that time. Other technical developments that may in the future lead to alternative assessment methods to RAMRIS include dynamic contrast-enhanced MRI (6;21;22), automated volumetric quantification, e.g. using active appearance modeling (referred to as the Rheumatoid Arthritis Magnetic Resonance Imaging Quantitative assessment system)(6), and whole-body MRI (23;24). These methods require further validation and testing.

It is still recommended to use postcontrast T1-weighted sequences for optimal assessment of synovitis, T1-weighted sequences that enable visualization in 2 planes for assessment of bone erosions, and T2-weighted fat-saturated (T2FS) or short tau inversion recovery (STIR) images for assessment of bone marrow oedema/osteitis, whereas tenosynovitis can be assessed by T2FS/STIR or by pre- and post-contrast T1-weighted images. Potentially new sequences may replace the need for intravenous contrast injection for synovitis assessment, but because studies so far have found a lower sensitivity and reproducibility of T2FS/STIR than post-contrast T1-weighted images (25;26), these cannot be generally recommended for synovitis assessment. For optimal assessment of cartilage/JSN, sequences specifically suited for cartilage assessment¸ such as such as fat-suppressed, T1-weighted 3D- gradient echo sequences, provide the highest image quality (5;17;27). Different MRI sequences for cartilage visualization have been extensively studied in knee osteoarthritis, but studies of the relative sensitivity to change and reproducibility of different sequences for cartilage/JSN assessments in RA hands and wrists have not been performed. RAMRIS has been successfully applied in other joints, such as proximal interphalangeal joints (hands), first interphalangeal joints and metatarsophalangeal joints. The validation of findings in these joints is, however, limited.

Based on the general current availability of high-quality MRI-units, which allows such sequences, it is recommendable to use thin slices (thicknesses of ≤2mm), or 3-D sequences with isotropic (i.e. cubic) voxels,

allowing reconstruction of the anatomy in 2 perpendicular imaging planes. It should be noted that even better spatial resolution can be achieved on certain MRI systems. However, the current OMERACT recommendations are not intended to be exclusive, but rather provide common standards/minimal requirements, which are feasible in most centers in which RA clinical trials are likely to be carried out. If of high quality, RAMRIS may be used even with low field strength units. If a change in methodology is introduced, it is important to compare its performance with the original method, for the specific scientific question asked (28).

Assessment of additional RA pathologies

The original OMERACT RAMRIS(3) evaluated bone erosion, bone marrow oedema/osteitis) and synovitis. An atlas illustrating the scoring method, aimed at improving accessibility and standardization among investigators worldwide, was published in 2005 (29). Acknowledging the fact that cartilage damage is an important part of the disease process in RA (20), we from 2008-2014 developed and validated an OMERACT method for assessing cartilage loss/JSN as a potential addition to the original RAMRIS system (30,31,32). Similarly, because tenosynovitis is a frequent and early inflammatory feature that can cause tendon rupture and may be associated with subsequent bone erosion (33;34), a RAMRIS tenosynovitis scoring system has recently been developed and validated (35) (Tables 1 and 2).

Thus, RAMRIS now covers a broader spectrum of pathologies seen in RA, which have all been shown to be assessable with high reproducibility and at least moderate sensitivity to change (31;32;35;36). The recommendation to include the additional pathologies and joints is based on the reasons described above.

In an individual clinical study, all or just a subset of these variables can be applied. Some studies may aim only to assess the anti-inflammatory efficacy, e.g. in a Phase 1 or 2 trial, and thus focus on synovitis, osteitis and tenosynovitis, whereas studies testing other mechanisms of action, e.g. osteoclast inhibition (37), may focus only on bone erosion and JSN to assess structural damage progression. More commonly, all RAMRIS variables will be relevant, because both inflammation and damage are integral parts of the RA disease process and this approach also allows assessing the spatial and temporal relation between them.

The first metacarpophalangeal joint (MCP1), which was not covered in the original RAMRIS because of technical limitations at the time, has since been successfully included in several clinical trials. Given the importance of the thumb to the functionality of the hand, including MCP1 is relevant.

Combined scores of inflammation (synovitis, osteitis and tenosynovitis) or damage (bone erosion and JSN) may offer superior discrimination of treatment effects, but their use thus far has been limited, and thus they require further research (Table 3). However, preliminary data suggest that addition of tenosynovitis (38,39,40) may increase the sensitivity to change and provide additional information. A "total damage" score combining cartilage loss and bone erosion has also been shown to demonstrate significant progression over time and discrimination of treatment effects (active versus placebo treatment)(5;40). Combining inflammatory and structural damage variables into a single score is not relevant, however, because they represent different constructs.

Discussion

This paper describes advances since the OMERACT RAMRIS was developed 15 years ago, and provides updated recommendations from the OMERACT MRI in Arthritis Working group regarding MRI assessment of RA patients according to RAMRIS.

The advances include increased knowledge on the validity and utility of RAMRIS, further validates its fulfilment of the OMERACT filter (4). Data have been provided regarding sensitivity to change, discrimination between therapies in clinical trials, and associations with patient-centered outcomes, such as functional ability and pain, improvements in MRI acquisition and updated RAMRIS recommendations, including new definitions and scoring methods for the additional pathologies (tenosynovitis and joint space narrowing). These improvements are expected to further increase the utility of RAMRIS in RA clinical trials and clinical cohorts.

Conflicts of interest:

None.

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Text boxes

Text box 1: Highlights of current article:

This article, for the first time since the publication of the OMERACT RA MRI scoring system in 2003, describes:

- Advances related to OMERACT RA MRI score (RAMRIS),
    - Clinical trial data,
    - MRI technical improvements
    - Development of assessment methods for new pathologies, i.e joint space narrowing (cartilage damage) and tenosynovitis
- Updated recommendations by the OMERACT MRI in Arthritis Working Group on how to use RAMRIS

Figure legends:

Figure 1: Pathologies and areas assessed by the 2016 updated RAMRIS recommendations.

Illustration of locations assessed for bone erosion and joint space narrowing (left), osteitis (center) and synovitis and tenosynovitis (right) of wrist and metacarpophalangeal joint. The drawing is an electronic case report form used for entering MRI scores on www.copecare.org.

Abbreviations: IC-CM: intercarpal-carpometacarpal joints; RC: radiocarpal joint; RU: distal radioulnar joint; I-VI and 1-3: extensor respectively flexor tendon compartments of the wrist; NA: not applicable; MCP: metacarpophalangeal joints; PIP: proximal interphalangeal joints

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