New approaches to imaging early inflammatory arthritis

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ABSTRACT

Imaging techniques such as musculoskeletal ultrasonography (MUS) and magnetic resonance imaging (MRI) are playing an increasingly important role in the assessment of patients with inflammatory arthritis. Such modalities are now used routinely in the evaluation of joint, tendon and soft tissue inflammation and bone damage in many early arthritis clinics. They have the ability to directly visualise, characterise and quantify the earliest inflammatory changes and have proved not only to be useful additional complimentary clinical tools to improve the speed and accuracy of diagnosis, direct appropriate treatment, monitor response to therapy, measure disease progression and outcome but also continue to contribute to our understanding of disease pathogenesis. These imaging methods may therefore offer a significant advantage as they endorse the principles of early diagnosis and optimal targeted therapy essential to providing the most favourable long term outcome for patients with inflammatory arthritis (1).

This article reviews the current evidence supporting the role of MUS and MRI in the assessment of patients with inflammatory arthritis.

Musculoskeletal ultrasonography

The trend towards earlier aggressive therapy for inflammatory musculoskeletal disease requires reliable initial diagnosis and optimal disease activity assessment. Interest has therefore been directed towards imaging techniques, such as MUS, as objective tools for the detection and monitoring of joint and soft tissue inflammation and bone damage. This has resulted in MUS being increasingly used by rheumatologists as an additional clinical tool in the assessment of their patients with rheumatic conditions (2-8). It has been described as an extension of the physical examination (9),as a MSUS examination can be performed by the physician at the time of consultation to complement clinical assessment resulting in improved accuracy of diagnosis and treatment (10). It is safe, non-invasive and emits no ionising radiation and rapid, 'real-time', dynamic examinations of multiple joints in multiple planes are possible at one sitting. These factors, together with the development of high frequency transducers and a steady reduction in equipment costs have encouraged increasing use of this modality by rheumatologists. However, as with any promising new technique, there is the need for further research and there remains a lack of MUS studies specific to the early stages of inflammatory arthritis and much of the current literature relates to patients with more established disease. In addition, there is currently a lack of standardization of methods with no consensus regarding pathological definitions and scoring systems, so this needs to be taken into account when interpreting and comparing the current literature. Nevertheless, there are a number of potential applications of MUS in early inflammatory arthritis including the accurate detection of inflammation and bone damage, monitoring response to therapy, guided intervention and assessments of prognosis and outcome.

Synovitis

A number of studies have reported the ability of MUS to detect early synovial inflammation and support the observation that MUS is superior to clinical examination at detecting synovitis in both small and large joints (11-19). Of particular note, a study of patients presenting to an early arthritis clinic detected synovitis using MUS in ten times more metatarsophalangeal joints than was detected on clinical examination (17). Other studies have attempted to validate these findings by comparison with other imaging techniques such as MRI, arthroscopy, scintigraphy and themography (13,18, 20-23). In a study

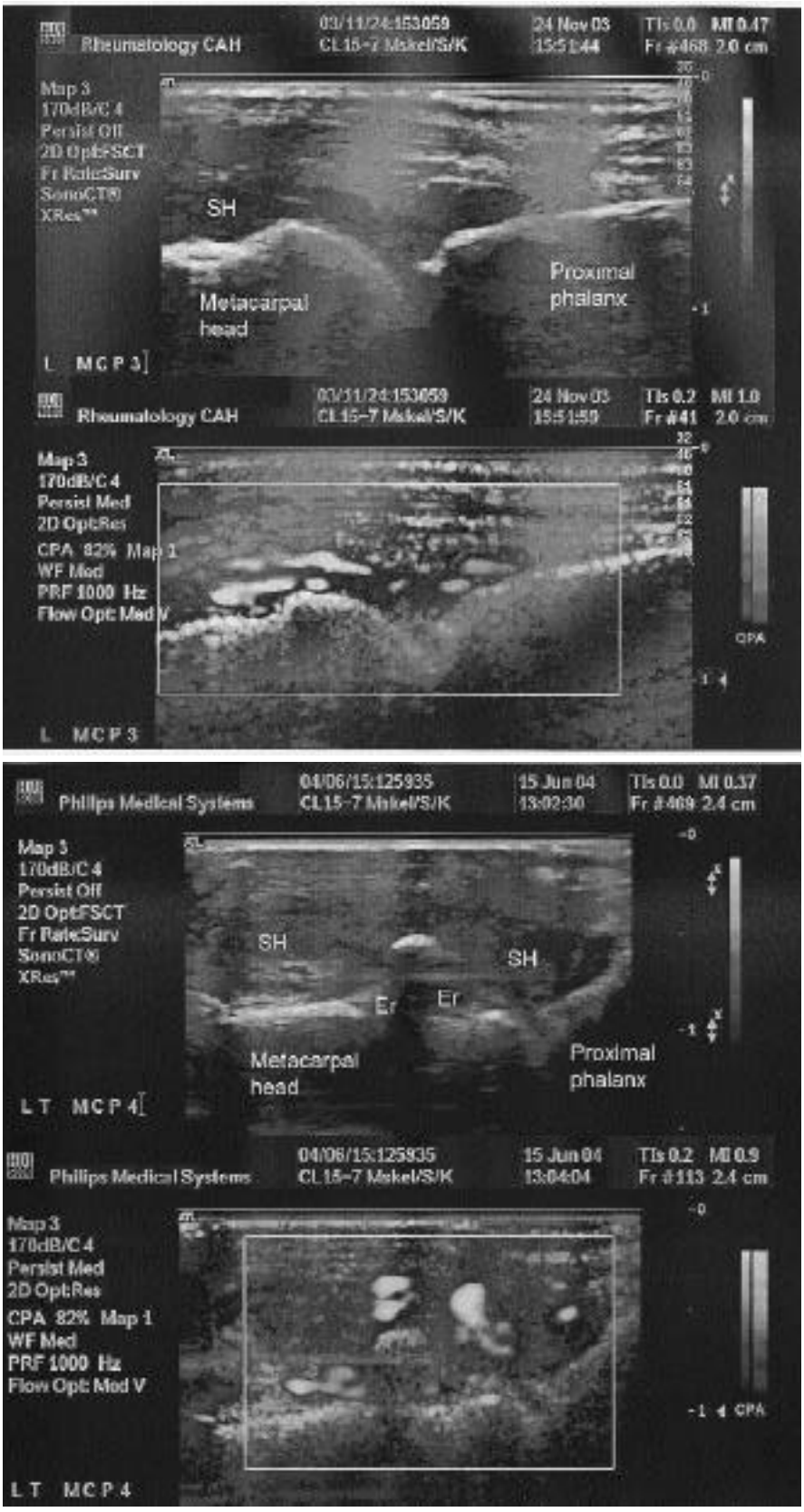

Fig. 1. Musculoskeletal ultrasonography (MUS) images.

of patients with early rheumatoid arthritis (RA), MUS appeared comparable to MRI at detecting synovitis in the second and fifth metacarpophalangeal (MCP) joints, although less sensitive at the third and fourth MCP joints where transducer access is more difficult (21). Another study in patients with inflammatory arthritis suggested that MUS may even be more sensitive than MRI at detecting synovitis in the finger joints (13). Other work suggests that MUS is a valid and reproducible technique at detecting synovitis in the knee when compared to arthroscopic evaluation (18). In addition, MUS has been successfully utilised in the assessment of tendon disease in RA and has been described as the gold standard imaging method for assessing tendon involvement in rheumatic diseases (24-26).

Whilst traditional grey-scale MUS has been successfully used for the detection of joint and soft tissue inflammation for some time, more recently additional MUS techniques, such as Doppler, have been introduced which offer the potential to improve the accuracy of a MUS assessment (27). Doppler is a technique for making non-invasive measurements of blood flow and power Doppler is particularly useful for assessing low velocity vascular flow in structures containing small vessels, such as the synovium. It therefore has the capability to measure and detect changes in the vascularity of joints and soft tissue as a consequence of inflammation (27). Observational studies have favourably compared power Doppler with clinical disease activity assessment and traditional grey scale MUS (19). More recently, validation has been assessed by comparison with histopathology in the knee in RA and osteoarthritis (28, 29) and dynamic MRI in the MCP joints in RA (30,31). Power Doppler has also been successfully used to assess inflammatory disease activity in RA (19, 32, 33) and monitor response to treatment (34-38). Intravenous microbubble echocontrast agents have the potential to further increase the sensitivity of the power Doppler signal by raising the intensity of weak signals to a detectable level. A number of studies have reported an increase in detection rate of the Doppler signal using this technique (32, 39-41), although this is not true of all cases (42), and further work is re-

quired. Correlation has also been sought with contrast-enhanced MRI, which has confirmed concordance in all cases in a single study (39) and arthroscopy which has demonstrated a higher sensitivity but lower rate of specificity using the contrast-enhanced technique (41).
There is currently only limited long term data on the sequential evaluation of synovitis with MUS and, in particular, serial longitudinal comparison with other imaging modalities, as most current studies have concentrated on demonstrating more short term changes in synovial inflammation in response to various therapeutic interventions. However, two year follow-up data on a cohort of patients receiving various drug treatments showed a reduction in levels of synovitis on MUS compared with baseline, with similar changes also visualised on MRI and scintigraphy and reflected in comparable clinical examination and laboratory measurements (22). Another longitudinal study demonstrated a lower frequency of patients with synovitis on MUS compared to MRI at baseline but a greater incidence of synovitis on MUS than MRI when the same patients were imaged 6 months later. MUS consistently detected more joint effusions than MRI at both time points (43).

Erosions
Radiographic bone erosions are often used in the diagnosis of RA. However, such changes are often absent in early disease. MUS has consistently been demonstrated to be more sensitive than conventional radiography at detecting bone erosions in the hands, wrists, feet and shoulder in rheumatoid arthritis (13, 22, 44-50). This is largely explained by the multi-planar nature of a MUS assessment and its ability to detect small lesions. Wakefield *et al*. (44)detected 6.5 times more erosions in the MCP joints of patients with early RA using MUS than were visible on x-ray compared to 3.4 times in established disease. MRI was used to successfully corroborate the accuracy of the MUS results and the same study also reported a high level of intra- and inter-observer reliability of the MUS findings. Other studies have shown that MUS may be less sensitive than MRI at detecting bone erosions in the shoulder (49-51), although this may be less important in the context of diagnosing an inflammatory polyarthritis. Further justification that MUS correctly identifies bone erosions is provided in a study in which MUS was used to facilitate biopsy of erosive changes identified by MRI and radiography. MUS was used to guide and confirm needle placement within an erosion and the sampled tissue demonstrated pathognomonic histopathological features to substantiate the imaging appearances (52).
The longitudinal progression of erosions on MUS has not been extensively studied but in a single study, erosive progression was seen more often on MUS and MRI over a two-year period than on radiographs, implying that these imaging techniques may be more sensitive measures of change in bone damage than x-ray (22). Another study has demonstrated the ability of MUS to follow erosion progression over a six month period, although in this particular paper, MUS identified a lower number of erosions than either MRI or radiography (43).

Monitoring response to therapy
MUS has been used to monitor response following a therapeutic intervention in patients with inflammatory arthritis. A number of studies have shown a reduction in MUS markers of synovial inflammation, including grey-scale and power Doppler parameters, following treatment with various pharmacologic agents which reflect similar changes in clinical and laboratory measures of disease activity (34-38, 53-57). These data suggest that MUS is a sensitive measure of detecting clinically important pathological changes in response to therapy. In addition, the ability of MUS to localize pathology and then accurately guide a diagnostic or therapeutic intervention directly to the appropriate site is another advantage of this technology.

Prediction of outcome
The use and interpretation of MUS findings as predictor of future outcome requires further investigation. However, in a recent longitudinal, randomized, placebo-controlled biologic interventional study in early RA(56), it was shown that baseline MUS measurement of synovial thickening and vascularity in the MCP joints correlated with the magnitude of radiographic joint damage over the following year. This association was not seen in the group treated with biologic therapy. This not only illustrates the capability of MUS in the assessment and prediction of outcome but also as a means of identifying appropriate poor prognosis patients who may derive greatest benefit from certain drug therapies.

Reliability
One of the perceived disadvantages of MUS is the user dependent nature of the modality and the level of skill acquisition required by the operator. This has been partially addressed with some reproducibility studies but more work is needed in this area. As previously stated, issues of lack of standardization of technique, variable definitions of pathology and scoring criteria need to be borne in mind. Reliability studies of semi-quantitative synovitis scoring have demonstrated generally good levels of dual inter-reader agreement in the small joints of the hand, wrist (15, 57) and knee (18) and acceptable levels of intra-reader agreement (18,57). Likewise, good inter and intra-reader agreement has been demonstrated for the detection of MCPjoint erosions (15,44).

Magnetic resonance imaging
As with MUS, interest in MRI in the evaluation of patients with early inflammatory arthritis has grown in recent years. The main advantages of MRI include its multiplanar properties enabling a detailed three dimensional assessment of a large number of anatomical structures in and around a joint, making it an ideal technique for detecting the earliest pathological changes associated with inflammatory arthritis. Improved access to this imaging modality, reduction in cost and developments in resolution, sequences and software have contributed to the increased popularity of MRI.
A variety of techniques have been used

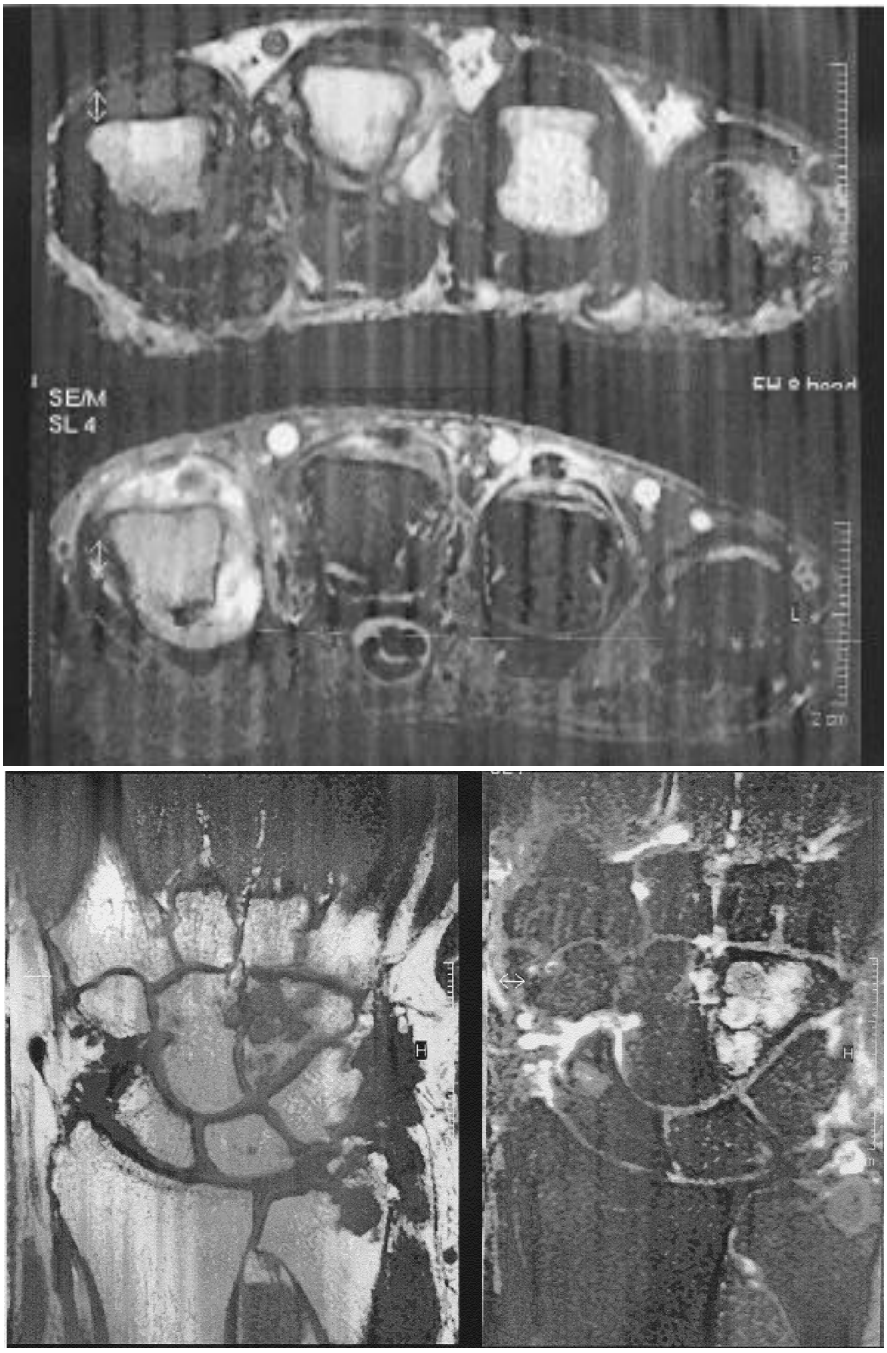

Fig. 1. Magnetic resonance imaging (MRI) images.

in the application of MRI in the assessment of early inflammatory arthritis which can make interpretation and comparison of data difficult. As a result, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) MRI group was established in 1999 in an attempt to standardize the use and interpretation of MRI data in clinical trials of patients with RA. This group has proposed standardized definitions of MRI pathology in RA (synovitis, bone oedema and bone erosion), a rheumatoid arthritis magnetic resonance imaging scoring system (RAMRIS) for the evaluation of inflammatory and destructive changes in the hand and wrist joints and recommendations regarding a core set of the most appropriate MRI sequences (58, 59).

Synovitis

MRI is particularly helpful in the objective evaluation of synovial inflammation especially when used in conjunction with an intravenous contrast agent such as gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA). This agent accumulates in areas of inflammation and can improve detection of synovitis and aid differentiation between synovial inflammation and fluid. Various parameters have been used to assess synovitis on MRI including synovial volume, maximal synovial thickness and rate of synovial enhancement following injection of contrast. A number of studies have demonstrated good correlations between MRI synovial hypertrophy and clinical measures of inflammation (60-62). There is also evidence to suggest that MRI may be a more precise method of detecting synovitis than clinical examination (63)and may be a useful and sensitive measure of inflammation in the early stages of RA, improving the accuracy of diagnosis (64). MRI may also provide additional information regarding RA disease activity to that obtained from standard clinical assessment (65). Gadolinium-enhanced MRI changes of synovial inflammation have been shown to correlate with corresponding histopathological changes in the knee joints of patients with RA (66-69) as well as macroscopic measures of synovial inflammation using arthroscopy in the knee (67)and mini-arthroscopy in the MCP joints (70). In addition, MRI quantification of synovial volume has been shown to accurately reflect RA disease activity (71, 72).

Erosions

The multiplanar nature of MRI and its ability to identify small cortical defects means that it is more sensitive than standard radiography at detecting bone erosions. It is therefore particularly useful for imaging patients with early inflammatory arthritis as radiography is frequently normal in such patients. Indeed, MRI has been successfully used to identify erosive changes before they appear on radiographs in this patient group. The increased sensitivity of MRI compared to radiography at detecting erosions, particularly in the MCP and wrist joints, has been illustrated in a number of studies illustrat-

ing its utility in the assessment of patients with early inflammatory arthritis (13,22,61,73-76). There is also evidence to suggest that many patients develop MRI erosions within a few months of symptom onset and most possess these changes by 1 year (62, 77). This is in contrast to much of the radiographic data which reports a much lower frequency of erosions, further supporting the role of additional imaging in this group of patients. Longitudinal studies have shown that it is possible to demonstrate progression of erosive changes on serial MRI assessment (72,73). It is also feasible to correlate short term progression of MRI erosions with similar changes on radiography although over a much longer time course. In a longitudinal natural history study of bone erosions using MRI and conventional radiography, it was noted that over three-quarters of new radiographic erosions were visible on MRI at least one year earlier illustrating that the information on joint destruction provided by radiographs may be considerably delayed compared with that provided by MRI (75). However, all MRI erosions may not necessarily evolve into comparable changes on x-ray although they continue to be visible and may progress when subsequent longitudinal imaging is undertaken to re-evaluate previously identified lesions (72). The benefit of MRI in improving the rate of detection of erosions may extend to the use of lower field dedicated extremity MRI scanners which not only appear to demonstrate more erosions than conventional radiography but may also increase the sensitivity of disease activity assessment by identifying synovitis in apparently clinically normal joints (78). MRI appears to be a reliable tool at detecting established erosions first visible on radiographs (74) with only occasional reports of disagreement in single isolated cases (78). Additional validation work includes correlation of MRI erosions with MUS findings in the second MCP joint (44)and macroscopic appearances on miniarthroscopy (70). As previously discussed, biopsy of MRI determined erosions confirms necrotic tissue consistent with erosive pathology (52).

Insights into pathogenesis

The ability of MRI to directly visualize the joint structures involved in RA pathogenesis has been helpful in further evaluating the relationship between synovitis and bone erosion. Numerous studies have illustrated that MRI synovitis measurements can be used to predict future erosive damage (62,71,72,79-81). In particular, the level of MRI synovitis can be used to predict the rate of development or progression of erosions (72,79,80). Erosive changes only appear to occur in joints with preceding synovitis and joints without synovitis do not seem to develop erosions (62,79). Bone marrow oedema represents increased water content reflecting inflammation within the bony trabecular architecture and rarely occurs in the absence of synovitis (82). The presence of bone marrow oedema also closely correlates with the presence of erosions (61). Bone marrow oedema has been shown to be predictive of later development of an erosion at that site (62), total radiographic Sharp score at 6 years (83) and subsequent functional outcome (84). Therefore, there seems to be close relationship between synovitis, bone oedema and subsequent bone erosion in RA. It appears that bone marrow oedema not only relates to ongoing inflammatory activity but may give prognostic information in relation to future erosive bone damage and functional outcome. Therefore, bone marrow oedema visualised on MRI may represent the pathophysiological connection between synovitis and the development of bone erosion and provide evidence of a direct causal link between inflammation and bone damage in RA.

MRI has also provided further insights into pathogenesis by defining the primary site and distinct patterns of pathology in subgroups of inflammatory arthritis (85,86). The role of biomechanical factors in relation to the distribution of synovitis and erosions in early RA has been evaluated with MRI with the radial collateral ligaments appearing to have a significant influence on patterns and severity of pathology (87).

Monitoring response to therapy

MRI may also be a promising tool for assessment of outcome following a therapeutic intervention. Various studies have demonstrated the ability of MRI to monitor response to therapy with reduction in MRI indicators of synovial inflammation reflecting changes in clinical disease activity following various treatment regimes (62,71, 79,88-92). MRI has also been shown to detect progression of erosions despite apparent clinical improvement following drug therapy, suggesting a role for MRI in monitoring disease activity, which may be more sensitive than currently utilized clinical methods (92).

Prediction of outcome

MRI may have an important role in the prediction of disease outcome in early RA. The likelihood of future development of joint erosions may be predicted by baseline MRI synovitis scores, including synovial volume and rate of post-contrast synovial enhancement, and the presence of bone marrow oedema, with patients with the highest scores being more likely to progress (62,71,72,79-81). In addition, an absence of MRI erosions at baseline and a low MRI score may be strongly predictive of the absence of radiographic erosive changes one year later (62) whereas in bones with MRI erosions at baseline, the relative risk of radiographic erosions at 5-year follow-up has been calculated at 4.5 (75). More long term studies indicate that MRI parameters at RA presentation can be used to predict long term radiographic outcome at six years (83). Recent data also suggests that MRI findings in early RA may be able to predict future functional outcome (84).

Reliability

Accuracy and consistency in the interpretation of MRI images is clearly a key area in the development of MRI as reproducible tool in the assessment of inflammatory arthritis. A number of studies have attempted to evaluate both inter and intra-observer reliability many of which have occurred as part of OMERACT exercises and are still ongoing. Reliability studies of numeric, semi-quantitative and semi-automated erosion scores have demonstrated gen-

erally good levels of agreement in both single intra-reader, dual inter-reader and multi-reader studies (61,93-97)although currently only a limited number of studies have evaluated the OMERACT RA-MRI erosion volume score (95, 97). Nevertheless, in the studies that have taken place, good levels of agreement have been noted using the OMERACT RA-MRI semi-quantative scores for synovial volume (95,97,98). To-date, one multi-centre study has attempted to evaluate the longitudinal reproducibility of the OMERACT RA-MRI semi-quantative scores and showed acceptable levels of agreement for erosions and synovitis although agreement was better for status than progression scores (98).

Conclusion

There is increasing data to support the validity of MUS and MRI in the evaluation of early inflammatory arthritis. Evidence confirms their utility in facilitating prompt recognition of pathology, precise measurement of disease activity, sensitive monitoring of response to therapy and effective assessment of disease outcome as well as providing valuable insights into disease pathogenesis. The increased cost and relative inaccessibility of MRI is outweighed by its powerful ability to accurately visualize joint and per-articular anatomy and pathology whereas the requirement to acquire a new skill needs to be balanced against the clinical advantages, accessibility, convenience and ability to image multiple joints in one examination period afforded by MUS. The application of these new approaches to imaging early inflammatory arthritis should enable earlier and more accurate diagnoses, targeted therapy and precise evaluation of therapeutic response ensuring optimal suppression of inflammation and therefore the most favourable outcome for patients.

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