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Title: Psoriatic arthritis: Lessons from imaging studies and implications for therapy

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Abstract

Introduction: Modern imaging may aid in diagnosis, prognosis and monitoring of therapeutic response in psoriatic arthritis (PsA). Detection of osteitis and technical advances like whole body magnetic resonance imaging (MRI) exemplify the value of this technology. Areas covered: Ultrasound (US) provides a clinic-based tool for evaluating both joint pathologies and extra-articular structures (especially enthesitis) including skin and nail disease. Recent studies have demonstrated subclinical disease in psoriasis without arthritis, as well as in PsA, with implications for diagnosis and treatment classification. Modern imaging can also facilitate decisions on tapering of expensive biologics, though real-world clinical studies are still lacking. Expert commentary: The increase in novel PsA therapies should increase the utilization of modern imaging, providing both increased validation of imaging biomarkers as well as responsive outcome measures.

1. Introduction

Over the past two decades, the modern imaging modalities of ultrasonography (US) and magnetic resonance imaging (MRI) have helped in understanding of the pathogenesis, and consequently improved treatment strategies, of psoriatic arthritis (PsA). Challenges in defining early PsA by plain radiography and the scarcity of reliable biomarkers for disease activity assessment have paved the way for MRI and US as robust techniques in early diagnosis, monitoring and prognostication of PsA. The need for early diagnosis is clear: though PsA develops either concurrently with or following skin lesions, in 15-20% patients onset of skin psoriasis is delayed up to 10 years following the onset of arthritis; [1] recent studies have shown higher radiographic structural damage and worsening of long-term physical function in patients with PsA following a diagnostic delay of even 6 months to 1 year after onset of symptoms. [2,3] With an increasing number of effective therapies and the concept of treat-to-target emerging in PsA, monitoring with sensitive imaging should presumably translate to better outcomes. Though biologic therapies are very effective, they are expensive with serious side effect profile. Imaging modalities may play a vital role in ~~reducing the cost of therapy by~~ identifying PsA patients in whom biologic therapy tapering or withdrawal can be a viable prospect. [4] This review aims at the utility of advanced imaging techniques in PsA and their implications on therapy, focusing on recent publications.

2. Imaging modalities in PsA

Conventional radiography has been the most widely used imaging technique in PsA. Though less sensitive when compared to other modalities, plain radiography is often used as the reference tool to determine specificity and sensitivity of advanced imaging techniques due to lack of other available options. Radiography is fast, reproducible and inexpensive, providing 2-dimensional visualization; but it has major limitations with imaging of soft tissue pathologies in PsA. With excellent portrayal of bone structures, computed tomography (CT) may be a 'gold standard' for assessing bony structural damage in PsA. However, inability to detect active inflammation and relatively high ionizing radiation exposure limit its utility in routine practice for diagnosis and management of PsA. [5]

Musculoskeletal US with B mode/grey scale (GS) and power Doppler (PD) for both inflammation and structural damage assessment, has been used in detection of enthesopathy, synovitis, tenosynovitis and dactylitis in patients with PsA. [6] Operator dependency has been the major potential weakness of US compared to MRI. However, Fillipucci et al, using high-resolution US for assessing enthesitis in lower limbs have showed moderate inter-observer agreement for both inflammation and damage (κ = 0.7). [7] Advances in technology have allowed US imaging with resolution power of 0.1mm using high frequency probes and identification of blood flow in small vessels of superficial tissues with sensitive power Doppler. [8] Contrast-enhanced US (CEUS), using microbubble contrast agents and specialized imaging techniques to depict blood flow has shown promise in early PsA studies. [9] The utility of MSUS in detecting

subclinical synovitis and enthesitis in order to identify patients who would benefit from early, aggressive therapy, may lead to its potential inclusion into PsA diagnostic criteria.

Contrast-enhanced high-field MRI (≥1T) is arguably the gold standard for imaging soft tissue and bony pathology in PsA. Most of the work in PsA has been done on high field MRI. MRI has found definite applications in diagnosis, defining pathogenesis and outcome measurement in other inflammatory arthritides like rheumatoid arthritis (RA). [10] Three-dimensional image acquisitions, very good reproducibility, ability to detect osteitis and delineation of various soft-tissue pathologies in PsA are the major advantages of MRI over other modalities. [11] The heterogeneity in joint involvement in PsA means the joints included in conventional (hand and/or foot) acquisitions may fail to capture widespread joint inflammation. However the more recently employed technique of whole body MRI (WBMRI) has demonstrated detection of multi-site enthesitis as well as axial assessment in PsA **(Figure 1)**.[12, 13] Use of office-based extremity MRI (eMRI) (0.2 – 1T) offers the opportunity for MRI to be used in out-patient clinics with patient comfort. Limited sensitivity in identifying osteitis and poor fat-fluid delineation are the potential limitations when imaging PsA patients using eMRI. [14] Dynamic contrast-enhanced MRI has improved assessment of synovial inflammation and vascularity in PsA, though tends to be reserved for use in clinical trials with limited joint regions imaged. [15] Tissues in normal tendon have a short T2 and MR signal in tendons decays rapidly, so the signal detectable by conventional MRI is small. This makes the structure appear dark with virtually all traditional pulse

sequences used in MRI. Ultrashort-time-echo (UTE) is a novel technique in MRI that detects inflammation signals from tendons with greater sensitivity than standard protocols, aiding better visualization of previously 'dark' structures. This may be useful for better imaging of enthesopathy in PsA. [16]

Other imaging modalities like skeletal scintigraphy, positron emission tomography and fluorescence optical imaging have been used in PsA though likely have limited utility in clinical practice.

3. Role of imaging in identifying pre-clinical psoriatic arthritis

Pre-clinical enthesopathy and inflammatory changes are increasingly being reported by US and MRI in patients with psoriasis without clinical arthritis. McGonagle and colleagues have linked site-specific micro-trauma and the associated inflammatory response to the development of PsA using imaging studies. [17] Microscopic inflammatory changes due to the normal healing process have been noted at sites of micro-trauma following mechanical stress. [18,19] These findings are similar to those seen in patients with early PsA.

Gisondi et al estimated the prevalence of lower limb entheseal involvement in 30 patients with psoriasis but without arthritis, using the Glasgow Ultrasound Enthesitis Scoring System (GUESS). A significantly higher mean GUESS was reported in psoriasis patients as compared to healthy controls (7.9 vs 2.9; $p < 0.0001$). These patients however were not followed up to determine subsequent development of arthritis. [20]

Gutierrez et al elucidated similar findings in lower limb entheseal sites using high-resolution GS and PD signals, with excellent agreement between the readers (k of 0.906). [21] Lower limb enthesitis, however, may also be increased due to mechanical factors including obesity, which is closely associated with PsA. Earlier US studies also demonstrated similar findings in asymptomatic patients with psoriasis. [22,23] In a more recent study Naredo et al studying 162 patients with chronic plaque psoriasis reported significantly higher frequency of synovitis (3.2% vs 1.3%; p <0.0005) and enthesopathy (11.6% vs 5.3%; p < 0.0005) in upper and lower limb joints of psoriasis patients without arthritis, as compared to healthy controls. Entheseal PD signals were found in 7.4% of psoriasis patients as compared to none in healthy controls (p = 0.05). [24] The predictive value of these PDUS findings need to be tested in longitudinal studies of at-risk populations. Treatment options for these pre-clinical MSUS findings in PsA patients are not well defined as yet, but imaging findings may be used in this disease like the anti-citrullinated peptide assay (ACPA) in RA to identify an 'at risk' group for early intervention.

Though more sensitive than US, there is a relative paucity of MRI studies on pre-clinical PsA. Offidani et al evaluated the involvement of hand joints using a super-conductive magnet 1.0T with a round surface coil in patients of psoriasis free of arthritis. At least one MRI sign of arthritis (subclinical arthritis) was observed in 68% of 25 patients. Capsular distension observed in 44% of patients was the commonest sign of inflammation. [25] Erdem et al showed abnormal MRI of the foot in 92% of the patients screened in their study, none of whom had pain or swelling on clinical

examination. No MRI abnormalities were noted in the healthy controls. Hind-foot was the most commonly involved anatomic region. [26] Emad et al reported evidence of enthesitis on knee MRI in 84.8% of psoriasis patients without arthritis. The number of entheseal lesions in right and left knees had significant positive correlation with soft tissue edema ($r=0.314$; $p = 0.030$). [27] None of these studies included a follow up arm of patients with subclinical imaging changes. A very recent study by Faustini et al has described at least one inflammatory MRI lesion in 47% of 55 psoriasis patients without arthritis. Synovitis was the most predominant inflammatory lesion, present in 38% patients. Within a year of follow up of 41 of these patients, the authors noted a surprisingly high proportion with subclinical synovitis (30%) developing PsA. Transition to PsA was higher among psoriatic patients with arthralgia and MRI changes (55.5%) compared to those with MRI changes alone (25%). [28] Again, longitudinal studies with larger numbers are warranted to evaluate MRI predictors of future PsA and may also provide guidance on which early pathological lesions are most responsive to therapy.

4. Utility of imaging in diagnosis of PsA

Early diagnosis of PsA is often a difficult task for clinicians. If the concept from RA holds true for this disease, detection of a 'window of opportunity' when early intervention can arrest long-term damage remains a key goal. MSUS assists in early detection and delineation of severity of inflammation, in all stages of PsA. [29] Freeston et al compared clinical examination and US findings in early PsA patients to study the prevalence of subclinical synovitis and to determine if US findings would affect

classification of patients to oligo- or polyarthritis subgroups. Increased US detection of synovitis was demonstrated in PsA patients when compared to clinical examination, which allowed 82% of patients clinically diagnosed as oligoarthritis earlier to be re-classified as polyarthritis, thus potentially changing their management. [30] The same group had earlier compared US and clinical examination for enthesitis in 42 early PsA patients and 10 healthy controls. US entheseal abnormality was seen in 43% of patients, as compared to 79% of patients showing clinical evidence of enthesits. Only 4% of non-tender entheses, all in the lower limb had US entheseal abnormality compared to 24% of tender entheses. PD findings were, however seen only in the PsA group. [31] Eder et al studied the ability of the Madrid sonographic enthesitis index (MASEI) to classify PsA patients and compare entheseal changes in patients with PsA, cutaneous psoriasis without arthritis and healthy controls. A MASEI score of ≥20 classified patients as having PsA among patients with psoriatic disease with a specificity of 89% and positive likelihood ratio of 2.63. [32]

The European League Against Rheumatism (EULAR) recommendations for the use of imaging in spondyloarthropathy in clinical practice endorse the role for US in diagnosing enthesitis, peripheral arthritis, tenosynovitis and bursitis. [33] MSUS findings have been shown to have a close correlation with relevant histopathological findings. Fiocco et al investigated the association of continuous mode CEUS with microvascular proliferation in synovial tissue of chronic PsA patients using histopathological and immunohistochemical (IHC) quantification. IHC staining of CD45, CD31 and CD105 was done to assess synovial cell infiltration and vascularity.

There was a strong significant correlation between IHC and US perfusion kinetics. [34] Ultrasound composite scores have been developed for assessment of inflammatory and structural changes in PsA. Ficjan et al studied 80 patients of PsA with gray scale and PD of 68 joints and 14 entheses and designed PsASon22 and PsASon13, both revealing moderate to high sensitivity in detecting inflammatory lesions with adequate construct validity and sensitivity to change. [35] Though this was a good step toward standardization of US examination in PsA, more research is warranted on optimal joint counts.

US with frequency probes of ≥18 MHz has also been used in the diagnosis and follow up of skin and nail disease. Thickening of the epidermis and dermis, along with a hypoechoic band in the upper dermis and absence of subcutaneous tissue involvement were detected by gray scale US. Highly sensitive PD detected increased blood flow in the dermis in psoriasis patients. [36] Aydin et al, in an US study using modified nail psoriasis severity index studied nail and adjacent tendons in 86 patients with nail psoriasis and showed extensor tendon enthesopathy in both psoriasis and PsA groups, thus supporting the role of the enthesis in the pathogenesis of nail disease. [37]

The precise role of US in differentiating PsA from other inflammatory arthritis needs to be elucidated. Features of synovitis as detected by gray scale or PD may be the same in all inflammatory arthritides and sometimes in osteoarthritis. Sandobal et al studied gray scale and PD findings at fingernail level in patients with PsA and cutaneous

psoriasis in comparison with RA and healthy controls. Nail changes were significantly higher in PsA and patients with psoriasis. PsA patients also had significantly higher PD signals in DIP joints and nail beds ($p = 0.0001$). Mean distance between the ventral nail plate and bone margin of distal phalanx differed significantly in patients with PsA and psoriasis versus RA ($p<0.0001$). [38] Gutierrez et al evaluated different patterns of inflammation at the MCP joint level in 80 RA patients and 20 with PsA. Peritendinous extensor tendon inflammation was again observed in 66% of patients with PsA compared to nil in the RA group.[39] In a recent study Zabotti et al employed US findings at the synovio-entheseal complex of small joints of hands to differentiate between 34 early RA and 26 early PsA patients. Peritendon extensor digitorum tendon inflammation was found to be significantly higher in PsA patients as compared to those with RA ($p = 0.0001$). Other significant findings included soft tissue edema ($p = 0.0002$) and central slip enthesitis ($p = 0.0045$), both seen exclusively in early PsA patients. [40] So US may be useful in differentiating early RA and PsA at the group level, though data are still needed to prove its efficacy in distinguishing early PsA from RA at the individual patient level.

MRI findings of synovitis, tenosynovitis and bone marrow edema in PsA are frequent. [41] However, sensitivity and specificity of MRI in detecting peripheral enthesitis has been shown to be limited because of its inability to detect changes in the fibrous part of enthesis due to less water content. [42] Advances like UTE have enabled to get around this limitation to some extent. Hodgson et al, investigating the utility of UTE in assessing Achilles tendon in patients with spondyloarthritis using a 3T conventional

MR scanner observed significantly higher MRI measurements at Achilles tendon of patients as compared to healthy controls. There was no association between MR findings and disease duration or inflammatory markers. [43]

Recent studies using WBMRI in PsA have provided a comprehensive assessment of inflammation and structural damage at peripheral, axial and entheseal sites in one scanning session. Poggenborg et al evaluated inflammatory and structural lesions in PsA, axial SpA and healthy subjects to assess global scores using a 3.0-T MRI. PsA patients were found to have significantly higher global osteitis scores as compared to controls. [44] The same group earlier studied the efficacy of WBMRI in detecting axial and peripheral enthesitis in patients with PsA, axial SpA and healthy controls. There was moderate agreement between WBMRI and clinical enthesitis. Enthesitis at greater trochanter (55%) and Achilles tendon insertion (43%) mostly appeared without clinical signs. Three WBMRI enthesitis indices were designed based on seven enthesitis indices described previously in different studies. [13] Most of the knowledge on assessment of the axial skeleton using MRI originates from SpA studies, and findings are similar to those in ankylosing spondylitis (AS). However, findings in PsA are more asymmetric and clinical findings have only a weak correlation with sacroilitis on MRI. [45]

The ability of MRI for differential diagnosis of PsA has been tested in different studies, with varying results. Here again, the studies showing encouraging results are based on findings in a cohort of patients, which may not reflect the true picture when

considering individual patients in routine clinics. Narvaez et al compared early PsA with early RA (symptom duration ≤ 1 year) based on MRI of hand and wrist. Enthesitis or extensive diaphyseal osteitis present in 71% of patients was exclusively seen in PsA ($p = 0.0001$). Involvement of flexor tendons ($p = 0.014$) and presence of diffuse soft-tissue edema ($p = 0.002$) was significantly higher in PsA patients. [46] Mathew et al have described the discriminative capacity of 0.2T eMRI to distinguish PsA from RA patients. Though the numbers were small, soft tissue inflammation was exclusively present in PsA patients. The first interphalangeal joint of thumb in PsA had significantly higher flexor tenosynovitis as compared to RA patients. Bone proliferation was also significantly higher at MCP ($p = 0.0001$) and DIP ($p = 0.005$) joints in PsA patients. [47] Braum et al evaluated the microanatomical differences in joint disease localization in patients with PsA, osteoarthritis (OA) and RA using high-resolution MRI with a small loop coil. Diffuse osteitis and periosteitis was exclusively seen in PsA and OA patients. Bone erosions in PsA patients were present closer to collateral ligament insertions compared to those in OA patients, which were mostly centrally located. [48] Evaluation of nail disease in PsA using MRI has evolved in the last few years, especially with advances in MRI coils. Patients with psoriasis, regardless of the presence of clinical nail lesions may show characteristic MRI nail changes. This may be helpful in categorizing patients with undifferentiated SpA without cutaneous psoriasis. [49,50]

5. Role of imaging in prognosis of PsA

There is scarcity of imaging studies in determining the prognosis of PsA. Most studies focus on clinical predictors of imaging damage. Previous US studies on preclinical PsA

patients have detected significant enthesitis **(Figure 2)** in patients with psoriasis. [20,21] Whether this finding is truly a harbinger of PsA or just a mechanical stress-related change needs to be answered with longitudinal studies. Aydin et al evaluated the imaging phenotypes in PsA patients and cutaneous psoriasis patients without arthritis using GS and PD signals at lower limb entheseal sites. PD signals were significantly higher in PsA as compared to cutaneous psoriasis patients. Increasing entheseal thickening with vascular changes may therefore represent a predictor of future PsA. [51] El-Miedany et al determined the use of US in predicting inflammatory and structural damage in PsA in a prospective cohort of 141 patients with 1-year follow up. Both gray scale and PD examination was performed on joints and tendons of all fingers and toes, along with 15 entheseal sites according to the Maastricht ankylosing spondylitis entheses score (MASES). An increased risk of structural progression with OR of 1.98, 2.61 and 2.66 was observed for baseline clinical, US-GS and US-PD evaluation, respectively ($p < 0.001$). Baseline enthesitis determined by PD signal had a 3.5 times risk of structural progression. Persistence of synovitis or enthesitis on US at 6 months of treatment was an independent predictor of future structural progression (OR 6.62; 95% CI 1.11-1.83; $p = 0.0001$). [52]

Evidence for the prognostic value of MRI in PsA is scarce. An earlier study by Tan et al investigating MRI features in 17 patients with arthritis mutilans and 11 patients of erosive PsA without bone lysis reported a significant positive correlation of MRI bone edema with MRI erosion scores, radiographic erosion and joint space narrowing scores ($r – 0.65$; $p = 0.0002$). [53] Being a cross-sectional study, caution should be

exercised in extrapolating this correlation to a cause and effect relationship. Poggenborg et al reported MRI bone marrow edema ~~on dynamic contrast MRI~~ to be associated with future erosion detected by CT in a 48-week longitudinal study of 41 PsA patients treated with adalimumab. [54] Thus, bone marrow edema on MRI does appear be a marker of future erosions in PsA.

6. Outcome measurement using imaging in PsA

The assessment and quantification of inflammatory and structural changes in PsA using imaging modalities has been a challenge in view of their varied manifestations. The role of US and MRI in measuring treatment outcome has been expanding in the last few years. The Outcome Measures in Rheumatology (OMERACT) group has proposed standardized definitions for US and MRI variables in PsA. While modern imaging has been included in many RA clinical trials, ~~there have been many fewer PsA trials with modern imaging outcomes~~ its utility in PsA trials has been scarce.

While US is commonly used as an outcome measure in routine clinical practice, poor validity and operator dependence have hampered its use in clinical trials. [55] The OMERACT group has provided definitions for US-detected bone erosion, synovial fluid, synovial hypertrophy, tenosynovitis and enthesitis. [56] Most of the semi-quantitative scoring systems have been extrapolated from those used in monitoring RA. [57-60] Gutierrez et al proposed a preliminary composite PDUS score for assessment of blood flow changes at joint, tendon, enthesis, skin and nail (5 targets) in patients of PsA on anti-TNF therapy. [61] This score needs to be validated in a longitudinal study

on larger number of patients. An RA global synovitis scoring system (GLOSS) was formulated by the OMERACT US group in 2014, combining synovial hypertrophy and PD signal into a composite score, and tested in a large RA cohort. A standardized US scoring system for detecting and grading tenosynovitis was also developed, validation of which is work in progress. [62] US enthesitis assessment tools like GUESS tool, examining five lower limb sites (Achilles, quadriceps, superior and inferior patellar tendons and plantar fascia), and MASEI, assessing six sites (GUESS sites + triceps tendon) have been developed in SpA cohorts. [63,64]

Dactylitis in PsA has been shown to be due to a range of inflammatory pathologies and extracapsular inflammation. [65, 66] Healy et al studied 17 PsA patients with dactylitis using 1.5T gadolinium-enhanced MRI. Synovitis and circumferential soft tissue edema was observed in 70% of tender dactylitic digits as compared to about 60% of non-tender dactylitic digits.[67] Coexisting synovitis has been defined only in 16-52% of patients with dactylitis. [68] Tan et al investigated PsA dactylitis in 12 patients and 10 volunteers using a high-resolution microscopy coil (23mm or 47mm diameter) and contrast enhancement MRI. Enthesitis at the collateral ligament insertions and extensor tendon insertion was noted in 75% and 50% digits, respectively. [69] More longitudinal studies are needed in dactylitis imaging to elucidate its components and to evaluate its utility as an outcome measurement tool.

The association between clinical and US variables of arthritis, enthesitis and tenosynovitis in PsA has not been studied in detail. In RA, studies have shown a weak

to moderate correlation between US and clinical findings. [70,71] Husic et al explored the association between disease activity index for psoriatic arthritis (DAPSA), composite psoriatic disease activity index (CPDAI) and semi-quantitative scores of US inflammation and structural damage. DAPSA showed weak-to-moderate correlation, while CPDAI did not show any correlation with US indices and scores. [72] Michelsen et al in a very recent study again investigated the connection between clinical and US evidence of inflammation. Clinical indices included were DAPSA, CPDAI and psoriatic arthritis disease activity score (PASDAS). The US composite scores were borrowed from RA scores. Global OMERACT-European League Against Rheumatism Synovitis Score (GLOESS) was used to score synovitis. The sum of GS and PD scores over joints, entheses and tendons were recorded. There was substantial disagreement between US and clinical findings. Only DAPSA correlated well with the PD global score (r 0.22; $p<0.01$). However when evaluation of entheses and tendons were included in the imaging assessments, there was improvement in the clinical and US correlations. This highlights the varied nature of inflammation in joints and peri-articular structures in PsA. Though there is scarcity of appropriate studies, US enthesitis has been described in a majority of patients with SpA and not in controls. [73,74]

Qualitative, semi-quantitative and quantitative MRI scoring systems have also been designed for monitoring inflammation and structural damage in PsA. The OMERACT group has designed PsA MRI score (PsAMRIS) modifying the RA MRI score (RAMRIS) to evaluate inflammatory and structural damages in PsA hands and feet. [75,76] Consensus was reached on definitions of synovitis, tenosynovitis, periosteal

inflammation, bone marrow edema, bone erosions and bone proliferations as the variables in PsAMRIS. Subsequently the PsAMRIS was validated in a randomized placebo-controlled trial for hand and foot imaging in PsA, with overall good intrareader agreement and inflammatory feature scores responding to change. [77] Strube et al demonstrated feasibility and good intra-reader reproducibility of PsAMRIS hand score in eMRI (0.2T). [78]

In a recent study to assess the association of high- and eMRI variables at various time points in the first 12 weeks following TNF alpha therapy initiation, 12 patients with active PsA and clinical dactylitis were included. Sequential high-field (1.5T) and low-field (0.2T) MRI of the affected hand or foot was done at baseline, 2 weeks, 6 week and 12 weeks. Swift response of MRI scores at 2 weeks was noted for tenosynovitis, synovitis and osteitis. [79] Yanaba et al investigated utility of PsAMRIS for assessing treatment outcome following administration of adalimumab in a small number of patients with PsA. Osteitis and periarticular inflammation significantly improved at week 8, and synovitis and tenosynovitis improved later on at week 24-32. Flexor tenosynovitis, synovitis and bone erosions persisted regardless of clinical improvement. [80] In a 6-month study on PsA patients being treated with adalimumab, Anandarajah et al reported significant improvement in clinical measures and MRI variables of osteitis and effusion but not synovitis. Erosions remained unchanged. [81] In a placebo controlled trial PsA patients received zoledronic acid or placebo. Osteitis scored by PsAMRIS decreased significantly in the zoledronic acid group, as compared to the placebo group. Bone proliferation and bone erosion progression showed no

difference between the groups. [82] In a proof of concept translational study to determine changes in clinical outcome, imaging and synovial markers in synovial fluid and tissue in peripheral SpA patients following serial intra-articular Etanercept injections, Fiocco et al reported early improvement in synovial thickness measures by contrast MRI and US, along with a significant correlation between clinical, imaging and biomarkers. [83]

WBMRI, as mentioned earlier, is a novel technique that can measure overall inflammation and structural damage at axial and peripheral skeleton, along with tenosynovitis and enthesitis. [84] Using WBMRI 76 peripheral joints, each disco-vertebral unit in the spine (ventral and posterior parts) and sacroiliac (SI) joints divided into quadrants (upper and lower in iliac and sacral parts) can be evaluated. Poggenborg et al developed a global inflammation and damage scores using WBMRI. Scores 0 or 1 (for absence or presence) were depicted for osteitis and erosions (in peripheral joints, spine and SI joints), synovitis (in peripheral joints), fat infiltration (in spine and SI joints) and ankylosis (SI joints). A global inflammation score was calculated as the sum of osteitis and synovitis in the peripheral joints and osteitis in spine and SI joints. Global WBMRI structural score was devised as the sum of erosions in peripheral joints, spine and SI joints, fat infiltrations in spine and SI joints and ankylosis in the SI joints. [44] Such scores need to be validated in different PsA at risk populations by longitudinal studies.

7. Imaging in determining remission / low disease activity

US and MRI have been shown to be more sensitive than clinical examination for detecting active inflammation in patients with PsA. [85,86] Minimum disease activity (MDA) was defined as achieving 5 out of the 7 following criteria – tender joint count ≤1, swollen joint count ≤1, psoriasis activity and severity index ≤1 or body surface area ≤3, patient pain visual analogue scale (VAS) ≤15, patient global disease activity VAS ≤20, health assessment questionnaire ≤0.5 and tender entheseal points ≤1. [87] This was later validated in a cohort of PsA patients treated with Infliximab. [88] Very recently Schoels et al have proposed cut-offs based on DAPSA for remission (≤4), low disease activity (>4 and ≤14), medium disease activity (>14 and ≤28) and > 28 for high disease activity. [89] Using the data from GRAPPA composite disease exercise on 503 PsA patients Coates et al investigated the relationship between MDA and low disease activity cut offs using psoriatic arthritis disease activity score (PASDAS) and CPDAI. Very low disease activity was defined as a MDA score of 7/7, with equivalent cut offs for PASDAS and CPDAI at 1.9 and 2, respectively. [90]

So far no US remission criteria have been developed. Michelsen et al defined remission using US as the absence of PD signals at joints, entheses and tendons and observed 50% of their cohort in remission according to this definition. [72] Husic et al have also tried comparing US and clinical definitions of remission and MDA. PD scores of 0 and ≤1 at joints, peri-tendinous tissue, tendons and entheses were used to define US remission and minimal ultrasound disease activity (MUDA), respectively. A DAPSA of ≤3.3 and Boolean's remission definitions significantly differentiated patients with and without MDUS. [71] The PsASon score proposed by Ficjan et al to monitor treatment

response in PsA had only weak to moderate correlation to clinical findings. [35] A five targets PD (5TPD) composite score for monitoring treatment in PsA was developed by Gutierrez et al. [60] A high 5TPD score was shown to correlate with higher extent of inflammation of different targets in PsA. Again, validation of these scores in longitudinal studies is warranted.

Remission in PsA is an evolving concept, as is the treatment concept of biologic drug tapering. Janta et al compared PsA patients treated with full and tapered doses of biologic agents using GS and PDUS at 46 joints, 40 tendons and 10 entheses. Regardless of the dose of biologic agent, PD synovitis was low in this cohort. [91] These results are encouraging for the role of US in tapering biologic therapy in PsA patients.

8. Expert commentary

Modern imaging provides a sensitive measure for detecting PsA, understanding the true extent of the disease (through detection of subclinical synovitis and enthesitis) and accurate monitoring of inflammation and damage. It is just starting to be exploited for improved understanding of pathogenesis (for example, with respect to bone marrow oedema and subsequent erosion progression). Ultrasound offers a clinically feasible tool for widespread joint evaluation and should help PsA diagnosis in seronegative undifferentiated arthritis, and aid decisions on when to stop and taper therapies, especially with highly effective yet expensive biologics. MRI offers a tool with high sensitivity for outcome measurement in clinical trials, with whole-body MRI close to providing an excellent tool for trials and clinical practice with its enthesitis and axial skeletal evaluation. However the evidence base for all these potential roles remains small and we need many more studies before imaging treatment targets can be established and before algorithms for routine use may be evaluated for cost-effectiveness.

9. 5-year view

Using the analogous rheumatoid arthritis situation, in the absence of an ACPA-like biomarker to aid early diagnosis, better studies on the role of imaging in very early disease detection could make the impact of modern imaging (US and WBMRI) very substantial. With growth in the number of effective PsA biologic therapies, it is likely there will be a small increase in the number of clinical studies and trials using modern

imaging for therapeutic outcomes. It is very likely that a pragmatic trial utilizing modern imaging at key decision steps in the patient treatment pathway (eg initiation of escalated therapy or biologic switch) will be conducted in the next 5 years.

10. Key issues

- US studies have shown significant subclinical enthesitis in psoriatic patients without arthritis. The predictive value of this observation, along with efficacy of US in categorizing 'at risk' population for early intervention, needs further study
- EULAR recommendations have endorsed use of US in early diagnosis of enthesitis, peripheral arthritis, tenosynovitis and bursitis. More research is however warranted on the optimal combination of joints for such screening
- US with high frequency probes and high sensitive power Doppler are finding application in diagnosis and monitoring skin and nail disease, and delineating the role of enthesitis in pathogenesis of PsA
- Baseline enthesitis and persistence of synovitis or enthesitis by US after 6 months of therapy have been shown to predict subsequent structural damage
- Development of composite US scores for standardized monitoring of treatment outcomes is work in progress. A preliminary PDUS composite score for assessment of blood flow changes at joint, tendon, entheses, skin and nail PsA patients on anti-TNF therapy has been proposed
- High-field MRI is the accepted gold standard for imaging soft tissue and bony pathology in clinical trials in PsA. Advancements in technology include ultra-

short echo time acquisition which improves assessment of peripheral enthesitis

- Whole-body MRI, an upcoming concept in PsA has yielded a comprehensive assessment of inflammation and structural damage by detecting multi-site enthesitis, peripheral synovitis and tenosynovitis and axial involvement, all in one scanning session. Global inflammation and damage scores for WBMRI have been developed to be used in clinical research.
- MRI with dedicated high-resolution magnetic coils can detect subclinical nail disease, which may be helpful in categorizing patients with undifferentiated spondyloarthritis without cutaneous psoriasis
- Bone marrow edema on MRI has been shown to be associated with subsequent erosions. This offers opportunities for earlier intervention, though more PsA imaging cohorts are needed
- The PsA MRI score (PsAMRIS) devised by the OMERACT group for hand and foot imaging has been validated for use in clinical trials for standardized measurement of treatment outcomes in PsA. This semi-quantitative score, with six variables has recently been used in a number of studies

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