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Rheumatoid Arthritis (Y Yazici, Section Editor)

An Update on Imaging in Rheumatoid Arthritis

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Abstract

Purpose of Review Modern imaging modalities allow accurate detection of both inflammation and damage in rheumatoid arthritis (RA) joints. This narrative review aims to summarize the recent literature relating to magnetic resonance imaging (MRI), musculoskeletal ultrasound (MSUS) and high-resolution peripheral quantitative computerized tomography (HR-pQCT).
Recent Findings Imaging has aided understanding of the pathogenesis of RA: HR-pQCT studies suggest that cortical micro-channels may facilitate erosive changes in the setting of synovitis. Both MRI and MSUS studies have aimed to quantify the degree of changes seen in asymptomatic people where age-related changes are common, highlighting the importance of understanding the thresholds of 'normality'. Whilst synovitis has been considered the characteristic feature of RA, there is growing evidence that imaging-detected tenosynovitis may be of importance in predicting the development of RA, diagnosing RA and predicting flare in stable RA. Much focus has been placed on recent MRI and MSUS studies demonstrating that systematic repeated imaging of RA treated with tight control strategies does not improve outcomes at the group level; however these studies did not explore pre-test probability issues at the individual patient level. The literature is somewhat mixed on whether MRI and MSUS may provide useful guidance on which patients in remission can safely have therapy de-escalated. Recent work has also continued to validate and refine pathology definitions and semi-quantitative scoring for these tools as outcome measures in clinical trials.
Summary A review of recently published literature allowed the identification of several themes: understanding pathogenesis, attempts to define 'normal' joints on imaging, the utility of imaging in the diagnosis of RA, predicting the development of RA in at risk populations and the relevance to Ra clinical practice and trials.

Introduction

Rheumatoid arthritis (RA) is chronic autoimmune condition characterized primarily by systemic, synovial and bone inflammation leading to joint destruction. Imaging of joints is therefore useful to identify key pathologies in order to aid diagnosis and management. Contemporary imaging of RA no longer relies on conventional radiographs (CR) alone; the two-dimensional nature of the technique, inability to image soft tissues and radiation exposure means its capabilities are limited compared with modalities including magnetic resonance imaging (MRI), musculoskeletal ultrasound (MSUS) and, in certain situations, high-resolution peripheral quantitative computerized tomography (HR-pQCT). Over the last 30 years, much work has been done to determine the utility of each of these methods in RA clinical trials and practice. Recent data from Europe suggests rheumatologist are commonly utilizing MRI, MSUS and CT in their routine clinical practice [1•], with widespread access to physician-performed ultrasonography. These imaging techniques all have value in the clinical or trial setting for the evaluation of RA, but their role differs depending on sensitivity for specific tissues, ease of quantification and feasibility of use.

Foundation work in MRI and MSUS has shown that both modalities are valid tools to detect synovitis, tenosynovitis and bursitis with better sensitivity than clinical examination [2, 3], although generally US is less sensitive than contrast-enhanced MRI in detecting synovitis and tenosynovitis [2]. MSUS studies describe these inflammatory pathologies in terms of the elemental lesions of greyscale effusion, greyscale synovial hypertrophy and Doppler signal (representing vascularity). In addition, MRI allows the detection of bone marrow oedema, an inflammatory osteitis (unable to be visualized with CR, MSUS or CT) demonstrated to be a precursor of bone erosions [4]. Established erosions, representing damage, are able to be imaged with CR, MRI, MSUS and CT [5, 6•, 7]. HR-pQCT remains a research tool, but its ability to provide information about bone microstructure has aided the understanding of RA pathophysiology in the last 5 years [8].

This narrative review will focus on the last few years of RA imaging original research publications to highlight advances in the field. A PubMed search was undertaken to identify articles relating to rheumatoid arthritis and MRI, HR-pQCT or MSUS published since 2016. As expected, the majority of publications employed MRI and US. The update is presented according to themes evident in the literature.

Understanding Pathogenesis

Angiogenesis is critical in RA pathological processes. A recent study found that MSUS Doppler signal in the joints of people with RA correlated with vascular endothelial growth factor (VEGF), consistent with previous evidence suggesting VEGF is implicated in the neo-angiogenesis seen in the RA synovium [9]. Furthermore, while erosion progression has long been related to joints with high levels of Doppler signal, recent work has shown this is particularly related to when Doppler signal is adjacent to or penetrating bone, supporting the pathogenic role of synovial angiogenesis in erosive damage [10]. This is consistent with the traditional 'outside-in' hypothesis, presuming inflammation of the synovium proceeds bone marrow oedema and erosion development. Recent MRI work supports this theory: as synovitis and tenosynovitis predate the development of osteitis in people with clinically suspect arthralgia who progress to RA [11]. This is further supported by work in established RA, in which clinical flares are characterized firstly by MRI-detected synovitis and tenosynovitis: bone marrow oedema is a delayed development [12].

Synovitis and bone marrow oedema may of course occur simultaneously, as microscopic bone canals allow communication between synovium and bone

marrow [11]. The field of HR-pQCT, with its resolution of around 20 μm, has provided insightful lessons about bone canals in recent years. HR-pQCT has led to the identification of cortical microchannels between the periosteum and endosteum (CoMICs) in areas of cortical bone that is not overlayed with articular cartilage [13•]. Whilst CoMICs are found in apparently healthy controls, they are found in increasing numbers and at an earlier age in the joints of people with RA [13•], leading to the hypothesis that they may facilitate the erosive process in the setting of RA synovitis [13•]. The sites of CoMiCs may also be of relevance. In a study imaging, the second metacarpophalangeal joint (MCPJ), healthy controls demonstrated CoMiCs more commonly at (erosion prone) palmar sites and least commonly on the ulnar side. In contrast, in people with RA, CoMiCs were as frequent on the radial side as the palmar side [13•]. Interestingly, early RA management with DMARDs was shown to halt progression in a small early RA cohort, although it was not associated with improved bone architecture over 12 months [14].

Defining 'Normal' on Imaging

In order for imaging to have clinical utility in the diagnosis of RA, understanding what imaging findings are seen in people without joint disease would provide perspective. Several imaging studies have demonstrated pathology in the hands or feet of people without symptomatic joint disease [15, 16•, 17]. An MRI study of asymptomatic healthy people found that over two-thirds of people had inflammatory features and more than three quarters have erosions [15]. Similarly MSUS has demonstrated greyscale synovial hypertrophy, effusion, power Doppler signal and erosions are common in the hands, wrists and feet of people without joint symptoms [9, 18]. These asymptomatic lesions are generally found to increase in prevalence with advancing age and are often described as being low grade [9, 18]; whilst the burden of lesions may increase with age, this is attributable to an increasing numbers of joints with low levels of inflammation, rather than increased intensity [16•].This generalized increase in inflammation appears to be true regardless of the underlying disease state [16•].

It is important to note that many of the imaging studies which have aimed to define normality did not screen for the presence of underlying osteoarthritis (OA) with radiographs or report OA MRI criteria, and therefore these cohorts may include people with asymptomatic OA, clouding the picture of 'normality'. It has long been established that OA increases in prevalence with advancing age, can be asymptomatic and is associated with imaging features of synovitis, bone marrow lesions/oedema and erosions [18, 19]. It may therefore be that many of the imaging lesions seen with sensitive 3D imaging modalities in asymptomatic patients is explained by underlying OA, especially in ageing cohorts.

Understating the spectrum of normality in an age-matched population may be important for optimizing the utility of 3D imaging modalities in RA; referencing an asymptomatic, age congruent population when scoring the presence of bone marrow oedema on MRI has been shown to reduce overdiagnosis of RA without affecting sensitivity [20].

Diagnosing RA

The gold standard of diagnosis of RA remains the clinician's opinion synthesized from the clinical history, examination, blood results and imaging [5]. And whilst the most recent ACR/EULAR classification criteria state that joint involvement 'refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis' [21], they appropriately indicate that imaging does not replace clinical examination, even as part of an algorithm incorporating history and blood tests.

Care should be taken when considering that individual pathological imaging findings are diagnostic of RA; they require the correct clinical context [5, 13•]. A recent MRI study found that utilizing MRI-detected synovitis to determine if people fulfil the 2010 ACR criteria for RA did not add value over clinical examination [22]. Similarly, a recent MSUS study found that US-detected synovitis was less useful in aiding clinician diagnosis of RA than the 2010 ACR classification criteria; however the presence of power Doppler signal was particularly useful in diagnosing seronegative RA where the ACR/EULAR criteria for RA diagnosis were not met [23]. Again the confounding presence of OA needs to be considered when interpreting these results.

MRI-detected tenosynovitis at metatarsophalangeal joints has been shown to be specific for RA, when compared with cohorts with other types of inflammatory and crystal arthritis and healthy controls [24]. Similarly, a recent MSUS study found US-detected tenosynovial hypertrophy (TSH), and related power Doppler (PD) signal is very uncommon in healthy controls, even in the setting of advanced age [18, 25].

Imaging to Identify Pre-RA

The knowledge that autoantibodies are present years before clinically evident RA has led to a massive effort to identify pre-RA phenotypes in at-risk populations. Whilst we know people without symptoms may have imaging-detected lesions in their hands and feet, the prognostic importance of imaging changes in people who are symptomatic has also been investigated. Interestingly, tendons again appear to be of importance in identifying at-risk individuals.

The Leiden Early Arthritis Cohort has demonstrated that, in people with undifferentiated arthritis, those with MRI-detected tenosynovitis had a sevenfold risk of developing RA [20]. Whilst MRI-detected tenosynovitis of the foot predicted progression to RA, it does not add value over MRI of the hand alone [26]. Similarly, the data from the Birmingham Early Arthritis Cohort suggested that MSUS-detected tenosynovitis (especially flexor tenosynovitis) in people presenting with clinical synovitis was more common in those who progressed to RA [27•].

Peritendinitis is a relatively recent concept within the RA imaging literature; tendons without sheaths, such as the extensor tendons of the fingers distal to the carpus, may still demonstrate inflammation that anatomically is not tenosynovitis. MRI-detected peritendinitis of the MCP extensors (visualized by MRI

or US) has also been shown to have a high specificity for RA [28].

Data from the Leeds group has shown that shown interosseous muscle tendon inflammation precedes the development of synovitis in anti-CCP-positive people with clinical symptoms [29], although this group also found intra-articular synovial Doppler signal to be predictive of the development of RA [30]. Recent data from Leeds also suggests that MSUS-detected erosions at certain sites in people at risk of RA have predictive value [6•, 30]. Further investigation of algorithms aiming to predict the development of RA should investigate the value of imaging lesions, particularly inflammatory lesions as these appear to have the most relevance.

Understanding Symptoms

Soft tissue imaging can help in understanding the pathologies underscoring our patients' symptoms. Swollen joints are not always the result of synovitis but can also be the result of tenosynovitis, bursitis or even unexplained on MRI [3], again reinforcing that rheumatologists need to think beyond synovitis. Patient-reported flares of RA were associated with MRI-detected synovitis and MRI and US-detected tenosynovitis, which tended to resolve with resolution of the flare; in contrast, bone marrow inflammation changes were delayed and tended to persist after resolution of symptoms [12, 31••]. Additionally, a MSUS study demonstrated that tenosynovitis improves in parallel with DAS28, which is related to patient-reported symptoms [32]. These studies support the role of soft tissue inflammation driving symptoms in early RA. In contrast, in people with established RA in flare, damage, not inflammation, is associated with worse pain and function [33]. Imaging can therefore aid in differentiation of what is driving individual joint symptoms in RA.

Imaging to Aid Management

In recent years, much effort has been directed at trying to understand if management algorithms informed by imaging can improve outcomes for people with RA. These efforts have largely focused on the role of MRI and MSUS.

Imaging provided the concept of sub-clinical disease: inflammatory changes that are present when patients are in apparent clinical remission. IMAGINE-RA was a 2-year randomized multicentre trial which assessed MRI-guided treat-to-target (T2T) strategy against a conventional DAS28CRP T2T strategy [34••]. All patients fulfilled the 2010 ACR criteria and were on conventional DMARD treatment, in clinical remission for 6 weeks at enrolment. The treatment target in the MRI arm was remission based on the absence of bone marrow oedema on MRI of the dominant hand, combined with DAS28-CRP clinical remission and no swollen joints. The conventional arm targeted DAS 28 CRP remission and no swollen joints. The co-primary endpoints were DAS 28-CRP remission and an absence of structural progression on plain film of the hands and feet at 24 months. Therapy escalated to biologics in almost half of the MRI arm, compared with 2% of the conventional treatment arm. The study did not meet either of its primary endpoints, although small improvements in MRI osteitis score and physical function were observed in the MRI intervention arm. Of importance, 17% of the intervention arm compared with only 6% of the

standard treatment arm developed severe adverse events comprising of infection, cancer and 2 deaths.

Three contextually similar MSUS studies have also been published in recent years. The studies compared the current 'best practice' approach of T2T comparing DAS against an ultrasonographic T2T approach. The ARCTIC study had 13 assessments over 24 months and was powered to demonstrate an absolute difference of 20% between groups meeting sustained DAS44 remission (<1.6) between 16 and 24 months [35]. Less than a quarter of all participants met the primary endpoint, and there was only a difference of 3% between arms. The MSUS arm was associated with an increase in biologic and parenteral steroid therapy, although this was not associated with an increased rate of adverse events. Additionally, no benefits were seen in MRI inflammation or damage scores at 2 years [36]. The TASER study performed MSUS assessments 3 monthly for 18 months and was powered to demonstrate a between-group difference in the mean change in DAS44 of 0.55, approximately half of a clinically significant change [37]. The TASER study also failed to meet its primary endpoint. The ECHO study, Canadian study that compared the efficacy of adding MSUS to routine care, again found that MSUS was associated with treatment escalation without improved clinical or patient-reported outcomes [38].

These negative studies are consistent in their findings that imaging of all patients at multiple time points is not necessary to optimize outcomes in RA, and, importantly, has the potential to lead to over-treatment and associated adverse events. However, the primary endpoint in these studies was ambitious. Reflecting on the BEST study, which was undertaken 20 years ago, it is known that T2T strategies result in clinical remission in a third of people with RA [39] and no radiographic progression in three quarters: utilizing clinical endpoints to guide therapy produces excellent clinical and radiographic results; the issue remains the feasibility of T2T in most healthcare systems. Despite commentary regarding these studies suggesting that 3D imaging may lead to overdiagnosis and overtreatment [40], it is also important to recognize these studies as designed did not reflect widespread contemporary use of a diagnostic test in rheumatology practice. In the clinical setting, imaging is not used in all patients but usually reserved to address a specific question such as a discrepancy between physician opinion and patient-reported outcomes (e.g. the patient with high DAS score but no swollen joints). Whilst in the setting of a randomized clinical trial, we assume such 'discrepant' patients are balanced between the arms, this cannot be confirmed from the published manuscripts. It may be that in individual discrepant patients, imaging may improve outcomes. Inherently, this remains a difficult concept to prove in a randomized controlled trial.

A separate issue is whether modern imaging may aid prognosis, in terms of predicting response to therapy. In early RA, MRI-detected inflammation has previously been shown to be a poor prognostic sign for erosion progression. In a recent RCT of seropositive, MTX-naïve patients with early RA, high levels of baseline MRI synovitis were associated with poorer outcomes in those treated with MTX alone compared with bDMARD (abatacept) and MTX; effects not seen in the subgroup with low levels of MRI inflammation [41]. Additionally, poor response to biologic therapy can be predicted by MRI synovitis and osteitis (but not clinical assessment) as early as 1 month after the initiation of therapy [42]. This may allow individuals with poor response to be identified early, and therapy switched appropriately.

Predicting disease flare remains complex. In the setting of established and DMARD-treated RA, a recent prospective 12-month cohort study tells us that people with low-disease activity commonly experience flares and that flares are associated with worse clinical and structural outcomes [43]. In the REMIRA study, 30% of patients had at least one flare and baseline MSUS greyscale synovial hypertrophy and power Doppler signal did not predict flare; unfortunately, MSUS was not performed at time of flare. This is in contrast to previous studies that suggested MSUS-detected synovitis can predict flare and radiographic progression [14, 44]. All these studies did not report on the presence of MSUS-detected tenosynovitis, and a recent study suggested that MSUS-detected tenosynovitis is associated with clinical relapse and is a more important predictor of relapse than subclinical synovitis [31•].

Therapeutic tapering remains an important consideration for RA patients in stable remission, as advised in the recent EULAR guidelines on the management of RA [45]. A recent Danish study imaged RA patients in stable DAS 28 CRP remission with MRI; the patients followed a predefined protocol of incremental reductions in bDMARD dose and eventual bDMARD withdrawal if clinical remission was maintained [46•]. Almost two-thirds of people with RA were able to successfully reduce or cease their bDMARD at 2-year follow-up. The number of previous bDMARD, the MRI-combined inflammation and the MRI-combined damage score at enrolment were all independent predictors of flare. When MRI parameters were removed from the model, no other variables predicted successful tapering.

Several studies have demonstrated Doppler signal to be predictive of relapse on tapering; however the evidence remains mixed [47, 48]. Data from the Dutch POET study suggested that MSUS-detected greyscale hypertrophy and intra-articular Doppler signal predicted relapse at the group level; however at the level of the individual patient, it added little value over routine clinical assessment, though both clinical and MSUS assessments only provided at best modest prediction of flare [48].

Imaging in Research

Outcomes in rheumatology clinical trials (OMERACT) are an international umbrella organization comprised of working groups of stakeholders who validate outcome tools in rheumatology. For the last few decades, the OMERACT organization has exerted much effort into developing and validating MRI and MSUS for use in rheumatoid arthritis clinical trials [49]. The MRI Working Group initially developed the RA MRI scoring system (RAMRIS) and demonstrated its validity, reliability and discriminative capacity. The value of this work lay in the ability for disease-modifying therapies to be evaluated in quicker time frames and smaller numbers than traditionally enabled by conventional radiography [50]. However recent technical advances improved the resolution of MRI such that in recent years the OMERACT MRI working group have revised RAMRIS to enable incorporation of joint space narrowing and tenosynovitis [50] to the scoring system, with the (as yet unproven) aim of increased discriminative power. The group has also worked on evaluating two-composite scoring systems using the inflammation and damage components of RAMRIS, again in an effort to potentially improve responsiveness over individual pathology

outcomes alone; preliminary work has demonstrated validity and some trends in increased responsiveness [51]. Data on the performance metrics of the machine-learning-derived automated quantitative MRI assessment system (RAMRIQ) is also being expanded, with recent data on its predictive validity [42].

The MSUS Working Group has over time developed and validated definitions of synovitis, tendon pathologies and erosions, demonstrating validity, reliability and responsiveness to change. Recent work on RA has focused on refining the definitions: synovitis is now defined by hypoechoic synovial hypertrophy, and the element 'synovial effusion' is removed from the definition due to a lack of reliability for this element [52]. Importantly, a simplified EULAR-OMERACT scoring system that combines a 4-point greyscale and Doppler signal has also been tested and found reliable across a range of joints [53, 54]; this should provide the tool underpinning future clinical trials. Development of the definition of synovitis and testing of 4-point scoring system to the sub-talar joint has also been completed [55]. The definitions of tenosynovitis and tendon damage have also been refined, and associated scoring systems have been reported [32].Whilst the definition of erosion has not altered, the group recognized that the current definition does not distinguish between the pathological erosion and non-pathological lesions, such as small cortical vascular channels, and requires future work [52].

The OMERACT HR-pQCT Working Group, also known as the SPECTRA collaboration, has agreed a definition of RA erosion using HR-pQCT and demonstrated criterion and construct validity of joint space narrowing and the reliability of scoring systems [56]. HR-pQCT is able to discriminate between erosion and small vascular channels [7].

Conclusions

Imaging has provided valuable insights into the pathogenesis of rheumatoid arthritis and aided clinical trials and management. In recent years, the role of imaging in diagnostic algorithms has been investigated, and MRI and MSUS appear to aid diagnosis in early RA, though clearly their feasibility in practice differs. Recent work has focused on the predictive value of imaging in very early inflammatory arthritis, and the presence of tenosynovitis may be important in this population. However, the sensitivity of these imaging modalities means that the spectrum of 'normal' needs to be understood to prevent over-diagnosis; this has proved challenging as ageing populations display low levels of background changes, particularly osteoarthritis. Despite the accuracy and sensitivity of modern imaging, studies aiming to use imaging to optimize RA treatment outcomes have failed to provide clear guidance on how to usefully apply imaging. Using imaging as routine in all patients treated with a tight control algorithm does not appear to benefit people with RA, and more thought on appropriate study designs that could be implemented in the real world is required. There is evidence to suggest that imaging does provide clues as to which patients may be able to de-escalate therapy. The OMERACT organization continue to refine MRI, HR-pQCT and MSUS as imaging tools to be used in rheumatoid arthritis clinical trials. As imaging technologies improve and our understanding of this disease and its onset evolves, it is important we continue

to evaluate and consider the use of imaging as an outcome tool and its cost-effective utility in clinical practice.

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Compliance with Ethical Standards

Conflict of Interest

Philip Conaghan reports personal fees from AbbVie, personal fees from BMS, personal fees from GSK, personal fees from Pfizer, outside the submitted work; John Smith declares that he has no conflict of interest.
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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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