

Rheumatoid Arthritis: MRI as an Efficacy Endpoint in Clinical Trials

Harris A Ahmad at BioClinica, Inc makes the case for magnetic resonance imaging as a primary efficacy endpoint in rheumatoid arthritis clinical trials

Since its advent, magnetic resonance imaging (MRI) has been used increasingly in the clinical assessment of rheumatoid arthritis (RA). The ability of MRI to detect soft tissue findings such as synovial and bone marrow changes in RA in multiple imaging planes has proved to be more effective than radiography in clinical assessment of the disease (1). This advanced assessment of disease progression has elevated its value for making earlier go/no go decisions in clinical programmes, particularly for evaluating disease-modifying anti-rheumatic drugs (DMARDs), since clinically relevant findings for RA can be seen months to years before radiographic findings, such as erosions, develop (2,3).

In light of the advantages of MRI in the assessment of RA for new therapies, a formalised scoring system to detect sensitivity to change of disease status was published in 2005, entitled Rheumatoid Arthritis Scoring in Magnetic Resonance Imaging (RAMRIS) (2-5). RAMRIS assesses the three key characteristics in RA of bony erosions, bone edema and synovitis (see Table 1). The scans are acquired using a non-gadolinium-enhanced T1 axial and coronal sequence, T1 short tau inversion recovery (STIR) sequence, and a gadolinium-enhanced T1 axial and coronal sequence. As an alternative to the STIR sequence, a T2 fat saturated sequence can be utilised for the assessment of bone edema. This advantageous soft tissue assessment, combined with the absence of radiation, has played a key factor in the increased use of the technique in the clinical setting and in worldwide multicentre clinical trials.

REGULATORY APPROVAL CHALLENGES

Regulatory authorities have not yet accepted MRI as an approved efficacy endpoint in clinical trials for the evaluation of DMARDs in treating RA. As a result, radiographic assessment of joint space narrowing, along with erosion assessment, continues to play an integral part for sponsors designing clinical trials for regulatory submission

in Phase III clinical trials. The advantages and disadvantages of MRI versus radiography are detailed in Table 2. While MRI remains a key go/no go decision tool in Phase II clinical trials for experimental therapies, as well as a sub-study role in Phase III biologic studies, several obstacles stand in the way of approval of MRI as a primary efficacy measure in the evaluation of experimental biologics for RA.

The most critical obstacle to the approval of MRI as an efficacy endpoint would be the last issued guidance by the

Figure 1: MRI and x-ray of a wrist of a rheumatoid arthritis patient. An erosion is visualised on the distal radius on MRI in coronal (a) and axial (b) planes, but not on the matching x-ray (c)



Source: Døhn et al, Detection of bone erosions in rheumatoid arthritis wrist joints with magnetic resonance imaging, computed tomography and radiography, Arthritis Research & Therapy 10: R25, 2008



FDA, in which MRI is judged as an unsubstantiated representation of clinical change (6). However, more than a decade has passed since this guidance was issued, and new data has emerged, validating the clinical use of MRI as a marker of disease progression. The modality's proven ability to image bone and soft tissue changes months beforehand, in comparison to radiography's limitations, has hopefully sparked a new debate among the regulatory authorities. Nevertheless, x-ray remains the imaging technique of choice, despite its shortcomings in detecting soft tissue disease and its relatively late detection of associated bone findings such as erosions (7) (see Figure 1). With this imaging technique, the European Medicines Agency (EMA) has stated that the long-term clinical benefit may be realised by halting the structural progression apparent on radiographs over the course of the disease (8).

	Scale	Joints	Sequence
Erosion scoring	0-10	Wrist MCP 2-5	Pre-T1 axial and coronal
Edema scoring	0-10	Wrist MCP 2-5	STIR coronal
Synovitis scoring	0-3	Wrist MCP 2-5	Pre-T1 axial and coronal Post-T1 axial and coronal

	X-ray	MRI
Equipment acquisition cost (9)	Low	High
Operating and maintenance cost (9)	Low	High
Central reader time	Moderate	High
Contrast injection risk (15)	No	Yes
Prior biologic approvals	All	None
Detection of early RA (11)	Very difficult	Excellent
Detection of bone edema (12)	Not possible	Excellent
Diagnosis of synovitis (13)	Not possible	Excellent

Another major obstacle to winning the FDA's approval of the imaging technique to replace x-ray in clinical trials involves the variables in acquisition, as seen in multisite worldwide clinical trials. Common variations or challenges in MRI include the incomplete coverage of key anatomical structures, improper timing, dosing and uptake of the gadolinium injection and artifacts such as motion (10). This variability can be improved with a robust quality control process by an imaging core lab, guiding imaging sites worldwide to improve the scanning technique through the use of position splints, gadolinium power injectors and improved positioning of the extremities with decreased scanning time.

A further disadvantage is the increased reader variability with the RAMRIS method. The scoring method assigns a numerical score for the wrist and metacarpal phalangeal joints for erosions, edema and synovitis. From the observation of several multisite, multireader clinical trials with RAMRIS, and published studies with multiple readers, the highest inter-observer disagreement was found in the wrist for synovitis assessment. In one study, the mean baseline and follow up interclass correlation coefficients representing the statistical measures of reader agreement were 0.69 and 0.78 respectively, which were the lowest among the three RAMRIS assessments of synovitis, erosions and edema (14). This variance in read scores, even among experienced radiologists in the field, poses a challenge to detecting an agreeable therapeutic signal of significance. This challenge can be overcome with the involvement of an imaging core lab that can conduct formalised reader training prior to the start of reading and monitoring of reader scores during the study to achieve superior detection of subtle changes in the disease with increased inter-observer agreement.

CONVINCING THE SPONSORS

For sponsors considering incorporating MRI into a clinical programme, the most significant challenge is often the higher cost of acquisition and operation of MRI equipment among worldwide clinical sites in comparison to x-ray. While an x-ray can cost less than \$150, the cost of an MRI is about \$2,500 (8). As mentioned, other related costs are the maintenance of MRI machine; the operating time needed to acquire the dedicated sequences in RAMRIS scoring (see Table 1), and the time and resources needed to repeat the sequences if technically inadequate. These challenges are being overcome as the industry advances with increased competition for MRI scanner manufacturing. In addition, there is momentum in the use of smaller magnets such as extremity MRI, which provides more efficient scanning time for the dedicated sequences needed in RAMRIS. Finally, the most frequent patient challenge of lying in a confined closed scanner space is being overcome with the increasing availability and quality of open MRI scanners.

In addition to these challenges, injection of gadolinium-based contrast agents (GBCAs) continues to be one of the most significant hurdles in the MRI assessment of RA over radiography, which does not require evaluation by a contrast agent. A gadolinium-enhanced sequence is vital in assessment of synovitis in the dominant hand of the affected patient, with valuable depiction of disease severity as a result of this assessment (2). However, due to significant adverse events such as nephrogenic systemic fibrosis, the FDA has guided against the use of the agent in those patients with impaired elimination of the drug due to acute kidney injury or chronic severe kidney disease, defined by a glomerular filtration rate (GFR) <30mL/min/1.73m². As an alternative to a gadolinium-enhanced sequence, a STIR sequence has shown respectable agreement for assessment of synovitis (16). It should be noted that the readers in this study had a wealth of experience

in the assessment of RA; therefore, with proper training and expertise, the disadvantage of contrast injection can be overcome.

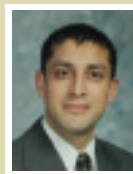
CONCLUSION

As the challenges of cost of acquisition, patient risk, and analysis of MRI in RA are dealt with, the modality will likely play an increasing role as an efficacy endpoint in clinical trials. The superior evaluation of therapeutic signal should gain increasing momentum among sponsors and regulatory authorities by overcoming these challenges of safety, reliability and feasibility. This is likely to create an increasing interest in the modality as a basis for acceptance as an efficacy measure among the regulatory authorities.

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About the author



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