

Articular ultrasonography in rheumatoid arthritis

Early diagnosis and therapeutic intervention is critical to the management of rheumatoid arthritis (RA) patients. Conventional radiography offers only late signs of preceding disease activity and the resulting cartilage and bone destruction. MRI is considered the new gold standard for the detection of joint inflammation and bone erosions but is invasive, costly and has limited availability. Ultrasonography compares well with MRI although it is generally inferior. However, ultrasonography is relatively inexpensive, quick to perform and readily accessible. By sensitively detecting joint inflammation and bone erosions ultrasonography has utility in assessing RA disease severity, diagnosing RA and differentiating it from other arthritides, monitoring disease progression and response to treatment. We anticipate that it will be used more extensively to test new treatments in early clinical studies, which have small patient cohorts over short periods of time.

KEYWORDS: erosions ■ gray-scale ultrasound ■ power Doppler ultrasound ■ rheumatoid arthritis ■ synovitis ■ ultrasonography

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Burden of rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which is characterized by erosion of cartilage and bone. The underlying cause of RA is not fully understood but it is considered to be an autoimmune disease. RA has a prevalence of 0.5–1% worldwide. A study reporting RA duration, of time from onset until work disability, found that 10% of patients stopped working in the first year after onset and approximately half stop working in the first decade [1].

Joint damage and disability both increase throughout the duration of treated RA. In the earliest phase of RA, x-ray damage and disability (health assessment questionnaire [HAQ] score) are not related. By 5–8 years, there are significant correlations (correlation coefficients between 0.3 and 0.5). In late RA (>8 years) most studies show highly significant correlations between 0.3 and 0.7 [2]. Therefore, avoiding or reducing joint damage in both early and late RA is likely to maintain function.

Pathophysiology of rheumatoid arthritis

It is a general belief that persisting inflammatory synovitis correlates with joint damage. Synovitis that is adherent to cartilage and locally invasive is termed 'pannus' and its development precedes destruction of cartilage and bone. Thus, it is a key event in the pathogenesis of RA [3]. Pannus in the active phase

of erosive disease is vascular [4,5]. Therefore, assessment of synovial vascularity in RA is predicted to provide information concerning the destructive potential of synovitis.

Current constraints in imaging (x-ray and MRI)

Radiographic evaluation of rheumatoid joints is used both to provide an objective measure of the extent of anatomical joint damage and to predict further progression. It is considered as the traditional gold standard in assessing joint damage of RA patients and characteristic x-ray findings are part of the American College of Rheumatology (ACR) classification criteria for RA [6]. It is relatively inexpensive, widely available and has standardized methods of interpretation, but has many limitations. These include the use of ionizing radiation and projectional superimposition. This can obscure erosions and mimic cartilage loss, an inevitable consequence of representing a 3D structure in only two planes. Experienced readers are required to interpret the films, often using time-consuming methods [7], and structural change cannot usually be reliably determined in less than 6–12 months. An additional limitation is that radiographic erosions are only present in a minority of patients with early RA, with a prevalence of 15–18% at 6 months disease duration [8,9]. Conventional radiography (CR) offers only late signs of preceding disease activity and the resulting cartilage and bone destruction. This is inadequate because, ideally, we need to

take action on the cause of the erosions before they occur. Furthermore radiographs taken at any given time point lack specificity for the identification of patients whose structural joint damage will not progress [10].

MRI with gadolinium enhancement can reveal both the extent of pannus and vascularity [11]. In 1996, Jevtic *et al.* reported the prognostic value of gadolinium-enhanced synovitis for predicting erosions in the small finger joints of established RA patients [12]. Another study using dynamic enhanced MRI (which uses postcontrast analysis to determine the maximal and initial rate of enhancement) in early RA patients demonstrated that the severity of synovitis predicted MRI erosion as well [13]. Using metacarpophalangeal (MCP) joints in 40 early RA patients, Conaghan *et al.* were able to demonstrate that erosion progression was proportional to the level of synovitis in a given joint, and that no erosions occurred in joints without synovitis [14].

Rates of early synovial enhancement (RESE) have been demonstrated to correlate closely with the histological grade of synovitis [15,16]. Such measures allow reproducible measurements of synovial tissue mass and show relationships to subsequent joint tissue destruction. However, they do not directly quantify pannus at the invasive front of the augmented synovial tissue mass. The use of MRI is unfortunately limited by restricted availability and high cost. The procedure itself is also time-consuming. For example, a hand and wrist take approximately 50 minutes to scan. Nonetheless, MRI with contrast enhancement for the visualization of synovitis and erosive disease is considered the new gold standard. Therefore, comparisons of other imaging modalities are made against MRI.

Articular ultrasonography

Three types of ultrasonography (US) will be discussed within this review.

■ Gray-scale US

In medicine, US employs high-frequency sound (ultrasound) waves to produce images of structures within the human body. These ultrasonic waves are sound waves that are above the frequency range of sound that is audible to humans. The ultrasonic waves are produced by the electrical stimulation of a piezoelectric crystal and can be aimed at a specific area of the body. As the waves travel through tissue, they are reflected back at any point, where there is a change in tissue density; for example,

at the border between cartilage and bone. The reflected echoes are received by an electronic apparatus that determines the echo intensity level and the position of the tissue giving rise to the echoes. Therefore, images created can be displayed in static form, or, in the use of rapid multiple sound scans, they can, in effect, provide a moving picture of the inside of the body. Gray-scale US is the simplest form of US and does not utilize the Doppler effect.

■ Color Doppler ultrasonography

The apparent difference between the frequency at which sound waves leave a source and that when they reach an observer, caused by relative motion of the observer and the wave source, is the phenomenon known as the Doppler effect. It was first described in 1842 by the Austrian physicist Christian Doppler. In color Doppler ultrasonography, the Doppler effect is combined with real-time imaging. The information from the Doppler US is superimposed onto the gray-scale image as a color signal, thus allowing simultaneous visualization of anatomy and flow dynamics. The direction of blood flow is highlighted using the color red or blue, indicating flow towards or away from the ultrasound transducer, respectively. Color Doppler ultrasonography is especially utilized to assess blood flow within arteries.

■ Power Doppler ultrasonography

Power Doppler ultrasonography (PDUS) encodes the amplitude of the power spectral density of the Doppler signal and is a sensitive method for demonstrating the presence of slow blood flow in small vessels. The power Doppler (PD) signal is actually a measure of the density of moving reflectors at a particular level, and thus of the fractional vascular volume [17,18]. PD is insensitive to flow in submillimeter vessels and thus, as a result, is only an indirect surrogate for measurement of capillary flow. The total integrated PD is displayed in color and incorporated into the gray-scale image.

This review on articular US relates to the imaging of the joint, which includes the cartilage and bone as well as the pathology that can arise within these structures. These pathologies consist of effusions, synovitis, cartilage damage and bone erosions, which can each be assessed by US. The definitions of the normal structures (joint, cartilage and bone) and pathology (joint effusion, synovitis and bone erosion) used in this review, as related to US, will be discussed.

Joint

A joint is a structure that separates two or more adjacent elements of the bony skeleton. Joints such as the MCP joints, in which the separated elements move on one another, have a joint capsule profile that can usually be visualized by US and represents the outer margin of the joint. The articular surfaces are covered with cartilage. Within the MCP joints, a hypoechoic intra-articular (IA) fat pad is often present and appears as an inverted triangular area with homogeneous echogenicity and is known as the triangular structure.

Cartilage

Articular cartilage is visualized on US as a homogeneous anechoic layer with sharply defined outer and inner margins [19].

Bone

The bony cortex is visualized on US as a continuous sharp hyperechoic line, which generates an acoustic shadow [19].

Joint effusion

A joint effusion (synovial fluid) is visualized on US as an abnormal hypoechoic or anechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) IA material that is displaceable and compressible, but does not exhibit Doppler signal [20].

Synovitis

Synovitis is visualized on US as synovial proliferation and is characterized by clusters of soft echoes (bushy and villous appearance) and/or homogeneous synovial hypertrophy. This is abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) IA tissue that is nondisplaceable and poorly compressible and may exhibit Doppler signal [19,20].

Bone erosion

Bone erosion is visualized on US as a IA discontinuity of the bone surface that is visible in two perpendicular planes [20].

In this review, the utility of US in several areas of RA will be addressed. These include:

- Assessment of disease severity
- Diagnosis of RA
- A tool for assisting IA aspirations and injections
- Monitoring the disease and the response to therapy
- Development of new treatments
- Predicting the course of the disease

Ultrasonography in assessing disease severity

The small joints of the hand are almost invariably involved in RA and therefore their evaluation is of considerable importance. Owing to their relatively shallow depth, they are easily amenable to evaluation with ultrasound, utilizing higher frequencies that produce high-resolution images.

High-frequency (gray-scale) US (HFUS) can reproducibly delineate synovial thickening in small joints of the hands in patients with active RA. However, the analysis of such images does not necessarily demonstrate a clear relationship with clinical assessments of disease activity [21]. This observation probably reflects the fact that high-frequency US identifies synovial thickening without differentiating actively inflamed or fibrous tissue.

Power Doppler ultrasonography enables visualization of synovial hyperemia in the inflamed RA joint [22,23]. MRI RESE after injection of gadolinium have been demonstrated to correlate closely with the histological grade of synovitis [15,24]. In turn, the synovial vascular signal on PDUS is closely correlated with the RESE, calculated from dynamic contrast enhanced MRI on the same day, in RA MCP joints [25,26]. PDUS signal intensity in rheumatoid knee joints has been compared directly with the histological assessment of synovial membrane microvascular density [27] and they correlate well. Consequently, there is considerable value in visualizing small and large joints of RA patients using PDUS as a quick, noninvasive and relatively inexpensive alternative to contrast enhanced MRI.

High-frequency and PDUS in combination are sensitive and reproducible tools for determining joint effusions and synovitis and have been demonstrated to be more sensitive than clinical scoring in determining disease activity [28,29].

US has been demonstrated to be more sensitive for detecting bone erosions in the small joints of the hands and feet than CR [30–33]. Furthermore, in these easily accessible joints, detection of bone erosions by US is in high agreement with MRI [30,31,33,34]. Overall, the majority of studies have demonstrated less sensitivity in US for the detection of erosions than MRI, the reference method [32–35]. However, one study detected more erosions using US than MRI [31].

The use of microbubble-based US contrast agents may improve the detection of IA vascularization in the finger joints of patients with RA [36,37], but with the disadvantages of cost, time, invasiveness, and the potential for increases in background noise.

Compared with 2D US, 3D US is in its relative infancy. A recent study compared the capability of 3D PDUS with contrast (gadolinium)-enhanced MRI to visualize synovial vascularity in clinically inflamed wrists of patients with RA. 3D vascularity of each wrist joint was visualized by a free-hand sweep using a 2D transducer (probe) in PD mode. A region of interest in an area of high Doppler signal intensity was obtained and 3D vascularity score was determined using a semi-quantitative scale, which took into account the number of blood vessels penetrating the joint capsule, the number of IA blood vessels, and the strength of blood flow. A 3D vascular tree consisting of peri- and IA blood vessels could be demonstrated in the same anatomical region of interest, in which an increased gadolinium enhancement was measured by MRI in all examined RA patients. Despite this, there was no statistically significant correlation between the estimation of synovial vascularity, by the use of the newly developed 3D score, and the calculated values of the MRI relative enhancement [38]. This study used a 2D US transducer, which was swept in one direction (free-hand technique) in order to obtain a sequence of 2D PD images to provide the third dimension. Recent technological advances have permitted the development of dedicated 3D transducers that generate an internal ultrasonographic sweep. This may improve the image acquisition and reduce operator-dependant variability. In fact a recent study has shown good to excellent agreement between US using a conventional 2D transducer and a dedicated 3D transducer in assessments of inflammation and erosions of RA hand and wrist joints [39].

Ultrasonography in the diagnosis of rheumatoid arthritis

A number of studies have investigated the potential for US to confirm or provide an earlier diagnosis of RA and also to differentiate it from other arthritides. US with the use of PDUS has been demonstrated to be superior to clinical evaluation in the detection of joint inflammation (effusions and synovitis). In addition, interobserver reliability was better for US findings than for clinical assessment [29].

By measuring MCP and proximal interphalangeal (PIP) finger joint cartilage thickness using gray-scale US, Moller *et al.* could differentiate between early symptomatic osteoarthritis (OA) and early RA, but not RA from healthy joints. Early OA joints had significantly reduced cartilage thickness compared with early RA. They also found that in patients with RA, US scores correlated with duration of treatment-resistant progressive RA. Therefore, direct visualization and quantification of cartilage in MCP and PIP joints can be useful for differentiating RA from OA in the context of an early arthritis clinic [40].

Wakefield *et al.* compared US with CR for the detection of erosions in the MCP joints of patients with early RA. A total of 40 patients underwent posteroanterior radiography and US of the MCP joints of the dominant hand. Erosion sites were recorded and subsequently compared using each modality. MRI was performed on the second MCP joints in 25 patients to confirm the pathologic specificity of sonographic erosions. US detected 6.5-fold more erosions than radiography, in 7.5-fold the number of patients. All sonographic erosions that were visible on radiography corresponded by site to MRI abnormalities. This study demonstrated that US is a reliable technique that detects more erosions than radiography in early RA [30].

A retrospective study by Agrawal *et al.* on the use of clinic-based musculoskeletal US has demonstrated its potential to improve the early diagnosis of inflammatory arthritis, which could ensure better outcomes with the appropriate treatment initiated at an earlier stage of the disease. Data were retrieved from new patient records and follow-ups.

Its impact on treatment decisions was noted. The most frequently scanned area was the hand (including the wrist). The results of the US were combined with clinical evaluation and blood tests that included serological markers such as IgM rheumatoid factor. Among new patients, a decision was made, based on the patient records, as to whether US had helped in confirming clinical diagnosis, had helped in changing the clinical diagnosis, or had been of no additional help over clinical evaluation. Among follow-ups, conclusions were drawn based on the patient records as to whether a revision of the existing diagnosis had been made based on US. Among new patients, 33.3% referred with inflammatory arthritis had no US evidence of inflammation in or around joints. In 76.3%, it helped in confirming or changing diagnosis. In 7.2% of follow-up it helped in the revision of diagnosis [41].

Ultimately, the diagnosis of RA will depend on a number of factors including a compatible patient history and clinical examination, as well as serological tests, and is unlikely to ever rest solely on the result of a single imaging modality. However, by allowing improved detection of vascularity, synovial thickening and erosions, ultrasound can confirm the presence of synovitis and the resulting damage in joints. This, together with the pattern of joint involvement, can help clinicians in reaching a specific diagnostic decision in patients with early undifferentiated arthritis, or it may be able to differentiate RA from other forms of arthritis. Although standardization and validation are still incomplete, US is already widely used for investigating joint inflammation.

Ultrasonography as a tool for assisting intra-articular aspirations & injections

It has long been considered that musculoskeletal US could be of help in guiding the needle positioning in interventional manoeuvres. In RA, despite the use of US-guided therapeutic injections, both in clinical practice and clinical trials [42–44], US-guided treatments with IA injections have not yet been shown to be better than blind injections. Luz *et al.* compared the efficacy and accuracy of blind and US-guided IA injections in RA patients with wrist synovitis. Their study was a prospective, double-blind, randomized controlled study, in which 60 RA patients were enrolled. Patients were blindfolded and equal numbers were randomly allocated to receive either IA wrist injections by blind injection or US-guided IA injections with a solution that included corticosteroid and contrast agent. All procedures were performed by an experienced rheumatologist. Radiographic films taken during the procedures were analyzed at the end by a blinded radiologist. No statistically significant difference between groups was observed with regard to the presence of IA contrast agent after the procedure or clinical response after 12 weeks follow-up [45].

US may have a place in clinical diagnostic aspiration and as a research tool for obtaining synovial fluid [46,47]. Balint *et al.* compared joint aspiration using a conventional technique with an US-guided technique in patients that had been referred for joint aspiration. In the conventional group, successful aspiration was achieved in 32% of joints. In the US-guided group, successful aspiration was achieved in 97% of joints [46]. Raza *et al.* compared the accuracy

of palpation-guided and high-frequency (gray-scale) US (HFUS)-guided needle placement in MCP and PIP joints in patients with clinically evident synovitis in either of these joint groups. Needle positioning was IA in 59% of palpation-guided injections whereas with ultrasound guidance, initial needle placement was IA in 96% of cases. Raza *et al.* developed a joint lavage technique to obtain synovial fluid from the joints that had ultrasound-guided needle placement, and synovial fluid cells were lavaged from 63% of these joints [47].

In terms of therapeutic benefit, US-guided corticosteroid injections may not be superior to blind IA injections, but for the purpose of clinical trials involving IA aspiration and/or injection, ultrasonographic guidance is a method of improving synovial fluid collection and ensuring correct delivery placement of the therapeutic drug. By identifying areas of synovial hypertrophy, US has also demonstrated its utility in both guiding biopsies of synovial tissue in the small joints of RA patients and permitting a minimally invasive technique [48].

Ultrasonography in monitoring the disease & response to therapy

Ultrasonography is a tool that can accurately measure disease severity and therefore should also be useful in monitoring the course of the disease and hence, the response to therapy. Synovitis, cartilage thickness and bone erosions imaged by US have been investigated.

A number of recent clinical studies have explored the potential for HFUS and PD technology to measure synovial thickening and vascularity, thereby delivering a reliable synovitis signal early during the course of therapy, which correlates with clinical outcome [49–52]. In a small open-label study of five RA subjects treated with etanercept for 1 month, a significant decrease in synovial vascularity of the MCP joints was observed ($p < 0.001$) with a median reduction of 88% [49]. This decline in vascularity was accompanied by a significant reduction in serum C-reactive protein levels as well as other clinical parameters of disease activity. Another pilot study of 11 RA subjects receiving infliximab (open label) for 6 weeks supported these observations with a significant reduction in ultrasound positive joints and in cumulative synovial thickness ($p < 0.05$). This reduction correlated with a decrease in disease activity [51]. PDUS has also demonstrated its utility for short-term monitoring of synovial vascularity changes induced by corticosteroids [53].

Moller *et al.* measured cartilage thickness of MCP and PIP joints with HFUS in patients with RA and found that reduction in cartilage thickness correlated with duration of treatment-resistant, progressive RA [40].

Rheumatoid arthritis follow-up studies have compared the abilities of CR, US and MRI to detect erosions. The majority of studies have demonstrated that MRI and/or US have a greater sensitivity than CR in the detection of erosions, and also a greater sensitivity to change [35,54–56]. The majority of studies have shown superiority of MRI over US [35,54,56], yet in the study by Scheel *et al.*, superiority of US over MRI for evaluation of PIP joints was observed [56]. Interestingly, two of the studies demonstrated a decrease in MRI and US signs of synovitis as well as clinical signs of synovitis, while the number of bone erosions detected by both imaging modalities increased [54,56]. Two studies by Brown *et al.* may provide an explanation for this. They found that most RA patients on DMARDs, who satisfied the remission criteria with normal findings on clinical and laboratory studies, had detectable synovitis by US [57]. They followed this DMARD-treated clinical remission cohort for 12 months and erosions were measured with US, MRI and CR. Synovitis detected by HFUS and PD in individual joints at baseline were significantly associated with progressive radiographic damage. In addition, there was a significant association between the PD score at baseline and structural progression over 12 months in totally asymptomatic MCP joints and 12-times higher odds of deterioration in joints with increased PD signal (odds ratio (OR): 12.21; $p < 0.001$) [58]. This subclinical inflammation explains the observed discrepancy between disease activity and outcome in RA in patients on conventional DMARDs. Therefore, although there may be a reduction in synovitis as documented in the previous studies [54,56], the synovitis that might have still been present may have had erosive potential. Scire *et al.* found that 41% of early arthritis patients in clinical remission on conventional DMARDs had a positive PD signal and that this predicted a short-term relapse [59]. These studies suggest that US imaging assessment may be necessary for the accurate definition of true remission.

Ultrasonography in the development of new treatments

Present treatments include steroids, NSAIDs, DMARDs and biological agents such as the inhibitors of TNF. The aims of therapy are to

relieve pain and stiffness and to prevent erosions, thereby halting the progression of disease and subsequent disability. A variety of DMARDs taken singly or in combination have proven efficacy in slowing the development of erosions but do not arrest the disease [60–63]. Anti-TNF therapies more directly target the disease process by neutralizing the proinflammatory cytokine TNF. Taken alone or in combination with DMARDs, they have had a major impact, improving the functional status of patients and further reducing progression in radiographic disease [64,65]. Despite this success, there are limitations to the use of anti-TNF agents that include intravenous or subcutaneous administration, high cost, and that a significant proportion of patients (approximately 40%) do not respond. Therefore, there is still a great need to develop agents that have efficacy in reducing inflammation, prevent erosions and have a good safety profile.

Current practice in developing new therapeutics for RA involves clinical assessment of response by means of regulatory end points that include composite measures of disease activity, such as the Disease Activity Score (DAS28), a continuous measure, and ACR categorical responses. However, many of the component measurements are subjective, imprecise and insensitive to change. In general, their use necessitates lengthy clinical trials using large cohorts of patients to evaluate new therapeutic compounds. CR, although objective, is relatively insensitive to change, and therefore also requires lengthy clinical trials using large cohorts of patients. MRI, while considered the new gold standard, is time consuming and often prohibitively expensive. For the purposes of early stage testing of novel therapeutics, we require a sensitive method to distinguish between treatment groups in cohort studies that permits small numbers of patients and is a reliable indicator of efficacy at an early time point, for example at 4 weeks. Ideally, such measures would also be predictive of a longer term response to repeated medication and give an early indication of disease modification. US is a noninvasive and sensitive imaging method for objectively determining both synovial thickening and increased vascularity in RA and may therefore be an ideal tool for the purpose of early stage testing of therapeutics. It is also more readily accessible and relatively inexpensive compared with MRI. Its superiority over CR to detect erosions in certain joints may also lend itself to early identification of disease modification by new therapeutic compounds using fewer patients in clinical trials of less than 12 months.

In the first randomized, placebo-controlled study of infliximab in RA subjects on methotrexate (MTX), PDUS was compared with radiographic evaluation of joint damage after 18 and 54 weeks of treatment [52]. A total of 12 subjects per treatment arm (MTX plus placebo and MTX plus infliximab) were recruited and treated with placebo or 5 mg/kg infliximab infusions at baseline, 2 and 6 weeks and then every 8 weeks for the duration of the study. PDUS was measured at baseline and after 18 weeks of therapy. This was compared with hand radiographs after 54 weeks. A significant decrease in synovial thickness (mean $\pm$ standard deviation (SD): 11.8 ± 6.8 placebo vs 6.8 ± 4.7 infliximab; $p < 0.05$) and synovial vascularity (median $\pm$ SD: 3989 ± 5792 placebo vs 92 ± 1610 infliximab; $p = 0.005$) was observed at 18 weeks from baseline. There was a $30.7 \pm 34.4\%$ decrease in the placebo group (MTX plus placebo infusions) and a $98.4 \pm 16.8\%$ decrease in the treated group (MTX plus infliximab infusions) compared with baseline at 18 weeks; this difference was significant ($p < 0.05$). There were striking positive correlations between baseline synovial thickness and radiographic progression at 54 weeks ($p = 0.02$) as well as between baseline synovial vascularity and radiographic progression ($p = 0.005$). The changes, over 54 weeks in the case of total van der Heijde-Sharp score and 18 weeks in the case of the ultrasonographic measurements, permitted distinction between subjects treated with infliximab and MTX from subjects treated with placebo and MTX.

In an open-label study, 2D and 3D US were utilized to assess the treatment response of 24 patients with active arthritis (17 RA and seven psoriatic arthritis patients) to first-time treatment with the TNF inhibitor adalimumab. Sequential clinical, laboratory and US examinations were performed at baseline and weeks 2, 6 and 12. 2D and 3D PDUS were completed by two independent investigators and the amount of color pixels and voxels (volume pixels) were calculated, respectively. Treatment response was observed as early as week 2 with a significant reduction of 2D ($p < 0.01$) and 3D scores ($p < 0.001$). However, it is important to note that at baseline, every patient was screened by US at bilateral wrists, MCP, PIP and MTP joints II–V, and the dominant joint that showed the most intensive Doppler activity was selected as a target joint for the follow-up examinations [66].

The potential of US in the early assessment of the anti-inflammatory effectiveness of new therapeutic agents, so-called ‘proof of concept’

studies, has yet to be fully explored. US also has the potential for patient selection by detecting those with synovitis who are most likely to respond to intervention and thereby reducing trial inclusion numbers further.

Ultrasonography in predicting the course of the disease

The severity of RA varies between patients, both in the extent and pattern of joint involvement and also in the rate of progression of erosions. The disease course of individuals who meet the criteria of classification for RA may vary greatly from self-limiting to progressive erosive disabling forms. For this reason, rheumatologists have even suggested sub-classifying RA according to different types of disease course [67].

Reducing joint damage in both early and late RA is achievable by pharmacological means. Current treatments include corticosteroids, NSAIDs, DMARDs and biological agents such as the inhibitors of TNF. Although the progression of structural damage to joints can be completely inhibited in a majority of patients treated with anti-TNF- α biological therapies, with particularly favorable results in the earliest stages of disease, the costs are very high and incremental over time, with the consequence that in the UK, according to current guidelines, biological therapies are rationed to patients who have failed to achieve an adequate response to at least two conventional DMARDs and have evidence of persistent disease activity. The difficulty with this form of rationing is that a significant proportion of patients with lower levels of disease activity continue to accrue structural damage to joints with consequent loss of function over time. Furthermore, TNF inhibitors are generally not available at the earliest stages of disease when there is the highest potential to prevent joint damage and subsequent disability. This is despite clear evidence of such benefits in study populations and preliminary data suggesting that early treatment with an anti-TNF agent may permit induction of biologic-free remission [52]. Cost-effective and optimal clinical use of expensive biological agents is further complicated by the fact that a significant proportion of RA patients are refractory to TNF blockade. This suggests that other proinflammatory molecules or immunological pathways drive the clinical syndrome in this population. Furthermore, serious adverse events, although relatively uncommon, can and do occur in an unpredictable manner. Therefore, it is highly desirable to predict which patients are at risk of erosions in those with early disease in order to initiate preventative measures as soon as possible.

The patient's treatment could then be adapted according to their risk, thereby more effectively preventing or retarding further erosions as well as avoiding the use of unnecessary treatments.

It would be advantageous for the tool(s) that predicts erosive disease to be safe, easy to use, inexpensive, widely available, accurate, non-invasive and to provide results that can be acted on immediately for the patient's benefit. HFUS and PDUS imaging have the potential to fulfil all of the above criteria.

Studies using MRI have shown the ability of gadolinium-enhanced synovitis in predicting erosions in early [13,14] as well as in established RA [12]. The high level of agreement between US and MRI for synovitis and erosions suggests that US may have value in predicting prognosis in RA [25,26,30,33,34].

Naredo *et al.* followed 42 early RA patients starting DMARD therapy for 1 year. The presence of synovitis was investigated in 28 joints using gray-scale US and PDUS at baseline, 3 and 6 months and 1 year. Radiographic assessment was performed at baseline and at 1 year. There was no significant correlation between the baseline US parameters and the 1-year follow-up radiographic scores. However, time-integrated values of PDUS parameters demonstrated a highly significant correlation with radiographic progression ($r = 0.59-0.66$; $p < 0.001$) after 1 year [68].

In early RA patients randomized to either anti-TNF plus MTX or placebo plus MTX, we demonstrated that baseline synovial thickening and degree of vascularity in the MCP joints assessed by US correlated with radiographic joint damage at 1 year in the placebo group, but not in the anti-TNF group [52].

The importance of the detection of synovitis in patients with RA treated with conventional DMARDs was clearly demonstrated by Brown *et al.* [57,58]. Synovitis detected by US in RA patients on DMARDs was strongly associated with radiographic structural deterioration in joints over 12 months, despite satisfying clinical remission criteria.

There is evidently much scope for further investigation of the potential for US in predicting erosive disease.

■ Reliability of ultrasonography

Unlike MRI, US is much more operator dependent and the experience of the sonographer will influence the result of the ultrasound examination. However, when focusing on specific joint groups and basic pathology, the skill of US

can be relatively easily and rapidly acquired, especially when taught by a more experienced sonographer [69,70]. There are large numbers of different ultrasound machines with different capabilities on the market as well as older generation machines still being used in some centers. The ideal situation is that independent sonographers using different ultrasound machines in different hospitals are capable of obtaining examination results that are comparable, both in clinical practice and for the purpose of research studies. Through bringing together experts in musculoskeletal US from all over Europe, the outcome measures in rheumatoid arthritis clinical trials (OMERACT) group have helped to standardize the definition of normal and pathological US findings [20,71]. However, difficulties remain in the standardization of image acquisition, the grading of pathologies and in how to analyze dynamic examinations such as the PDUS clips, which are affected by the cardiac cycle.

Many studies have attempted to validate US. Some have examined the interobserver variability between two readers who have analyzed the examinations acquired by a single sonographer. Not surprisingly, a high level of agreement has been found in these studies when assessing synovitis (HFUS synovial thickening or PD signal) with κ values ranging from 0.49 to 0.82 [72,73].

More scrupulous tests of US are those studies that make interobserver comparisons between two or more sonographers who have independently acquired the examinations from the same patients. In these studies, a lower agreement has been found when assessing synovitis (HFUS synovial thickening or PD signal) with κ ranging from 0.28 to 1.0, but the results are still encouraging [29,57,74-76] with the majority of κ values being over 0.6. In addition, the more experienced the sonographers, the higher the agreement between them [74]. Semi-quantitative scales have been reported to have slightly less agreement than quantitative scales [74], but further studies are needed to confirm these findings.

Intra-observer reliability has been assessed by blinded rescoring by the same reader of archived US images, 3-12 months after the initial assessment in the same patient subset. These studies report good agreement when assessing synovitis (HFUS synovial thickening or PD signal) with κ values ranging from 0.55 to 1.0 [29,57]. To our knowledge, there are no studies reporting the intra-observer reliability of the same sonographer repeating his/her scan on the same patient (not simply re-reading the acquired images) and subsequently reading both sets of patient images.

The interobserver reliability of 3D US has also been explored. 3D assessments were acquired by a free-hand sweep using a 2D transducer (probe) in the following two studies. The first, an open-label study of an anti-inflammatory therapy in RA patients, found that quantification of 3D PD images (voxel count) showed higher interobserver agreement compared with 2D quantitative analyses, and similar findings were observed with 2D and 3D semiquantitative grading [77]. The second, another open-label study by Albrecht *et al.*, obtained similar κ values (0.8) for 2D and 3D US, judging effusions with a semiquantitative scale or measuring PD signal (pixel count for 2D and voxel count for 3D). Patients in this study had a mixture of arthritides (17 RA or seven psoriatic arthritis) [66]. 3D US using a dedicated 3D transducer has the potential to enhance the interobserver agreement between two individual sonographers over that of 2D US. This is because possible inaccuracy created by the need for precise probe placement during 2D image acquisition is reduced or removed entirely depending on the target joint.

Albrecht *et al.* found moderate intermachine agreement with a κ value of 0.57 for 2D PDUS score. This intermachine agreement was based on a comparison between a more advanced machine (used for their main study) and an older device [66]. Therefore, agreement may improve when comparisons are made between similar generation machines.

Conclusion

It is fundamental for the successful treatment of patients with RA that early diagnosis of the disease and commencement of disease-modifying therapy take place before destructive changes develop. US is a sensitive tool for objectively detecting joint inflammation that precedes erosive damage. US is also more sensitive in detecting erosions than CR, although overall it is inferior to MRI, which is considered the new gold standard. However, MRI is expensive, has restricted availability and the procedure itself is time-consuming. US is noninvasive, accessible and relatively quick compared with MRI. Therefore, in the context of an early arthritis clinic, US in combination with other clinical features and blood tests could establish an earlier diagnosis in patients with RA and is already being utilized by practicing rheumatologists to this end.

The ability of US to sensitively detect joint inflammation and erosions and thereby measure disease severity has meant that it is also able to effectively monitor the response of RA patients

to therapeutic intervention. This ability has been taken further in the context of clinical trials. The development of reliable and reproducible biomarkers is essential to drug development, and one of the main goals of researchers is to conduct early clinical trials with small patient numbers over short periods of time. US has the potential to fit the requirement of a sensitive method to distinguish between these treatment groups.

Persisting inflammatory synovitis in RA patients detected by US has been seen to predict future joint damage. Of course, true remission may need to be defined by lack of US evidence of synovitis. This has relevance clinically in tailoring the management of each patient on an individual basis according to their erosive potential. In the context of clinical trials, demonstrable suppression of synovitis may be predictive of a longer-term response to repeated medication and may give an early indication of disease modification.

A criticism of US versus MRI has been the operator dependence in securing adequate ultrasound examinations for clinical or trial purposes. The validity of US assessment has been addressed in a number of studies that have assessed interobserver variability and the majority have produced favorable results. Where validation is lacking is in comparisons between different ultrasound machines and the potential of 3D US to improve interobserver agreement between independent sonographers.

Future perspective

Over the next 5–10 years we anticipate that the utility of US as a sensitive outcome measure in early ‘proof of concept’ clinical trials undertaken with small patient numbers will help to identify the most promising therapeutics, thus supporting its future use in Phase III trials. It is likely that US will also be utilized in Phase III trials to quantify the therapeutic effect on synovitis, to measure the change in number of erosions and to discern the achievement of true remission. US may be used to explore the pharmacodynamic attributes that belie the variable onset of action and efficacy of DMARDs as well as biological agents.

We anticipate that US will be more widely employed in rheumatology clinics. We predict that US demonstration of early erosive change will be used as a classification criterion for RA together with other clinical parameters in an effort to diagnose RA earlier and to promote early optimum suppression of synovitis. For patients with established disease, we expect that US will have an increasing role in the detection

of subclinical synovitis warranting therapeutic intervention. We also expect that the skill of US will become more widespread among rheumatologists and it may become a mandatory requirement of trainee rheumatologists.

Efforts will be made to standardize the grading of pathologies so that comparisons can be made more readily between studies conducted in different centers.

As dedicated 3D probes become more available, future validation studies will explore the potential of 3D US to improve the inter-observer agreement and perhaps also reduce the skill required of the sonographer. More complex software will be required to help analyze

the 3D images and this may go beyond measuring PD voxels to measuring cartilage volumes in joints to monitor disease progression and response to treatment.

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Executive summary

- Rheumatoid arthritis (RA) is a chronic inflammatory disease that is characterized by erosion of cartilage and bone. It has a prevalence of 0.5–1% worldwide and is a significant cause of disability. Early diagnosis and therapeutic intervention is critical in the management of RA patients.
- Conventional radiography offers only late signs of preceding disease activity and the resulting cartilage and bone destruction. MRI is considered the new gold standard for the detection of joint inflammation and bone erosions but is invasive, costly and has limited availability. Ultrasonography (US) compares well with MRI although it is generally inferior. However, US is relatively inexpensive, quick to perform and readily accessible.
- By sensitively detecting joint inflammation and bone erosions, US has utility in assessing RA disease severity, diagnosing RA and differentiating it from other arthritides, monitoring disease progression and response to treatment.
- Despite the operator dependence of US, validation studies report good interobserver agreement when US is performed by two or more independent sonographers.
- Owing to the reliability of US to sensitively detect synovitis, we anticipate that it will be to be used more extensively in early 'proof of concept' studies testing new treatments that have small patient cohorts over short time periods.
- We expect that the skill of US will become more widespread among rheumatologists and it may become a mandatory requirement of trainee rheumatologists.

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