

Imaging in rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, and osteoarthritis: An international viewpoint on the current knowledge and future research priorities

Xenofon Baraliakos¹ , Philip G. Conaghan^{2,3} , Maria-Antonietta D'Agostino^{4,5} , Walter Maksymowych⁶ , Esperanza Naredo⁷ , Mikkel Ostergaard^{8,9}, Georg Schett¹⁰, Paul Emery^{2,3} 

Abstract

Imaging is increasingly used in the routine management of rheumatic diseases as well as in the clinical trials of these disorders. This viewpoint, authored by a group of international imaging experts following two meetings dedicated to imaging in rheumatology, reports a consensus about the current knowledge and addresses where further research should be focused based on the views of the international imaging experts and discussion of the evidence with attending imaging practitioners. The goal was to maximize the potential of imaging to improve the clinical management of four rheumatic diseases. These rheumatic diseases include rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, and osteoarthritis.

Keywords: MRI, imaging, musculoskeletal



ORCID IDs of the authors:

X.B. 0000-0002-9475-9362;
P.C. 0000-0002-3478-5665;
M.A. 0000-0002-5347-0060;
W.M. 0000-0002-1291-1755;
E.N. 0000-0003-0017-0096;
P.E. 0000-0002-7429-8482.

Cite this article as: Baraliakos X, Conaghan PG, D'Agostino MA, Maksymowych W, Naredo E, Ostergaard M, et al. Imaging in rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, and osteoarthritis: An international viewpoint on the current knowledge and future research priorities. *Eur J Rheumatol* DOI: 10.5152/eurjrheum.2018.18121

Introduction

Increasing evidence of the impact of imaging on the management of rheumatic diseases has resulted in the publication of the first European League Against Rheumatism (EULAR) recommendations for the use of imaging in the diagnosis and management of rheumatoid arthritis (RA), spondyloarthritis (SpA), and osteoarthritis (OA) in the previous years (1-3). The widespread use of imaging in clinical practice and, more recently, clinical trials means that a review of its role is timely (4-9).

In this context, an international group of imaging experts led two annual meetings attended by imaging practitioners to discuss recent advances in imaging in rheumatology. Ultrasound (US), magnetic resonance imaging (MRI), and conventional radiography (CR) were the main imaging modalities discussed. The experts not only focused on clinical practice but also considered where imaging could enhance clinical trial development. The experts presented summaries of the key learnings for clinical practice, and in collaboration with the attending imaging practitioners, identified the possible research gaps to fulfill (what is unknown/should be known) to further inform clinical practice and future clinical trials based on what is known. The results of these discussions are summarized in this article, serving as a viewpoint for a future clinically oriented research agenda in the field of imaging in the abovementioned diseases.

Rheumatoid arthritis

What is known?

The current knowledge provides a strong rationale for the application of US and MRI to RA diagnosis and management (Table 1).

Ultrasound is more sensitive than clinical examination for identifying minimal synovitis (10, 11). Both US and MRI can detect synovitis (usually low volume), and occasionally, erosions in individuals without inflammatory arthritis or symptoms (12, 13). These findings likely represent mechanically induced problems and OA, but remind us that diagnostic tests should be used in clinical context. However, US can improve the certainty of a diagnosis of RA above the clinical criteria (14, 15), and can be used to predict the progression to clinical RA from undifferentiated inflammatory arthritis and for anti-citrullinated protein antibody (ACPA)-positive,

¹ Rheumazentrum Ruhrgebiet Herne, Ruhr-University Bochum, Bochum, Germany

² Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

³ NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK

⁴ Department of Rheumatology, APHP, Ambroise Paré Hospital, Boulogne-Billancourt, France

⁵ INSERM U1173, Laboratoire d'Excellence INFLAMEX, UFR Simone Veil, Versailles-Saint-Quentin University, Saint-Quentin en Yvelines, France

⁶ Division of Rheumatology, University of Alberta School of Medicine and Dentistry, Alberta, Canada

⁷ Department of Rheumatology, Joint and Bone Research Unit, Hospital Universities Fundación Jiménez Díaz and Autonomy University, Madrid, Spain

⁸ Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Denmark

⁹ Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

¹⁰ Department of Internal Medicine 3-Rheumatology and Immunology, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany

Address for Correspondence:

Paul Emery, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds; 3NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK

E-mail: p.emery@leeds.ac.uk

Submitted: 24 August 2018

Accepted: 3 October 2018

Available Online Date: 16 November 2018

©Copyright by 2018 Medical Research and Education Association - Available online at www.eurjrheumatol.org.

Table 1. US and MRI in RA (current knowledge)

What is known?

- US and MRI are more sensitive than clinical examination for identifying minimal synovitis and can aid diagnosis when there is diagnostic doubt.
- US- and MRI-detected inflammation can predict progression to clinical RA from undifferentiated inflammatory arthritis and for ACPA-positive, non-specific symptoms.
- Subclinical synovitis detected by US and MRI predicts subsequent damage and flare, even when clinical remission is present.
- US and MRI may be used to predict treatment response and be useful in monitoring disease activity.
- MRI is more responsive to change in joint damage than CR and can assist in monitoring of disease progression.
- MRI is more sensitive than clinical examination and can detect bone marrow edema, which is a strong predictor of subsequent radiographic progression in early RA.

non-specific symptoms (16-18), US-detected synovitis predicts subsequent damage and flare (19), and prompt treatment has been shown to reduce inflammation, thereby limiting structural damage (20, 21).

Previous studies show the discordance between clinical and US evaluation in patients in Disease Activity Score 28 joints (DAS28) remission (22, 23). US-detected synovitis and joint damage can be considered for the prediction of further joint damage (24), even when clinical remission is present, although some studies suggest that the agreement is higher when remission is assessed by the Boolean criteria (25). Moreover, US-detected synovitis may be more predictive of a therapeutic response than clinical features of disease activity (26, 27).

How US may be applied in RA clinical management was recently discussed in a consensus-based proposal from international US experts who developed five algorithms for the use of US in diagnosis, treatment monitoring, and remission (28). These five algorithms recapitulate the recent data in literature and the actual use in clinical practice. US is usually used to confirm the presence of an active synovitis, permitting for an early classification of patients with suspecting arthritis. The optimal set of joints to be

scanned remains debatable, though most studies propose the inclusion of the small joints of the hands and feet as a minimum, as their responsiveness was recently demonstrated in a multicenter therapeutic trial (27, 29). Despite the amount of evidence supporting the interest to use US for guiding treatment decision and achieve clinical remission, two recent studies have questioned the added value of US in a treat-to-target approach of patients with very early RA. In these studies, both (DAS28-driven and US-driven) approaches showed the same efficacy in achieving DAS-derived remission (4, 5). The conclusions claimed the lack of utility of US; however, major methodological issues recorded in these trials have an impact on their interpretation. These methodological issues include the absence of blinding in performing US, the non-application of US to every patient but only to a selected group, and other technical issues (30).

Magnetic resonance imaging is more sensitive than clinical examination in the detection of synovitis (1), and can uniquely detect bone marrow edema (osteitis), which is a strong predictor of subsequent radiographic progression in early RA (31, 32).

Subclinical MRI inflammation predicts clinical arthritis with subsequent erosive progression

independently of other factors, such as ACPA (22, 23, 33, 34). The relevance of MRI-detected inflammation to important patient outcomes has been demonstrated in a cross-sectional study (35) involving 514 patients with early arthritis and in two longitudinal studies involving 501 patients with methotrexate naïve RA, reporting that MRI-detected inflammation was associated with functional disability (36).

Thus, MRI is a tool that can improve the certainty of a diagnosis of RA (37, 38), predict progression to clinical RA from undifferentiated inflammatory arthritis (39), with evidence that it is more responsive to change in joint damage at earlier time points than CR (40), and detect inflammation that predicts subsequent joint damage (41, 42), even in the presence of clinical remission.

What is unknown/should be known?

Despite the abundance of research on the potential benefits of US and MRI in RA clinical management, many critical questions remain unanswered and should be the focus for future research (Table 2).

The most critical research priority for imaging practitioners is how to incorporate US and MRI into routine practice to provide added value for RA management. Additionally, payers will want to

Table 2. Clinical practice research agenda for US and MRI in RA**What is unknown and should be known?**

- What is the optimal set of joints to be scanned by US, and how frequently can clinical examination be enhanced?
- What is the optimal selection of joints and timing of MRI for the assessment of diagnosis and prognosis in RA?
- What are the thresholds of abnormality of imaging-detected inflammation to guide intervention?
- What are further data on MRI diagnostic value for patients not fulfilling the American College of Rheumatology/EULAR 2010 classification criteria?
- What is the role of MRI in predicting response to therapy and in defining remission?
- What is the cost-effectiveness of using US in diagnosis, treatment monitoring, and remission and of MRI in clinical practice?
- What is the added value of US in a tight control regimen in established RA?

Table 3. Clinical trials in RA (research agenda)**What is unknown and should be known?**

- What is the value of MRI-detected damage as an endpoint in RA clinical trials?
- Which data are required to support regulatory acceptance of MRI structural outcome and inflammatory outcome measures relevant for new drug development/approval?
- Can tenosynovitis scoring be added to RAMRIS, and what value does this offer?
- What is the added value of further trials based on MRI assessment of the joints other than the hand, in which most studies have been conducted?
- What cutoff values for clinical remission assessed by MRI and US (and their correlation) should be used in clinical trials?

know if this is cost-effective. In this context, a research agenda for clinical practice should focus on which joint sets and scoring systems are optimal to use for which purpose (diagnosis, monitoring, and remission) and which thresholds of imaging-detected inflammation, especially in low disease activity states, to guide intervention. This is a difficult task particularly considering that in many countries significant barriers to using US and MRI in practice exist (e.g., cost, time, and access/machine availability). Robust evaluations of the added value of using US for clinical management in established RA populations using a blinded study design are needed. Research needs to be tailored to better understand which subgroups/patient types can benefit most from US and MRI evaluations in a resource-limited environment.

Table 3 presents the proposal for a research agenda for future RA clinical trials. For MRI, early erosion progression has been documented as a valid measure of structural damage that could decrease sample size and study duration if it was used as an endpoint in RA clinical trials (6, 43-45), but further corroborative research is needed if MRI is to gain regulatory agencies' acceptance.

A greater sensitivity of MRI structural outcome measures and of MRI-detected inflammation as an outcome measure relevant for the development/approval of new drugs is necessary. Magnetic resonance imaging trial outcomes will be enhanced by the advent of evolving image analysis techniques, such as those involving supervised machine learning (RAMRIQ), recently shown to be more responsive than both RAMRIS and DCMRI (46).

In addition, further evaluation of MRI-detected tenosynovitis scoring could lead the way for including this measure as a component of RAMRIS for the assessment of tenosynovitis of the hand in RA clinical trials. Trials using MRI assessment of the joints other than the hand joints are also a data gap.

In addition to these research priorities, our understanding of the development of RA pathology is being enhanced by newer imaging techniques. For example, micro-computed tomography (CT) studies have demonstrated that structural bone damage can be detected before the clinical onset of arthritis in individuals with ACPA (47). This suggests that bone damage may not be an exclusive result of synovitis.

Moreover, micro-CT imaging has revealed more profound changes in the trabecular bone architecture in seropositive RA than in seronegative RA and psoriatic arthritis (PsA) (48), suggesting that seropositive RA could be phenotypically distinct.

Conclusion

In RA clinical trials, imaging provides an objective measurement of damage and MRI and US both enable early objective detection of disease activity that will predict subsequent erosion progression. MRI with central reading is well placed to provide smaller number, shorter duration trials proving therapeutic efficacy, whereas US studies in multicenter trials are now emerging. In clinical practice, X-ray and US are usually more feasible, though US can provide assessment of inflammation and in multiple joint areas. Modern imaging should be used as an adjunct to clinical decision-making where there is uncertainty of RA diagnosis or difficulties in treatment planning. In this context, although there are limited data from studies, US, for example, may be useful in 10%-20% of patients. This may change as we move to earlier diagnosis in preclinical, autoantibody-positive patients.

Psoriatic arthritis**What is known?**

The heterogeneous inflammatory involvement in PsA (intra-/extra-articular) and the resulting challenges of clinical assessment result in a need for better assessment methods.

Modern imaging may aid in the diagnosis, prognosis, and monitoring of therapeutic response in PsA by providing sensitive measures of the extent of disease (detection of subclinical synovitis and enthesitis) and for monitoring inflammation and damage. The evidence base for these roles is not nearly as extensive as for RA but is improving. Table 4 summarizes the key advances relevant to clinical practice to date.

Ultrasound can visualize the peripheral joints and entheses involved with PsA and could aid diagnosis by identifying patients with subclinical PsA or establishing a diagnosis in early inflammatory arthritis.

Ultrasound is better than clinical examination in the detection of enthesal abnormalities of the lower limbs in spondyloarthritis (SpA) and can document enthesal abnormalities in clinically asymptomatic patients with psoriasis (49, 50), raising the possibility that an US score could be a valid tool in the diagnosis of PsA

Table 4. US and MRI in PsA (current knowledge)**What is known?**

- US visualizes the peripheral joints and entheses and is better than clinical examination in detecting enthesal abnormality.
- US studies have shown significant subclinical enthesitis and synovitis in patients with psoriasis without arthritis.
- US-detected subclinical enthesitis in psoriasis may differ from subclinical enthesitis in PsA (patients with PsA having more power Doppler).
- Baseline enthesitis and persistent synovitis or enthesitis by US after 6 months of therapy predicts subsequent structural damage.
- DAPSA and Boolean definitions of remission appear to be the best predictors of US remission.
- MRI visualizes all relevant inflammatory and structural pathologies of PsA and is more sensitive to inflammatory and destructive changes than X-ray and clinical examination.
- Whole-body MRI can assess inflammation and structural damage by detecting multisite enthesitis, peripheral synovitis, and tenosynovitis and axial involvement.

Table 5. Research agenda for US and MRI in PsA**What is unknown and should be known?**

- What is the role of US- or MRI-detected subclinical enthesitis as predictor for the development of PsA in patients with psoriasis?
- What are the optimal joint sets for screening/diagnostic investigation by US/MRI?
- What is the predictive value of US monitoring compared with clinical/laboratory monitoring?
- What is the predictive capability of US-detected inflammatory patterns in PsA therapy response?
- What is the prognostic value of subclinical US/MRI abnormalities in PsA remission?
- What is the predictive value of MRI findings for therapeutic response and subsequent damage progression in PsA?
- What is the optimal MRI monitoring strategy in PsA clinical trials?
- What is the utility of novel MRI techniques (whole-body MRI, dynamic MRI, and other quantitative methods) in PsA clinical trials and practice?
- How can dactylitis and enthesitis be better defined by MRI, and how should these features be assessed in PsA clinical practice?

and underlining the need for subclinical enthesopathy and synovitis to be further investigated as a predictor for the development of PsA in patients with psoriasis (51-53).

Emerging evidence also suggests that US may play a role in the differential diagnosis of PsA and RA, with high-frequency US detecting soft tissue inflammation and enthesitis in the fingers of patients with PsA absent from the fingers of patients with RA, and that US-detected subclinical enthesitis in psoriasis differs from subclinical enthesitis in PsA, with patients with PsA having more power Doppler (7, 54).

Ultrasound composite scoring systems have shown promise for monitoring response to therapy (55, 56). Persistence of synovitis or enthesitis on US at 6 months of treatment in patients with PsA has been shown to be an independent predictor of future structural progression (57).

Recent studies have noted discrepancies between US and clinical findings for the assessment of remission, with two studies finding that the Disease Activity Index for Psoriatic Arthritis (DAPSA) and DAS28 correlated better with US findings than the Composite Psoriatic Disease Activity Index and Psoriatic Arthritis Disease Activity Score. Both studies showed that the DAPSA and Boolean definitions of remission were the best predictors of US remission (58, 89).

A recent study reported that power Doppler US-detected synovitis (PDUS) was a strong predictor of short-term flare of disease in patients with PsA in clinical remission; 65% of patients with at least one joint with PDUS synovitis at baseline had a disease flare during follow-up compared with 5.9% without baseline PDUS synovitis (relative risk=11, 95% confidence interval 2.8-44, $p<0.001$) (60).

Magnetic resonance imaging visualizes all the relevant pathologies of PsA (inflammatory in the soft tissues and bone, as well as structural damage) and is more sensitive to inflammatory and destructive changes than X-ray and clinical examination (61). Certain findings, such as extracapsular inflammation and enthesitis, are very characteristic for PsA, although not pathognomonic (62). Data on the added value of identifying peripheral PsA and the prognostic value of MRI in PsA are limited, but a preliminary study suggests a potential worth exploring.

Studies have found a higher frequency of arthritic and enthesal changes with MRI in patients with psoriasis than in healthy subjects (8, 63, 64), and a recent study showed that patients with psoriasis with tender joints and MRI inflammation had a 56% risk of PsA within 1 year compared with a 15% risk in patients with no tender joints and no MRI inflammation (65).

A relationship between MRI bone edema and subsequent CT progression has been reported (66), but overall, whether any MRI features can predict treatment response and/or subsequent joint damage in PsA remains to be determined. Moreover, there are no general rules for which joints to assess for activity and damage, due to the heterogeneous presentation of the disease. However, the most validated scoring system, Outcome Measures in Rheumatology (OMERACT) Psoriatic Arthritis Magnetic Resonance Image Score, showed good overall intrareader agreement in the hand and foot and inflammatory feature scores responsive to change (67-69).

Whole-body MRI is a novel imaging method that has been examined in small groups of patients with PsA (70, 71). Initial data suggest moderate agreement between MRI-detected enthesitis and clinical examination, raising the possibility of a whole-body MRI enthesitis index as a potential tool for assessment of disease activity (72).

The OMERACT MRI in the Arthritis Special Interest Group has conducted a literature review and suggested consensus MRI definitions of important pathologies and a preliminary assessment system, taking the first steps toward a whole-body MRI scoring system (73).

What is unknown/should be known?

More studies are needed before modern imaging can be recommended for routine use of PsA diagnosis and assessment for imaging practitioners. The predictive value of the observation of significant subclinical enthesitis in

Table 6. Imaging axial SpA (current knowledge)**What is known?**

- CR of the SIJs should, generally, be the first imaging method to diagnose sacroiliitis as part of axial SpA.
- MRI should be used if diagnosis of axial SpA cannot be established based on clinical features and CR.
- CR detects new bone formation and is important for long-term monitoring of structural damage.
- MRI allows early detection and monitoring of inflammation and structural damage in the sacroiliac joints and the spine.
- CR detects syndesmophytes, which are predictive of new development of syndesmophytes.
- MRI predicts the development of new radiographic syndesmophytes.
- MRI-detected inflammation (bone marrow edema) is a predictor of good clinical response to anti-TNF-alpha treatment in addition to elevated CRP.

patients with psoriasis without arthritis needs further study, and research should focus on identifying the optimal combination of joints for screening. Further research is needed to develop composite US scores for monitoring of treatment outcomes. A better understanding and definition of the different types of PsA is also needed prior to extrapolating MRI findings and "RA lessons" to PsA clinical practice. Table 5 proposes a research agenda.

In RA, micro-CT studies are illuminating our understanding of the pathology of PsA. These studies have suggested that trabecular bone mineral density and microstructure are significantly lower in patients with PsA than in patients with psoriasis where milder changes are observed. Further studies are warranted to confirm if bone loss starts early in PsA, perhaps at the stage of skin disease only, with implications for clinical practice if the concept of subclinical musculoskeletal disease in patients with psoriasis is supported (48).

Conclusion

Ultrasound is a useful bedside tool to enhance clinical assessment in PsA, from facilitating early diagnosis to improving management in established disease. MRI has a similar ability to detect and monitor peripheral soft tissue inflammation in the joints and entheses and, in addition, can provide information on peripheral bone inflammation (osteitis) and on inflammation and damage in the axial joints and entheses.

Axial spondyloarthritis**What is known?**

Imaging is a useful tool in the diagnosis and prognosis (disease course and treatment response) of axial spondyloarthritis (axSpA), most experience being with X-rays and MRI, whereas more sophisticated imaging techniques

are under investigation. In clinical research, imaging is the key component of the criteria for classifying axSpA based on the presence of sacroiliitis by radiography or by MRI plus at least one SpA feature. MRI has been shown to contribute to predicting a Bath Ankylosing Spondylitis Disease Activity Index 50 response in active patients treated with anti-tumor necrosis factor (TNF) agents (74).

However, several important considerations should be kept in mind in terms of the use of imaging in clinical practice. The axial site with most bone marrow edema might not match the site with most pain (75), clinical assessment of disease activity might not correlate with MRI activity (76), MRI activity may fluctuate over time (77), and structural progression in axSpA may be independent of TNF in the short-term (78-80), but with the time-averaged disease activity leading to more structural damage in the spine over time, particularly in males (81) in both the short- and the long-term follow-up, up to 12 years. In addition, findings of sacroiliac joint (SIJ) ankylosis and fat metaplasia have been found to be associated with an increased propensity for radiographic progression in the spine (WPM 2017). A recent open-label analysis of radiographic outcomes >2 years with secukinumab showed less radiographic progression than observed in previous open-label trials of TNF inhibitor (TNFi) therapy (82). However, the study population had a shorter disease duration and lower modified Stoke Ankylosing Spondylitis Spinal Score at baseline than the trials of TNFi therapy (78-80). In addition, there were no control radiographs included so any reader bias would be to score any change conservatively because of the awareness that all patients were on active treatment.

Recent data from open-label studies on the effect of TNFi on progressive spinal damage in AS

suggest that this class of drugs appears to reduce radiographic progression, especially with early initiation (83) and with longer duration of follow-up (84).

The thoracic spine is most commonly affected in axSpA and is best assessed by MRI (85), whereas SpA-related new bone formation is difficult to assess in this area with CR (86). Moreover, progression of radiographic sacroiliitis by at least one grade after 2 years occurs in only a small percentage of patients with early axial SpA, with C-reactive protein (CRP) and MRI being positive predictors of progression from non-radiographic to radiographic sacroiliitis according to the modified New York criteria (87, 88).

A recent study provides an important validation of MRI structural lesions versus CT (9). It also shows that radiography is a poor indicator of structural damage when compared with MRI and raises the question as to why radiography is used as a structural damage endpoint versus MRI, especially in clinical trials.

Imaging targets should be short-term (reduction of inflammation), mid-term (avoidance of post-inflammatory lesions), and long-term (reduction/avoidance of X-ray progression) using a treat-to-target concept (89). Early assessment and treatment of patients are important considering that significant regression of spinal inflammation can occur as early as 6 weeks after TNFi treatment (90), and that mobility limitation correlates with inflammation in the early phases of the disease (91). Ongoing systemic inflammation as measured by CRP values despite TNFi therapy is a factor predicting the development of radiographic progression (92), suggesting that effective suppression of inflammation, including MRI inflammation, may be important for effective disease modification. Whether an early suppression of inflammation leads to a decrease risk for new bone formation, though, remains to be demonstrated. Fat metaplasia in both the SIJs and the spine has been identified as an independent predictor of radiographic progression in the spine (93, 94). Table 6 summarizes the current knowledge regarding imaging and axial SpA in clinical practice.

What is unknown/should be known?

A significant amount of research is required to optimize the use of imaging tools, and thus, the routine clinical practice of diagnosing and treating/monitoring axial SpA. The predictive potential of various MRI lesions with respect to new bone formation is an important area of further research. Other areas relate to more

Table 7. Imaging axial SpA (research agenda)**What is unknown/should be known?**

- What is the potential role of very early intervention, prediction, and identification of patients likely to progress early?
- What is the significance of fat metaplasia as a lead indicator of radiographic progression?
- What is the role of MRI in defining remission in treat-to-target strategies, and is subclinical inflammation on MRI of prognostic significance?
- What is the predictive potential of MRI lesions with respect to new bone formation?
- What is the validation of MRI lesions as lead indicators of radiographic progression in the spine?
- What is the interaction of different types of inflammatory and structural lesions detected by MRI and CR to predict disease progression?
- What are more rational clinical trial study designs for disease modification (disease duration <10 years, patients selected for disease progression, positive CRP, presence of MRI inflammation, and baseline presence of definite syndesmophyte)?

Table 8. Imaging OA (research agenda)**What is unknown/should be known?**

- What is the added value of imaging (any modality) to clinical or differential diagnosis?
- What is the cost-effectiveness of imaging in OA clinical practice?
- Can imaging identify subgroups/phenotypes to enable targeted treatment?
- Is the use of imaging to measure therapy response of clinical benefit?
- Can imaging features predict therapy response to specific therapies?
- What are the benefits of imaging in less studied OA sites, such as the foot and shoulder?
- What is the added value of weight-bearing versus non-weight-bearing X-rays?
- Can imaging guidance be developed to improve the efficacy of treatments?

advanced MRI techniques with which increased sensitivity should indicate improved prediction for prognosis and therapy decisions. Imaging modalities other than radiographs and MRI should also be evaluated in the future, such as low-dose CT that shows promise for studies of syndesmophyte development and growth (95). Table 7 proposes a research agenda for imaging in axial SpA that focuses on the priorities for imaging practitioners.

Osteoarthritis

What is known?

The application of MRI and US has completely changed our understanding of the complex, multi-tissue processes underpinning the OA phenotype. They have demonstrated that multiple tissue pathologies are highly prevalent in individuals aged >50 years even with normal X-rays (with and without symptoms) (96). Imaging continues to inform us about the pathological processes. For example, the commonly seen bone marrow lesions (BMLs, associated with both pain and structural pro-

gression) likely represent a response to adjacent cartilage loss (97). Though this increased understanding of OA pathology has not yet resulted in new therapies, it has led to therapies using novel imaging inclusion criteria, such as a trial of zoledronic acid in patients with positive BML (98), and the use of a biomechanically modifying device has been reported to reduce the size of BMLs, and the use of a device-modifying biomechanics has been reported to reduce the size of BMLs in patellofemoral OA (99).

The first EULAR recommendations on the use of imaging in OA clinical practice were recently published (3). Imaging is recommended to aid confirm the diagnosis of OA only in atypical presentations and only in follow-up if there is an unexpected rapid progression of symptoms or a change in clinical characteristics. CR should generally be used before other modalities. US, MRI, and CT are recommended to make additional diagnoses involving soft tissues/bone. Imaging is also recommended for guiding injections in difficult to access joints, such as the hip.

What is unknown/should be known?

The EULAR recommendations identified significant gaps in evidence pertaining to routine use, particularly the use of imaging in identifying therapeutic targets and a lack of data for the added value of imaging above clinical evaluation alone.

A research agenda was consequently developed (3). Until these knowledge gaps are filled, regular use of imaging cannot be recommended for diagnosis, follow-up, or predicting outcome of non-pharmacological treatments of OA.

Magnetic resonance imaging provides a more complete assessment of the joint and could play a diagnostic role in patients whose symptoms are not explained by radiographic change. Although OA desperately lacks a licensed disease-modifying therapy, MRI currently plays a pivotal role in sensitively quantifying structural change in intervention studies and providing the novel tools required by the industry and academia to develop such therapies. Stratification for the presence/severity of imaging-detected pathologies may be one route to successful therapy development (100, 101). Table 8 proposes topics for a research agenda in imaging of OA based on the current expert opinion.

Conclusion

In clinical trials, although X-rays are the current regulatory standard, MRI offers a tool to sensitively and directly quantify the cartilage, thereby vastly reducing the participant numbers required in trials. It also demonstrates multiple OA pathologies and supports studies of structure modification and symptom–structure associations. In clinical practice, there is little use for imaging in the diagnosis of typical clinical presentations, though imaging will aid with the differential diagnosis, or occasionally, with guiding therapy.

Overarching conclusion

Magnetic resonance imaging and US are crucial tools for the sensitive and accurate diagnosis and management of RA, PsA, axial SpA, and OA in routine clinical practice. Despite the fact that the utility of these modalities has been documented in many studies, some areas are unexplored. Further research is necessary to clarify the optimal role of modern imaging.

Peer-review: Externally peer-review.

Acknowledgements: This manuscript has been developed subsequent to the AbbVie-sponsored Imaging Excellence Summits in 2015 and 2016; however,

AbbVie was not involved in the development of the manuscript. The authors maintained complete control over the content, and this manuscript reflects the opinions of the authors. PGC and PE are funded in part through the National Institute for Health Research (NIHR) Leeds Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. AbbVie selected the 23-24 October 2015 and 21-22 October 2016 discussion participants and reviewed the final manuscript draft for scientific accuracy, but the authors determined final content. All authors made substantial contributions to the article or critically revised it for important intellectual content and approved the final manuscript. Rhonda Siddall of Patient Central, Norwood, Greenacres Fold, Oldham, UK provided medical writing and editorial support to the authors in the development of this manuscript; financial support for these services was provided by AbbVie.

Author Contributions: Concept - X.B., P.G.C., M.A., W.M., E.N., M.O., G.S., P.E.; Design - X.B., P.G.C., M.A., W.M., E.N., M.O., G.S., P.E.; Supervision - X.B., P.G.C., M.A., W.M., E.N., M.O., G.S., P.E.; Literature Search - X.B., P.G.C., M.A., W.M., E.N., M.O., G.S., P.E.; Writing Manuscript - X.B., P.G.C., M.A., W.M., E.N., M.O., G.S., P.E.; Critical Reviews - X.B., P.G.C., M.A., W.M., E.N., M.O., G.S., P.E.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This manuscript reports the discussion from the 23-24 October 2015 and 21-22 October 2016 AbbVie-sponsored Imaging Excellence Summits. The meetings were conducted to understand the recent advances in imaging in rheumatology and their implications for clinical trials and clinical practice. The programme involved a total of 146 experts from 53 countries, who were selected for participation by AbbVie. AbbVie provided funding to invited participants, including honoraria for their attendance at the meetings. Travel to and from the meetings was reimbursed. No payments were made to the authors for the development of this manuscript.

References

- Colebatch AN, Edwards CJ, Østergaard M, van der Heijde D, Balint PV, D'Agostino MA, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis* 2013; 72: 804-14. [\[CrossRef\]](#)
- Mandl P, Navarro-Compan V, Terslev L, Aegerter P, van der Heijde D, D'Agostino MA, et al. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. *Ann Rheum Dis* 2015; 74: 1327-39. [\[CrossRef\]](#)
- Sakellariou G, Conaghan P, Zhang W, Bijlsma JWJ, Boyesen P, D'Agostino MA, et al. EULAR recommendations for the use of imaging in the clinical management of peripheral joint osteoarthritis. *Ann Rheum Dis* 2017; 76: 1484-94. [\[CrossRef\]](#)
- Dale J, Stirling A, Zhang R, Purves D, Foley J, Sambrook M, et al. Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomized clinical trial. *Ann Rheum Dis* 2016; 75: 1043-50. [\[CrossRef\]](#)
- Haavardsholm EA, Aga AB, Olsen IC, Lillegraven S, Hammer HB, Uhlig T, et al. Ultrasound in the management of rheumatoid arthritis: ARCTIC randomized controlled strategy trial. *BMJ* 2016; 354: i4205. [\[CrossRef\]](#)
- Baker JF, Østergaard M, Emery P, Baker DG, Østergaard M. Validity of early MRI structural damage end points and potential impact on clinical trial design in rheumatoid arthritis. *Ann Rheum Dis* 2016; 75: 1114-9. [\[CrossRef\]](#)
- Lin Z, Wang Y, Mei Y, Zhao Y, Zhang Z, et al. High-frequency ultrasound in the evaluation of psoriatic arthritis: a clinical study. *Am J Med Sci* 2015; 350: 42-6. [\[CrossRef\]](#)
- Emad Y, Ragab, Bassyouni I, Moawayh O, Fawzy M, Saad A, et al. Enthesitis and related changes in the knees in seronegative spondyloarthropathies and skin psoriasis: magnetic resonance imaging case-control study. *J Rheumatol.* 2010; 37: 1709-17. [\[CrossRef\]](#)
- Diekhoff T, Hermann KG, Greese J, Schwenke C, Poddubnyy D, Hamm B, et al. Comparison of MRI with radiography for detecting structural lesions of the sacroiliac joint using CT as standard reference: results from the SIMACT study. *Ann Rheum Dis* 2017; 76: 1502-8. [\[CrossRef\]](#)
- Wakefield RJ, Green MJ, Marzo-Ortega H, Conaghan PG, Gibbon WW, McGonagle D, et al. Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. *Ann Rheum Dis* 2004; 63: 382-5. [\[CrossRef\]](#)
- Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. *Arthritis Rheum* 2008; 58: 2958-67. [\[CrossRef\]](#)
- Padovano I, Costantino F, Breban M, D'Agostino MA. Prevalence of ultrasound synovial inflammatory findings in healthy subjects. *Ann Rheum Dis* 2016; 75: 1819-23. [\[CrossRef\]](#)
- Mangnus L, van Steenberg HW, Reijnen M, van der Helm-van Mil AH. Magnetic Resonance Imaging-Detected Features of Inflammation and Erosions in Symptom-Free Persons from the General Population. *Arthritis Rheumatol* 2016; 68: 2593-602. [\[CrossRef\]](#)
- Matsos MP, Khalidi N, Zia P, Chow A, Ioannidis G, Khalidi N, et al. Ultrasound of the hands and feet for rheumatological disorders: influence on clinical diagnostic confidence and patient management. *Skeletal Radiol* 2009; 38: 1049-54. [\[CrossRef\]](#)
- Agrawal S, Bhagat SS, Dasgupta B. Improvement in diagnosis and management of musculoskeletal conditions with one-stop clinic-based ultrasonography. *Mod Rheumatol* 2009; 19: 53-6. [\[CrossRef\]](#)
- Filer A, De Pablo P, Allen G, Nightingale P, Jordan A, Jobanputra P, et al. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. *Ann Rheum Dis* 2011; 70: 500-7. [\[CrossRef\]](#)
- Salaffi F, Ciapetti A, Gasparini S, Carotti M, Filippucci E, Grassi W. A clinical prediction rule combining routine assessment and power Doppler ultrasonography for predicting progression to rheumatoid arthritis for early-onset undifferentiated arthritis. *Clin Exp Rheumatol* 2010; 28: 686-94.
- Nam JL, Hensor EM, Hunt L, Conaghan PG, Wakefield RJ, Emery P. Ultrasound findings predict progression to inflammatory arthritis in anti-CCP antibody positive patients without clinical synovitis. *Ann Rheum Dis* 2016; 75: 2060-7. [\[CrossRef\]](#)
- Saleem B, Brown AK, Quinn M, Karim Z, Hensor EM, Conaghan P, et al. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. *Ann Rheum Dis* 2012; 71: 1316-21. [\[CrossRef\]](#)
- Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs inpatients with early rheumatoid arthritis. *Rheumatology (Oxford)* 2004; 43: 906-14. [\[CrossRef\]](#)
- Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: a meta-analysis. *Arthritis Rheum* 2006; 55: 864-72. [\[CrossRef\]](#)
- Brown AK, Quinn MA, Karim Z, Conaghan PG, Peterfy CG, Hensor E, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. *Arthritis Rheum* 2006; 54: 3761-73. [\[CrossRef\]](#)
- Gandjbakhch F, Conaghan PG, Ejbjerg B, Haavardsholm EA, Foltz V, Brown AK, et al. Synovitis and osteitis are very frequent in rheumatoid arthritis clinical remission: results from an MRI study of 294 patients in clinical remission. *J Rheumatol* 2011; 38: 2039-44. [\[CrossRef\]](#)
- Dohn UM, Ejbjerg B, Boonen A, Hetland ML, Hansen MS, Knudsen LS, et al. No overall progression and occasional repair of erosions despite persistent inflammation in adalimumab-treated rheumatoid arthritis patients: results from a longitudinal comparative MRI, ultrasonography, CT and radiography study. *Ann Rheum Dis* 2011; 70: 252-8. [\[CrossRef\]](#)
- Sakellariou G, Scirè CA, Verstappen SM, Montecucco C, Caporali R. In patients with early rheumatoid arthritis the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis. *Ann Rheum Dis* 2013; 72: 245-9. [\[CrossRef\]](#)
- Ellegaard K, Christensen R, Torp-Pedersen S, Terslev L, Holm CC, König MJ, et al. Ultrasound Doppler measurements predict success of treatment with anti-TNF-alpha drug in patients with rheumatoid arthritis: a prospective cohort study. *Rheumatology (Oxford)* 2011; 50: 506-12. [\[CrossRef\]](#)
- D'Agostino MA, Wakefield RJ, Berner-Hammer H, Vittecoq O, Filippou G, Balint P, et al. Value of

- ultrasonography as a marker of early response to abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results from the APPRAISE study. *Ann Rheum Dis* 2016; 75: 1763-9. [CrossRef]
28. D'Agostino MA, Terslev L, Wakefield R, Østergaard M, Balint P, Naredo E, et al. Novel algorithms for the pragmatic use of ultrasound in the management of patients with rheumatoid arthritis: from diagnosis to remission. *Ann Rheum Dis* 2016; 75: 1902. [CrossRef]
29. Mandl P, Naredo E, Wakefield RJ, Conaghan PG, D'Agostino MA, OMERACT Ultrasound Task Force. OMERACT Ultrasound Task Force. A systematic literature review analysis of ultrasound joint count and scoring systems to assess synovitis in rheumatoid arthritis according to the OMERACT filter. *J Rheumatol* 2011; 38: 2055-62. [CrossRef]
30. D'Agostino MD, Boers M, Wakefield, Emery P, Conaghan PG. Is it time to revisit the role of ultrasound in rheumatoid arthritis management? *Ann Rheum Dis* 2017; 76: 7-8. [CrossRef]
31. Hetland ML, Ejlberg B, Horslev-Petersen K, Jacobsen S, Vestergaard A, Jurik AG, et al. MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomized controlled trial (CIMESTRA). *Ann Rheum Dis* 2009; 68: 384-90. [CrossRef]
32. Hetland ML, Stengaard-Pedersen K, Junker P, Østergaard M, Ejlberg BJ, Jacobsen S, et al. Radiographic progression and remission rates in early rheumatoid arthritis-MRI bone oedema and anti-CCP predicted radiographic progression in the 5-year extension of the double-blind randomized CIMESTRA trial. *Ann Rheum Dis* 2010; 69: 1789-95. [CrossRef]
33. van Steenberg HW, Mangnus L, Reijnierse M, Huizinga TW, van der Helm-van Mil AH. Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis. *Ann Rheum Dis* 2016; 75: 1824-30. [CrossRef]
34. Rondina RG, de Mello RAF, Valim V, Lourenco RB, Batista EFP, de Oliveira Júnior R. Discordance between clinical and imaging criteria: assessment by magnetic resonance imaging of the foot of patients with rheumatoid arthritis. *Rheumatol Int* 2017; 37: 1357-64. [CrossRef]
35. Burgers LE, Nieuwenhuis WP, van Steenberg HW, Newsom EC, Huizinga TW, Reijnierse M, et al. Magnetic resonance imaging-detected inflammation is associated with functional disability in early arthritis-results of a cross-sectional study. *Rheumatology* 2016; 55: 2167-75. [CrossRef]
36. Glinatsi D, Baker JF, Hetland ML, Hørslev-Petersen K, Ejlberg BJ, Stengaard-Pedersen K, et al. Magnetic resonance imaging assessed inflammation in the wrist is associated with patient-reported physical impairment, global assessment of disease activity and pain in early rheumatoid arthritis: longitudinal results from two randomised controlled trials. *Ann Rheum Dis* 2017; 76: 1707-15. [CrossRef]
37. Sugimoto H, Takeda A, Masuyama J, Furuse M. Early-stage rheumatoid arthritis: diagnostic accuracy of MR imaging. *Radiology* 1996; 198: 185-92. [CrossRef]
38. Sugimoto H, Takeda A, Hyodoh K. Early-stage rheumatoid arthritis: prospective study of the effectiveness of MR imaging for diagnosis. *Radiology* 2000; 216: 569-75. [CrossRef]
39. Machado PM, Koevoets R, Bombardier C, van der Heijde DM. The value of magnetic resonance imaging and ultrasound in undifferentiated arthritis: a systematic review. *J Rheumatol* 2011; 87: 31-7.
40. Haavardsholm EA, Østergaard M, Hammer HB, Bøyesen P, Boonen A, van der Heijde D, et al. Monitoring anti-TNF alpha treatment in rheumatoid arthritis: responsiveness of magnetic resonance imaging and ultrasonography of the dominant wrist joint compared with conventional measures of disease activity and structural damage. *Ann Rheum Dis* 2009; 68: 1572-9. [CrossRef]
41. Østergaard M, Hansen M, Stoltenberg M, Sejer Hansen M, Bijlsma JWJ, Dudek A, et al. New radiographic bone erosions in the wrists of patients with rheumatoid arthritis are detectable with magnetic resonance imaging a median of two years earlier. *Arthritis Rheum* 2003; 48: 2128-31. [CrossRef]
42. Conaghan PG, O'Connor P, McGonagle D, Astin P, Wakefield RJ, Gibbon WW, et al. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual patients with early rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 64-71. [CrossRef]
43. Baker JF, Østergaard M, Emery P, Baker DG, Conaghan PG. Development and validation of rheumatoid arthritis magnetic resonance imaging inflammation thresholds associated with lack of disease progression. *Clin and Exp Rheumatol* 2017; 35: 607-13.
44. Østergaard M, Emery P, Conaghan PG, Fleischman R, Hsia EC, Xu W, et al. Significant improvement in synovitis, osteitis, and bone erosion following golimumab and methotrexate combination therapy as compared with methotrexate alone: a magnetic resonance imaging study of 318 methotrexate-naïve rheumatoid arthritis patients. *Arthritis and Rheum* 2011; 63: 3712-22. [CrossRef]
45. Peterfy C, Strand V, Tian L, Østergaard M, Lu Y, DiCarlo J, et al. Short-term changes on magnetic resonance imaging predict long-term changes on radiography in rheumatoid arthritis: an analysis by an OMERACT Taskforce of pooled data from four randomized, controlled trials. *Ann Rheum Dis* 2017; 76: 992-7. [CrossRef]
46. Conaghan PG, Østergaard M, Bowes MA, Wu C, Fuerst T, van der Heijde D, et al. Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow oedema, synovitis and bone erosion in methotrexate-naïve, early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques. *Ann Rheum Dis* 2016; 75: 1024-33. [CrossRef]
47. Kleyer A, Finzel S, Rech J, Manger B, Krieter M, Faustini F, et al. Bone loss before the clinical onset of rheumatoid arthritis in subjects with anticitrullinated protein antibodies. *Ann Rheum Dis* 2014; 73: 854-60. [CrossRef]
48. Kocijan R, Finzel S, Englbrecht M, Engelke K, Rech J, Schett G, et al. Differences in bone structure between rheumatoid arthritis and psoriatic arthritis patients relative to autoantibody positivity. *Ann Rheum Dis* 2014; 73: 2022-8. [CrossRef]
49. Balint PV, Kane D, Wilson H, McInnes IB, Sturrock RD. Ultrasonography of enthesal insertions in the lower limb in spondyloarthropathy. *Ann Rheum Dis* 2002; 61: 905-10. [CrossRef]
50. D'Agostino MA, Said-Nahal R, Hacquard-Bouder C, Brasseur JL, Dougados M, Breban M. Assessment of peripheral enthesitis in the spondyloarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. *Arthritis Rheum* 2003; 48: 523-33. [CrossRef]
51. Gisondi P, Tinazzi I, El-Dalati G, Gallo M, Biasi D, Barbara LM, et al. Lower limb enthesopathy in patients with psoriasis without clinical signs of arthropathy: a hospital-based case-control study. *Ann Rheum Dis* 2008; 67: 26-30. [CrossRef]
52. Gutierrez M, Filippucci E, De Angelis R, Salaffi F, Filosa G, Ruta S, et al. Subclinical enthesal involvement in patients with psoriasis: an ultrasound study. *Semin Arthritis Rheum* 2011; 40: 407-12. [CrossRef]
53. Naredo E, Moller I, de Miguel E, Batlle-Gualda E, Acebes C, Brito E, et al. High prevalence of ultrasonographic synovitis and enthesopathy in patients with psoriasis without psoriatic arthritis: a prospective case-control study. *Rheumatology* 2011; 50: 1838-48. [CrossRef]
54. Aydin SZ, Ash ZR, Tinazzi I, Castillo-Gallego C, Kwok C, Wilson C, et al. The link between enthesitis and arthritis in psoriatic arthritis: a switch to a vascular phenotype at insertions may play a role in arthritis development. *Ann Rheum Dis* 2013; 72: 992-5. [CrossRef]
55. Gutierrez M, Di Geso L, Salaffi F, Bertolazzi C, Tardella M, Filosa G, et al. Development of a preliminary US power Doppler composite score for monitoring treatment in PsA. *Rheumatology* 2012; 51: 1261-8. [CrossRef]
56. Ficjan A, Husic R, Gretler J, Lackner A, Graninger WB, Gutierrez M, et al. Ultrasound composite scores for the assessment of inflammatory and structural pathologies in psoriatic arthritis (PsASon-Score). *Arthritis Res Ther* 2014; 16: 476. [CrossRef]
57. El Miedany Y, El Gaafary M, Youssef S, Ahmed I, Nasr A. Tailored approach to early psoriatic arthritis patients: clinical and ultrasonographic predictors for structural joint damage. *Clin Rheumatol* 2015; 34: 307-13. [CrossRef]
58. Husic R, Gretler J, Felber A, Graninger WB, Duftner C, Hermann J, et al. Disparity between ultrasound and clinical findings in psoriatic arthritis. *Ann Rheum Dis* 2014; 73: 1529-36. [CrossRef]
59. Michelsen B, Diamantopoulos AP, Hammer HB, Soldal DM, Kavanaugh A, Haugeberg G. Ultrasonographic evaluation in psoriatic arthritis

- is of major importance in evaluating disease activity. *Ann Rheum Dis* 2016; 75: 2108-13. [\[CrossRef\]](#)
60. Ruta S, Martin J, Acosta Felquer ML, Ferreyra-Garrot L, Rosa J, García-Monaco R, et al. Utility of Power Doppler Ultrasound-detected synovitis for the prediction of short-term flare in psoriatic patients with arthritis in clinical remission. *J Rheumatol* 2017; 44: 1018-23. [\[CrossRef\]](#)
 61. Wiell C, Szkudlarek M, Hasselquist M, Møller JM, Vestergaard A, Nørregaard J, et al. Ultrasonography, magnetic resonance imaging, radiography, and clinical assessment of inflammatory and destructive changes in fingers and toes of patients with psoriatic arthritis. *Arthritis Res Ther* 2007; 9: R119. [\[CrossRef\]](#)
 62. Schoellnast H, Deutschmann HA, Hermann J, Schaffler GJ, Reittner P, Kammerhuber F, et al. Psoriatic arthritis and rheumatoid arthritis: Findings in contrast-enhanced MRI. *AJR Am J Roentgenol* 2006; 187: 351-7. [\[CrossRef\]](#)
 63. Offidani A, Cellini A, Valeri G, Giovagnoni A. Subclinical joint involvement in psoriasis: magnetic resonance imaging and X-ray findings. *Acta Dermatol Venereol* 1998; 78: 463-5. [\[CrossRef\]](#)
 64. Erdem CZ, Tekin NS, Sarikaya S, Erdem LO, Gulec S. MR imaging features of foot involvement in patients with psoriasis. *Eur J Radiol* 2008; 67: 521-5. [\[CrossRef\]](#)
 65. Faustini F, Simon D, Oliveira I, Kleyer A, Haschka J, Englbrecht M, et al. Subclinical joint inflammation in patients with psoriasis without concomitant psoriatic arthritis: a cross-sectional and longitudinal analysis. *Ann Rheum Dis* 2016; 75: 2068-74. [\[CrossRef\]](#)
 66. Døhn UM, Boonen A, Hetland ML, Hansen MS, Knudsen LS, Hansen A, et al. Erosive progression is minimal, but erosion healing rare, in rheumatoid arthritis patients treated with adalimumab. A 1 year investigator-initiated follow-up study using high-resolution computed tomography as the primary outcome measure. *Ann Rheum Dis* 2009; 68: 1585-90. [\[CrossRef\]](#)
 67. Glinatsi D, Bird P, Gandjbakhch F, Mease PJ, Bøyesen P, Peterfy CG, et al. Validation of the OMERACT psoriatic arthritis magnetic resonance image score (PsAMRIS) for the hand and foot in a randomized placebo-controlled trial. *J Rheumatol* 2015; 42: 2473-9. [\[CrossRef\]](#)
 68. Østergaard M, McQueen F, Wiell C, Bird P, Bøyesen P, Ejbjerg B, et al. The OMERACT psoriatic arthritis magnetic resonance imaging scoring system (PsAMRIS): Definitions of key pathologies, suggested MRI sequences and preliminary scoring system for PsA hands. *J Rheumatol* 2009; 36: 1816-24. [\[CrossRef\]](#)
 69. Bøyesen P, McQueen F, Gandjbakhch F, Lillegraven S, Coates L, Wiell C, et al. The OMERACT Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) is reliable and sensitive to change: Results from an OMERACT workshop. *J Rheumatol* 2011; 38: 2034-8. [\[CrossRef\]](#)
 70. Weckbach S, Schewe S, Michaely HJ, Steffinger D, Reiser MF, Glaser C. Whole-body MR imaging in psoriatic arthritis: additional value for therapeutic decision making. *Eur J Radiol* 2011; 77: 149-55. [\[CrossRef\]](#)
 71. Poggenborg RP, Pedersen SJ, Eshed I, Sørensen IJ, Møller JM, Madsen OR, et al. Head-to-toe whole-body MRI in psoriatic arthritis, axial spondyloarthritis and healthy subjects: First steps towards global inflammation and damage scores of peripheral and axial joints. *Rheumatology (Oxford)* 2015; 54: 1039-49. [\[CrossRef\]](#)
 72. Poggenborg RP, Eshed I, Østergaard M, Sørensen IJ, Møller JM, Madsen OR, et al. Enthesitis in patients with psoriatic arthritis, axial spondyloarthritis and healthy subjects assessed by 'head to toe' whole-body MRI and clinical examination. *Ann Rheum Dis* 2015; 74: 823-9. [\[CrossRef\]](#)
 73. Østergaard M, Eshed I, Althoff C, Poggenborg RP, Diekhoff T, Krabbe S, et al. Whole-body magnetic resonance imaging in inflammatory arthritis: systematic literature review and first steps toward standardization and an OMERACT scoring system. *J Rheumatol* 2017; 44: 1699-705. [\[CrossRef\]](#)
 74. Rudwaleit M, Schwarzlose S, Hilgert ES, Listing J, Braun J, Sieper J, et al. MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. *Ann Rheum Dis* 2008; 67: 1276-81. [\[CrossRef\]](#)
 75. Blachier M, Coutanceau B, Dougados M, Saraux A, Bastuji-Garin S, Ferkal S, et al. Does the site of magnetic resonance imaging abnormalities match the site of recent-onset inflammatory back pain? The DESIR cohort. *Ann Rheum Dis* 2013; 72: 979-85. [\[CrossRef\]](#)
 76. Machado P, Landewé RB, Braun J, Baraliakos X, Hermann KG, Hsu B, et al. MRI inflammation and its relation with measures of clinical disease activity and different treatment responses in patients with ankylosing spondylitis with a tumour necrosis factor inhibitor. *Ann Rheum Dis* 2012; 71: 2002-5. [\[CrossRef\]](#)
 77. Baraliakos X, Sieper J, Chen S, Pangan AL, Anderson JK. Non-radiographic axial spondyloarthritis patients without initial evidence of inflammation may develop objective inflammation over time. *Rheumatology (Oxford)* 2017; 56: 1162-6. [\[CrossRef\]](#)
 78. van der Heijde D, Landewé R, Einstein, Ory P, Vosse D, Ni L, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis Rheum* 2008; 58: 1324-31. [\[CrossRef\]](#)
 79. van der Heijde D, Landewé R, Baraliakos X, Houben H, van Tubergen A, Williamson P, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. *Arthritis Rheum* 2008; 58: 3063-70. [\[CrossRef\]](#)
 80. van der Heijde D, Salonen D, Weissman BM, Landewé R, Maksymowych WP, Kupper H, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. *Arthritis Res Ther* 2009; 11: R127. [\[CrossRef\]](#)
 81. Ramiro S, van der Heijde D, van Tubergen A, Stolwijk C, Dougados M, van den Bosch F, et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. *Ann Rheum Dis* 2014; 73: 1455-61. [\[CrossRef\]](#)
 82. Braun J, Baraliakos X, Deodhar A, Baeten D, Sieper J, Emery P, et al. Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study. *Ann Rheum Dis* 2017; 76: 1070-77. [\[CrossRef\]](#)
 83. Haroon N, Inman RD, Learch TJ, Weisman MH, Lee M, Rahbar MH, et al. The impact of tumour necrosis factor alpha inhibitors on radiographic progression in ankylosing spondylitis. *Arthritis Rheum* 2013; 65: 2645-54.
 84. Baraliakos X, Haibel H, Listing J, Sieper J, Braun J. Continuous long-term anti-TNF therapy does not lead to an increase in the rate of new bone formation over 8 years in patients with ankylosing spondylitis. *Ann Rheum Dis* 2014; 73: 710-5. [\[CrossRef\]](#)
 85. Braun J, Baraliakos X, Golder W, K Hermann, J Listing, J Brandt, et al. Analysing chronic spinal changes in ankylosing spondylitis: a systematic comparison of conventional x rays with magnetic resonance imaging using established and new scoring systems. *Ann Rheum Dis* 2004; 63: 1046-55. [\[CrossRef\]](#)
 86. Baraliakos X, Listing J, Rudwaleit, Sieper J, Braun J. Development of a radiographic scoring tool for ankylosing spondylitis only based on bone formation: addition of the thoracic spine improves sensitivity to change. *Arthritis Rheum* 2009; 61: 764-71. [\[CrossRef\]](#)
 87. Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Märker-Hermann E, Zeidler H, et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011; 70: 1369-74. [\[CrossRef\]](#)
 88. Dougados M, Sepriano A, Molto A, van Lunteren M, Ramiro S, de Hooge M. Sacroiliac radiographic progression in recent onset axial spondyloarthritis: the 5-year data of the DESIR cohort. *Ann Rheum Dis* 2017 Jul 6. doi: 10.1136/annrheumdis-2017-211596. [Epub ahead of print]. [\[CrossRef\]](#)
 89. Smolen JS, Schols M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis* 2017; 77: 3-17. [\[CrossRef\]](#)
 90. Rudwaleit M, Baraliakos X, Listing J, Brandt J, Sieper J, Braun J. Magnetic resonance imaging of the spine and the sacroiliac joints in ankylosing spondylitis and undifferentiated spondyloarthritis during treatment with etanercept. *Ann Rheum Dis* 2005; 64: 1305-10. [\[CrossRef\]](#)
 91. Machado P, Landewé R, Braun J, Hermann KG, Baker D, van der Heijde D. Both structural damage and inflammation of the spine contribute to impairment of spinal mobility in patients with ankylosing spondylitis. *Ann Rheum Dis* 2010; 69: 1465-70. [\[CrossRef\]](#)
 92. Braun J, Baraliakos X, Hermann KGA, Xu S, Hsu B. Serum C-reactive protein levels demon-

- strate predictive value for radiographic and magnetic resonance imaging outcomes in patients with active ankylosing spondylitis treated with golimumab. *J Rheumatol* 2016; 43: 9. [\[CrossRef\]](#)
93. Maksymowych WP, Wichuk S, Chiowchanwisawakit P, Lambert RG, Pedersen SJ. Fat metaplasia on MRI of the sacroiliac joints increases the propensity for disease progression in the spine of patients with spondyloarthritis. *RMD Open* 2017; 3: e000399. [\[CrossRef\]](#)
94. Machado P, Baraliakos X, van der Heijde D, Braun J, Landewé R. MRI vertebral corner inflammation followed by fat deposition is the strongest contributor to the development of new bone at the same vertebral corner: a multilevel longitudinal analysis in patients with ankylosing spondylitis. *Ann Rheum Dis* 2016; 75: 1486-93. [\[CrossRef\]](#)
95. Tan S, Yao J, Flynn JA, Yao L, Ward MM. Quantitative syndesmophyte measurement in ankylosing spondylitis using CT: longitudinal validity and sensitivity to change over 2 years. *Ann Rheum Dis* 2015; 74: 437-43. [\[CrossRef\]](#)
96. Guermazi A, Niu J, Hayashi D, Roemer FW, Englund M, Neogi T, et al. Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). *Br Med J BMJ* 2012; 345: e5339. [\[CrossRef\]](#)
97. Bowes MA, McLure SW, Wolstenholme CB, Vincent GR, Williams S, Grainger A, et al. Osteoarthritic bone marrow lesions almost exclusively collocate with denuded cartilage: a 3D study using data from the Osteoarthritis Initiative. *Ann Rheum Dis* 2016; 75: 1852-7. [\[CrossRef\]](#)
98. Laslett LL, Dore DA, Quinn SJ, Boon P, Ryan E, Winzenberg TM, et al. Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial. *Ann Rheum Dis* 2012; 71: 1322-8. [\[CrossRef\]](#)
99. Callaghan MJ, Parkes MJ, Hutchinson CE, Gait AD, Forsythe LM, Marjanovic EJ, et al. A randomised trial of a brace for patellofemoral osteoarthritis targeting knee pain and bone marrow lesions. *Ann Rheum Dis* 2015; 74: 1164-70. [\[CrossRef\]](#)
100. Bowes MA, Vincent GR, Wolstenholme CB, Conaghan PG. A novel method for bone area measurement provides new insights into osteoarthritis and its progression. *Ann Rheum Dis* 2015; 74: 519-25. [\[CrossRef\]](#)
101. Roemer FW, Guermazi A, Collins JE, Losina E, Nevitt MC, Lynch JA, et al. Semi-quantitative MRI biomarkers of knee osteoarthritis progression in the FNIH biomarkers consortium cohort - Methodologic aspects and definition of change. *BMC Musculoskelet Disord* 2016; 17: 466. [\[CrossRef\]](#)