RHEUMATOLOGY

Rheumatology 2021;60:vi38–vi52
doi:10.1093/rheumatology/keab504

Integrating imaging and biomarker assessment to better define psoriatic arthritis and predict response to biologic therapy

Ashley Elliott[1], Dennis McGonagle[2,3] and Madeleine Rooney[1]

Abstract

Abstract. The treatment options for PsA have substantially expanded over the last decade. Approximately 40% of patients will not respond to first-line anti-TNF-α therapies. There is limited data to help clinicians select the most appropriate biologic therapy for PsA patients, including guidance for decisions on biologic therapy switching. In this review we will examine the current understanding of predictors of response to treatment. Imaging technology has evolved to allow us to better study psoriatic disease and define disease activity, including synovitis and enthesitis. Enthesitis is implicated in the pathogenesis, diagnosis and prognosis of PsA. It appears to be a common thread among all of the various PsA clinical presentations. Enthesitis mainly manifests as tenderness, which is difficult to distinguish from FM, chronic pain and mechanically associated enthesopathy, and it might be relevant for understanding the apparent 40% failure of existing therapy. Excess adipose tissue makes if more difficult to detect joint swelling clinically, as many PsA patients have very high BMIs. Integrating imaging and clinical assessment with biomarker analysis could help to deliver stratified medicine in PsA and allow better treatment decision making. This could include which patients require ongoing biologic therapy, which class of biologic therapy that should be, and who alternatively requires management of non-inflammatory disease.

Key words: PsA, US, biologics, enthesitis, synovitis, proteomics, genomics, predict response, onychopathy

SUPPLEMENT

Rheumatology key messages

- Co-morbid osteoarthritis, fibromyalgia or obesity can contribute to treatment failure and make recognition of joint inflammation difficult.
- Imaging, particularly US assessment, along with a predictive proteomic panel could allow for better stratification of disease.
- Better stratification could have major implications for biologic therapy initiation and class switching.

Advances in the treatment of PsA

Psoriasis (PsO) affects 2% of the population, and one-third of these individuals will develop PsA [1]. There are a range of overlapping articular patterns, including deforming peripheral arthritis, dactylitis, enthesitis-dominant disease, and axial disease. Recent treatment recommendations highlight the heterogeneity of PsA and emphasize the need to target the various disease domains [2].

Rheumatologists are focused on treating disease early [3], with those who do not respond to conventional DMARDs having a number of options. These include small-molecule synthetic DMARDs like apremilast. However, biologic agents are the cornerstone of effective PsA disease control. Anti-TNF-α (TNFi) drugs have revolutionized PsA disease management and were, until recently, the only family of biologics available. Further effective options now include mAb therapy targeting IL-17, IL-12/23 and IL-23 and, latterly, combinatorial

[1]Centre for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK, [2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK and [3]Leeds Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, Leeds, UK

Submitted 12 March 2021; accepted 8 June 2021

Correspondence to: Ashley Elliott, Centre for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, 97 Lisburn Road, Belfast BT9 7BL, UK.
E-mail: aelliott09@qub.ac.uk

cytokine inhibition with Janus Kinase (JAK) inhibitors. Currently, the decision to start or switch to a particular biologic is based on a number of factors not necessarily linked to the disease itself, including patient choice, co-morbidities, and drug cost and safety profile. There is little evidence guiding choose between them.

Remaining unmet need in PsA

Despite all these advances, around 40% of patients will not respond to conventional synthetic DMARDs (csDMARDs), TNFi therapies or other biologic therapies [1]. These apparent treatment failures may occur as a result of co-morbid FM or OA, and by elucidating the predominant issue we can avoid inappropriate treatment and futile drug therapy cycling [4, 5]. Researchers have highlighted key areas of unmet need in PsA, including better tests for diagnosis, radiographic progression and predicting response to treatment [6]. In this review we will assess what is known about predictors of response to treatment in terms of clinical assessment, imaging technology, and laboratory analysis. In particular, we make the case that utilizing US and proteomics may increase the likelihood of making better clinical decisions.

Challenges in assessing patients with PsA

The assessment of inflammatory arthritis focuses on the swollen and tender joint scores. Most PsA patients will present with an oligoarticular or polyarticular pain pattern that may involve the DIPs. Imaging has shown good correlation with objective findings like joint swelling and inflammatory SF [7, 8]. On the other hand, it has called into question the reliability of certain clinical signs, such as a tender joint that may not necessarily be the result of active inflammation [7]. In those with obesity and tenderness, for instance, this may masquerade as synovitis, which may lead to inappropriate therapy changes.

While a focus on synovitis is important and mirrors work done in RA, this neglects the full extent of PsA. If we are to improve a patient's quality of life, we need to appreciate the impact of skin, enthesitis and nail disease. Unlike enthesitis, the objective assessment of skin and nail disease is readily achievable. We are moving away from assessments like the DAS-28, developed for RA, which focus on joint disease, and creating tools that reflect the complexity of PsA. A number of these scoring systems are referenced in Table 1 [9–12]. The scores in this crowded field appear to have a similar ability to define and monitor disease activity, with recent data suggesting the Psoriatic Arthritis Disease Activity Score may be superior [13]. It is interesting to note that in conditions like multiple myeloma, where pathogenesis is well understood, there has been a single disease outcome, the M-band, for over 50 years. In PsA, however, there is an ongoing proliferation of composite outcomes that fail to differentiate genuine PsA-related pain and inflammation from non-PsA–related disease. Allowing for the fact that axial disease is intimately associated with enthesitis/osteitis at that location, it is interesting to note that the majority of PsA composite scores miss the centrality of the enthesitis-related pathology.

An entheses is the insertion of a tendon, ligament, capsule or fascia into bone. A positive test for enthesitis is traditionally defined as tenderness at the site of an enthesis (Fig. 1). Clinical enthesitis is seen in at least 30% of PsA patients, with around 60–80% developing it at some stage in their disease process. Imaging detects an even higher prevalence of subclinical disease [14], and it is much more common than in other inflammatory arthropathies [14]. Enthesitis is associated with greater PsA disease activity [15], radiographic damage [16], and reduced quality of life [17]. Mice model studies have implicated enthesitis as the primary process [18] and, in those with PsO, subclinical enthesopathy on imaging may predict those who will develop PsA [19]. Unlike synovitis with joint swelling, enthesitis is much more difficult to diagnose objectively. Focal entheseal tenderness without swelling, which is the norm for enthesitis, is virtually impossible to differentiate from the mechanical enthesopathy that is sometimes linked to obesity, chronic pain and FM. US imaging has demonstrated that over 90% of patients with PsA will demonstrate entheses involvement, and this includes around 60% with active power Doppler changes [20] (Fig. 1 and Supplementary Fig. S1, available at *Rheumatology* online).

Various enthesitis scoring systems have been developed [21], with the Leeds Enthesitis Index being specifically designed for PsA (Fig. 2) [22]. Enthesitis scoring tools are known to have limitations in terms of reliability, validity and sensitivity. The Leeds Enthesitis Index assessment of the medial femoral condyle represents one example of close juxtaposition of the enthesis with the medial gutter synovium, and we feel that objective differentiation from joint synovitis at this site has not been adequately addressed. Clinical assessment is unable to identify more specific disease characteristics associated with the pathology of enthesitis, such as tendon thickening, bursitis, bone erosions, enthesophytes or calcifications [23].

Clinical features associated with predicting treatment response

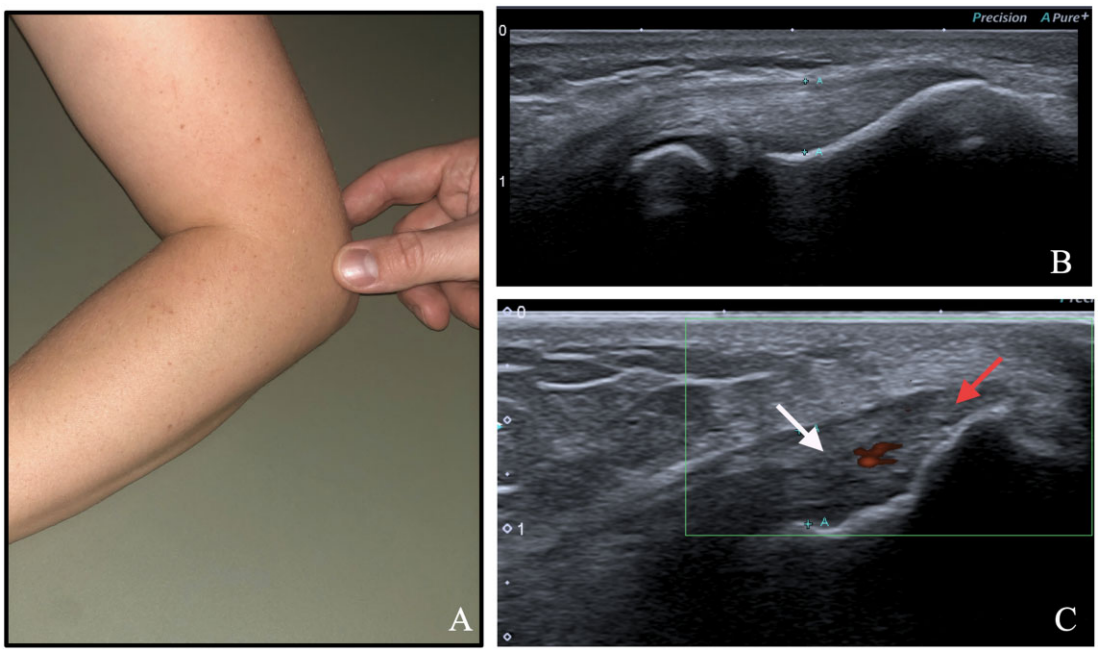
Recent ACR PsA guidelines advocate the early introduction of biologic treatment in cases of aggressive disease, even if no csDMARDs have been used [24]. The European (EULAR) guidelines support the use of early biologic therapy if axial or entheseal disease is the predominant issue [25]. The recommended first-line biologic therapy is TNFi treatment unless it is contraindicated. There is a paucity of data in the literature to guide treatment decisions in PsA [26]. Data from prospective

Table 1 PsA composite scoring tools

Domain	MDA [9]	PASDAS [10]	DAPSA [11]	cDAPSA [11]	CPDAI [12]
Peripheral arthritis score	X	X	X	X	X
Patient pain score			X	X	
Patient subjective overall assessment	X	X	X	X	X
Physician assessment	X	X			
Skin	X				X
Enthesitis	X	X			X
Dactylitis		X			X
Axial disease					X
CRP		X	X		
HAQ	X				X
SF-36 PCS		X			

cDAPSA: Clinical Disease Activity Index for Psoriatic Arthritis; CPDAI: Composite Psoriatic Disease Activity Index; DAPSA: Disease Activity Index for Psoriatic Arthritis; MDA: minimal disease activity; PASDAS: Psoriatic Arthritis Disease Activity Score; SF-36 PCS, Short-form 36 Physical Component Summary; X: assessment included.

Fig. 1 Clinical and US assessment of the lateral epicondyle.

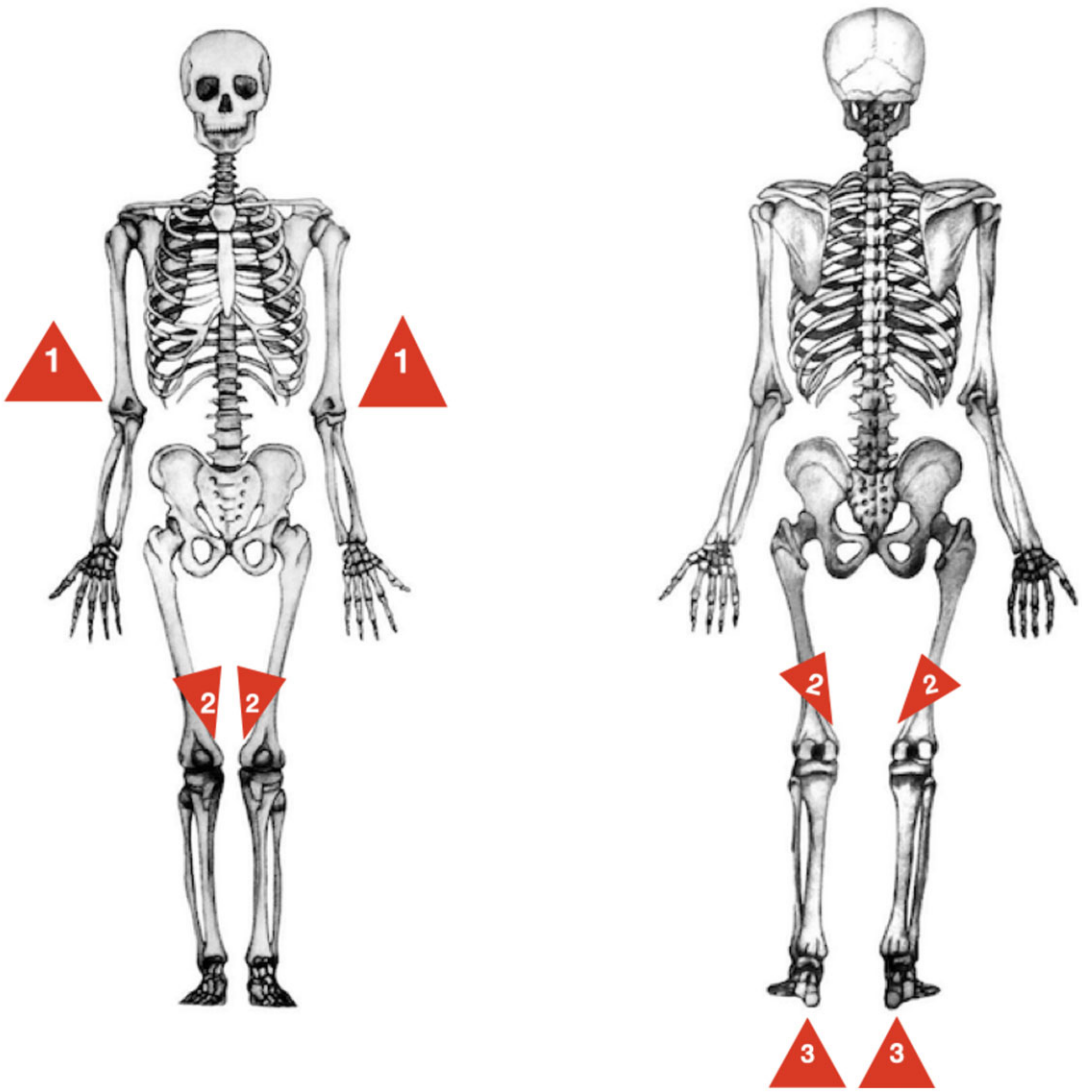


(A) Clinical examination of the lateral epicondyle. (B) A normal common extensor origin entheses insertion at the lateral epicondyle on US. (C) US with evidence of active inflammation at the common extensor origin with positive power Doppler signal a thickened tendon and loss of its normal fibrillary appearance (white arrow) and calcification, a sign of chronic damage (red arrow) (images A.E.).

research has demonstrated that obesity, female gender, old age, and a longer duration of the disease were associated with a lower probability of achieving sustained remission [27, 28]. Moreover, a low HAQ score and a high CRP level at baseline were associated with a better response [29, 30]. Unfortunately, to date there has been no suggestion that different musculoskeletal subtypes of PsA do better or worse on TNFi treatment [31, 32].

There are limited retrospective studies to guide change of treatment after TNFi failure [33]. In general, treatment responses and the length of drug survival decreased in patients receiving a second or third TNFi

Fig. 2 The Leeds Enthesitis Index



Six-point score assessing: (1) lateral epicondyle of the humerus—insertion of the common extensor origin; (2) medial femoral condyle—insertion of the medial collateral ligament; (3) insertion of the Achilles tendon into the calcaneus.

[34]. If the patient develops inefficacy to a TNFi then consideration should be given to anti-drug antibodies, with options being an in-class drug switch, dose increase or the addition of MTX. Two of the predictors of switching, in addition to the clinical characteristics associated with lack of remission, are high fatigue and pain scores at baseline [34]. We need to clarify how much of the fatigue and pain is related to active disease as opposed to co-morbid conditions.

We know that the newer agents, including IL-17 inhibitors (IL17i), ustekinumab, IL-23 inhibitors, JAK inhibitors and apremilast, all are effective, based on randomized controlled trials in achieving ACR20 and psoriasis area and severity index (PASI 75) responses in patients who had failed to respond to one or more TNFis [35, 36]. There are further emerging data regarding the newer agents. Recent studies suggest that ixekizumab and secukinumab are superior to adalimumab in treating skin disease and equally effective in treating joint disease and enthesitis [37, 38]. This data is supported by recent studies that demonstrate the superiority of bimekizumab, targeting IL17A and IL17F, over both adalimumab and ustekinumab in treating PsO and phase 2 data supporting its use in joint disease [39,40,41]. The IL23 inhibitors appear to be particularly effective in treating skin disease compared to other biologic agents [42,43,44]. Guselkumab has similar joint outcomes to IL17i and TNFi and an indirect analysis suggested guselkumab maybe superior to ustekinumab in treating joint disease [45,46]. A small open-label trial suggested ustekinumab could be more efficacious in treating enthesitis than a TNFi [47].

These findings underpin the importance of IL-12, IL-23 and IL-17 in enthesitis. However, as stated, there are limitations to the reliability of clinical examination in enthesitis, and thus there is not yet enough data to support the superiority of any. The extent of PsO is the only emerging clinical domain that could potentially be used to decide between these therapies at present, especially after the failure of a TNFi. Other considerations for a switch of drug class include the presence of IBD (avoiding IL-17i), and preference for an oral medication (JAK inhibitors) or a reduced dosing schedule (ustekinumab).

Imaging features predictive of treatment response

The limitations of clinical assessment in PsA have led to EULAR recommending the use of MRI and US for diagnosis, activity monitoring, and structural change evaluation in peripheral SpA. Traditional plain radiographs still form an important baseline test in clinical assessment. We know that erosive changes on X-ray will be seen after 2 years of disease [48]. Other changes include joint space narrowing, periosteal new bone formation, osteolysis, and ankyloses. In the spine, generic SpA changes are seen in PsA, but by the time these appear on plain film the disease has usually advanced [49]. Chronic damage at the entheses are also visible with plain films [50].

MRI

MRI has improved our understanding of the pathogenesis of PsA as well as of soft tissue changes that enable monitoring over time. It is the modality of choice in axial disease and has resulted in a better understanding of a classic feature of PsA: dactylitis, a mixture of flexor tenosynovitis, joint synovitis, and marked soft-tissue oedema [51]. It can demonstrate arthritis prior to development of symptoms. It can assess all the articular features of PsA, including synovitis, enthesitis, tendonitis, and soft-tissue changes and is especially useful in detecting changes at or below the bone level. The Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) is a validated tool that can assess synovitis, tenosynovitis and bone changes and has been utilized in clinical studies [52]. MRI has the ability to detect active joint inflammation and bone marrow oedema at the SI joint before chronic irreversible damage occurs [53]. It has demonstrated response in terms of peripheral synovitis to TNFi and IL-17i therapy [54–57]. Enthesitis studies are in progress for PsA, but to date research with MRI has focused on AS and demonstrated response to TNFi [58, 59]. Newer techniques, including ultrashort time to echo MRI, are being developed [60], and a summary of MRI definitions and research tools in PsA is provided in Table 2 [61–73]; these will be important in comparing treatments and stratifying patients.

MRI has technical challenges in assessing the entheses in certain locations due to low water accumulation [74]. Other general limitations include expense, availability, and contraindications to its use.

US

Musculoskeletal US can assess all the elements of psoriatic disease in real time. Its utility in inflammatory arthritis is established, and it can demonstrate unique features in PsA, including extrasynovial findings of enthesitis, hand extensor peritendonitis, thickening of the pulleys of the flexor tendons, soft-tissue oedema, and bone proliferation. Good correlation with US scanning of synovitis and tenosynovitis with composite DASs has been demonstrated [75, 76]. Enthesitis US scanning correlation is more varied and likely represents the limitation of clinical assessment [77].

Studies have demonstrated that 20% of PsA patients suffer from concomitant FM, and these patients [78] have higher DASs and find it harder to achieve disease remission. Recent US research has shown, however, that these patients have similar levels of objective evidence of inflammation, in terms of both enthesitis and synovitis, to those with PsA only [78, 79].

To date there are no studies utilizing US to compare responses to different forms of biologic therapy, and a recent systematic review of US [19] highlighted the lack of research that focused solely on PsA. The limited data available has demonstrated response in terms of US synovitis and tenosynovitis to therapy [57, 80], but no prognostic US signs have been demonstrated in PsA [81]. There have been a number of scoring systems for inflammatory polyarthritis that are relevant in PsA (Table 2) [61–73]. Two US scores (PsA-Son22 and PsA-Son13) were developed [61] specifically for PsA and scan joints, peri-articular structures and entheses, demonstrating change over time.

Enthesitis and US imaging

The OMERACT group has recently defined enthesitis on US [55], and a number of US scoring systems for enthesitis have been proposed (Table 2) [61, 62, 64, 66]. GRAPPA and OMERACT are currently validating their own enthesitis tools in PsA. The Glasgow Ultrasound Enthesitis Scoring System [58] and the Madrid Sonographic Enthesitis Index (MASEI) [63] were designed to assess enthesitis more generally in SpA and are sensitive to change over time with treatment. The MASEI score, in particular, assesses structures in both the upper and lower limbs and, apart from the common extensor origin and supraspinatus tendon, covers those sites proposed by the various working groups [65, 66]. A high MASEI score ($\geq$18 out of 136) has been shown to have sensitivity (83.3%) and specificity (82.8%) for SpA diagnosis [63].

Table 2 MRI and US imaging definition and tools by PsA phenotype

PsA phenotype		US	MRI
Enthesitis dominant	Definition as per OMERACT	Hypoechogenicity, increased thickness of tendon insertion, calcifications, enthesophytes, erosions and Doppler signal at the enthesis ≤2 mm near the bony cortex [61]	Intratendon/intrafascia hypersignal, peritendon/perifascia hypersignal, bone marrow oedema, bursitis, tendon/fascia thickening, enthesophyte and bone erosion [62]
	PsA/SpA score examples/joints included	MASEI [63]—(6) at, pf, dpt, ppt, qt and tt GUESS [64]—(5) at, pf, dpt, ppt, qt OMERACT US [65] WG (4) le, at, qt, ppt GRAPPA US [66] WG—(6) ppt, dpt, at, le, ss and pf	HEMRIS [62]: pf and at
Polyarthritis	Definition as per OMERACT	Synovitis: presence of a hypoechoic synovial hypertrophy regardless of the presence of effusion or any grade of Doppler signal Tenosynovitis: Anechoic and/or hypoechoic (relative to tendon fibres) tendon sheath widening. Doppler signal in two perpendicular planes excluding normal feeding vessels	Synovitis, tenosynovitis, peri-articular inflammation, bone oedema, bone erosion and bone proliferation are key pathologies. Also of importance but not included in the PsAMRIS score was peritendonitis, tendonitis and tendinopathy.
	PsA score examples; joints included	PsASon13/22 [67]—specific for PsA; hand MCP/PIP/DIP, feet MTP/DIP, large joints and 4 entheses German US7 [68]—dominant hand 7 joints (wrist, 2nd and 3rd MCP and PIP, and 2nd and 5th MTP) SOLAR [69]—developed for RA; shoulder, hip, knee and elbow	PsAMRIS [70] MCP/PIP/DIP joints on the 2nd to 5th fingers
Axial dominant	Definition. ASAS MRI working group [71]	N/A	Activity changes—bone marrow oedema, capsulitis, joint space enhancement, inflammation at an erosion, enthesitis, joint space fluid Structural damage changes—erosion, fat lesion, fat metaplasia in an erosion cavity, sclerosis, ankylosis and non-bridging bone bud
	SpA spine and SI joint score examples	N/A	SPARCC MRI index [72], Berlin MRI score [73]

ASAS: assessment of Spondyloarthritis International Society; at: achilles tendon; dpt: distla patellar tendon; GRAPPA: Group for Research and Assessment in Psoriasis and Psoriatic Arthritis; GUESS: Glasgow Ultrasound Enthesitis Scoring System; HEMRIS: heel enthesitis in MRI scoring system; le: lateral epicondyle; MASEI: Madrid Sonographic Enthesitis Index; N/A, not applicable; pf: plantar fascia; ppt: proximal patellar tendon PsAMRIS: Psoriatic Arthritis Magnetic Resonance Imaging Score; qt: quadraceps tendon; SPARCC: Spondyloarthritis Research Consortium of Canada; SOLAR: Sonography of Large Joints in Rheumatology; ss: supraspinatus tendon; tt: triceps tendon; WG: Working group.

Studies have been performed assessing TNFi, DMARD or NSAID response on US enthesitis in SpA [82–90]. These have shown US entheseal morphological abnormalities will respond to TNFi therapy [87]. They have either not included or are not specific for PsA, or have only included small numbers of patients on various treatments. A well-designed prospective study followed PsO patients treated with ustekinumab who had US-confirmed inflammatory entheseal changes. They demonstrated a significant improvement in subclinical enthesitis [91]. This again suggests that US findings are genuine and can aid PsA treatment decisions.

Can imaging help in assessing treatment response?

Going forward, we have a choice to scan and research each domain of PsA separately or attempt to cover all domains with one composite score. The PsA-Son scores include entheses examination, and other composite US scores have attempted to reflect the heterogeneity of PsA. The five Targets PwD (power doppler) for Psoriatic Disease is another example [92]. This score recognizes the various domains in PsA and can be used to monitor power Doppler at the joint, enthesis, skin, nail, tendons and synovial sheath. This score is much more feasible, but it focuses on areas that are difficult to scan, including the skin and nails.

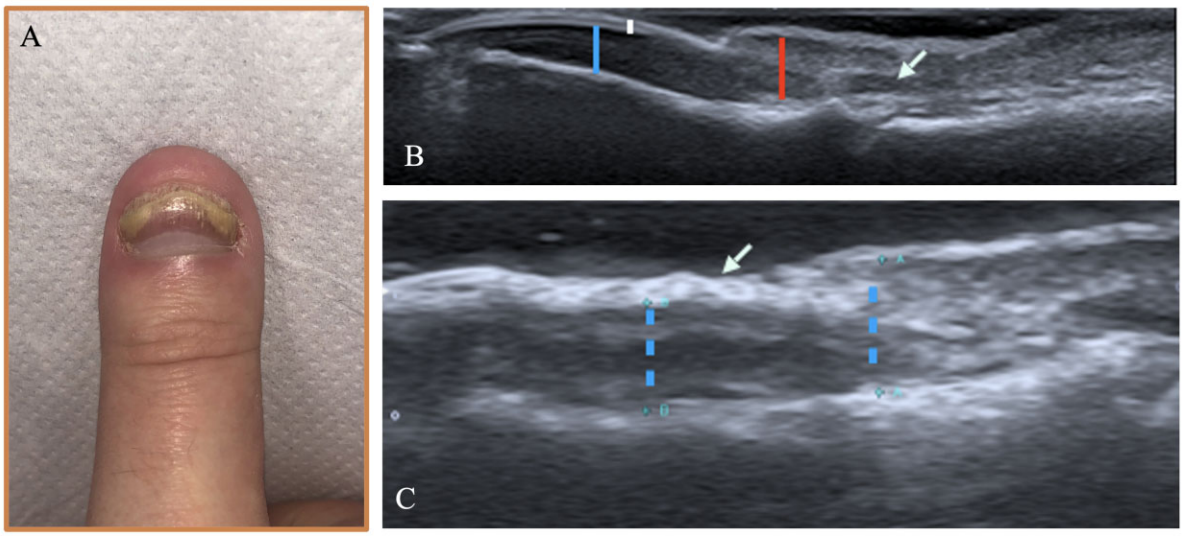
There is evidence of an association between nail disease (Fig. 3) (both clinical and subclinical) and enthesitis at the DIP joint in PsO [93, 94]. US is able to assess the nail bed, matrix and plate as well as its relationship with the DIP joint of the finger. A high transducer probe can diagnose subclinical psoriatic nail disease and potentially monitor response to treatment. Interestingly a study of PsO patients with nail disease noted a higher incidence of subclinical systemic enthesitis [95]. Thus, nail bed disease merits further investigation to again better stratify patients by phenotype.

The wide range of assessment options highlight the heterogeneity of PsA and the need to better define patients. A score that is all-encompassing in PsA is attractive but will be time-consuming and risk being confined to use as a research tool. An Italian group have designed a study that will produce a weighted score of articular, entheseal and soft-tissue lesions in an attempt to predict response to any form of treatment in PsA [96]. A more realistic approach maybe to split up the disease manifestations and then complement our more detailed understanding of pathology with biomarker analysis. An approach that first stratifies patients clinically and utilizes imaging to objectively confirm these findings will be vital in order to better define disease and its response to therapy. In terms of axial disease, MRI is the modality of choice; for synovitis, tendonitis and enthesitis, US is emerging as the preferred option.

Biomarkers

For a molecular biomarker to be applicable to clinical practice, it should be easy to obtain, sensitive, specific,

Fig. 3 Clinical and US imaging of psoriatic nail disease



(A) Onychopathy in a patient with PsA and evidence of both nail matrix and nail bed disease. (B) How a nail unit [including nail matrix (red line), nail plate (white line) and nail bed (blue line)] along with associated DIP entheses (white arrow) appears on US. (C) How the nail will appear on US with nail disease, demonstrating loss of definition between the nail plates and thickening of the nail matrix (α calipers) and nail bed (β calipers) (images A.E.).

reproducible, and prognostic [97]. Currently, there are no validated biomarkers in PsA. The main molecular sites of biomarker discovery have focused on genomics and proteomics, both peripherally in the serum and in the involved tissue in PsA.

Genetic markers associated with treatment response

We know that PsA has a strong genetic component. Key single nucleotide polymorphisms (SNPs) are implicated in the pathogenesis, including HLA and non-HLA loci. A number of key genetic associations (including the haplotype B*27:05-C*01:02 and its two constituent alleles, B*27:05 and C*01:02) are strongly associated with the development of enthesitis [6].

Polymorphisms in the TNF promoter regions have relevance in predicting response to treatment. The TNFα-induced protein 2 gene (*TNFAIP3*) or *A20* have been associated with response to TNFi treatment [98]. *TNFAIP3* was first described as a negative feedback inhibitor of TNFα, terminating activation of the NFκB transcription factor.IL-17 also induces expression of the *TNFAIP3* gene. Interestingly A20 interacts with IL-17 differently compared with other pathways, [99] and research is needed to clarify whether polymorphisms at *A20* alter the effectiveness of IL-17 inhibitors compared with TNFi. Other SNPs that have been under investigation include polymorphisms at the *TNF-α* gene [100, 101], TNF receptor 1A gene (*TNFR1A*) and the TNF-related apoptosis-inducing ligand receptor 1 gene (*TRAIL-R1*) [102], along with the *FCGR2A* polymorphism FCGR2A-131H [103].

Studies assessing response to biologic treatment have been small and have contained a mixture of patients with both PsO and PsA. *IL23R* has also been shown to be a strongly associated non-HLA gene for PsA, and population studies have demonstrated that SNPs at *IL-23R* impair Th17 effector function [104]. Studies in PsO have demonstrated that SNPs in the promoter region of *IL17RA* significantly influence the response to anti-TNF drugs at week 12 [105]. We cannot, however, draw any significant conclusions on the utility of genomic biomarkers until much larger cohorts of samples have been examined and larger genomic panels have been assessed. Future work should also focus on alternative SNP targets, including the IL-23/Th17 axis.

Soluble biomarkers predictive of treatment response

Proteomics is the study of protein expression under different conditions in a biological sample. It is unlikely that a single protein will have diagnostic utility; instead, a biomarker panel may be of greater use. To interrogate the entire proteome will require multiple proteomic methods, for greater discovery capacity [106]. Proteomic technology includes Mass Spectrometry, multiplexed ELISA and antibody microarrays, e.g. OLINK. The novel aptamer-based multiplex SOMAscan [107], which can allow for larger proteomic panels to be analysed, also has exciting potential.

A reduction in serum MMP-3 levels and an increase in serum melanoma inhibitory activity levels occur following biologic treatment [108]. Chandran *et al.* [109] also identified reduction in MMP-3 levels to be associated with response to TNFi therapy. Conflicting results have been observed for serum COMP levels following TNFi [110, 111]. Given that large entheses in the peripheral and axial skeleton have relatively abundant fibrocartilage present, we believe that a focus on such markers may be of particular interest to enthesitis-related pathology. No significant change in low-molecular-mass hyaluronan was observed following adalimumab treatment [112].

Traditional serum inflammatory markers such as CRP are not reliable indicators of disease activity in PsA patients, and values are generally normal in those with isolated enthesitis. Given the relatively avascular nature of the enthesis and the associated restriction on the magnitude of inflammation that this may entail, the application of serum biomarkers for disease stratification and monitoring represents a considerable challenge. In animal models, IL-23 is implicated in enthesitis, with inflammatory effects mediated through IL-17 and TNF, and new bone formation driven by IL-22 [113]. Other studies have demonstrated activated Th17 cells expressing the IL-23 receptor, ROR-γt and stem cell antigen 1 resident at the enthesis [114]. Following IL-23 stimulation, mice develop enthesitis, with the inflammation spreading into the adjacent synovium. Enthesitis was IL-17A dependent, and this is consistent with the SKG mouse model of enthesitis [115]. Studies using transgenic mouse models with TNF overexpression resulted in early triggering of enthesitis [18]. Of note, myeloid-specific A20-deficient mice also demonstrated early enthesitis, with subsequent response *in vivo* to JAK inhibition [116]. These models highlight the important role that the newer biologic agents targeting IL-17, IL-12/23 p40, JAK and IL-23 should have in treating enthesitis.

Randomized controlled trials identified several biomarkers, including adiponectin and factor VII, which appeared to predict response in both skin and joints scores following golimumab therapy [117]. Several potential biomarkers were strongly associated with ACR20 and/or DAS28 score response and are referenced in Table 3 [108–110, 112, 117–121]. MMP-3 baseline results did not correlate with either skin or joint outcomes. The correlation between inflammatory markers and joint scores, especially the DAS-28 count, which includes CRP or ESR, is not surprising. Certain proteins like VEGF, MMP-3 and ICAM-1 have also been identified as potential biomarkers in TNFi studies looking at RA [122]. We do not want develop a panel that only identifies one presentation of PsA, namely a polyarthritis presentation similar to RA. The focus should be on assessing those

Table 3 Predictive proteomic biomarker studies in PsA

Study	Participants	Treatment	Duration	Source	Potential proteins biomarker
Tak *et al.* 2010 [108]	24	PBO *vs* ADA	4 and 12 weeks	Synovial fluid	MMP-3, MIA
Chandran *et al.* 2013 [109]	40	TNFi	Mean 11 months	Serum	COMP, MMP-3
Pedersen *et al.* 2010 [118]	37 SpA (12 PsA)	TNFi	$\leq$3 years	Serum	IL-6, VEGF, YKL-40, MMP-3, total aggrecan
Cauza *et al.* 2006 [110]	9	IFX	6 weeks	Serum	COMP
Hellman *et al.* 2019 [112]	20	ADA	12 weeks	Skin and serum	Hyaluronan
Wagner *et al.* 2013 [117]	100	GOL *vs* PBO	4 and 14 weeks	Serum	APOC3, ENRAGE, IL-16, VEGF, PYD, MMP-3, MPO CRP, CEA, ICAM1 MIP1A
Schafer *et al.* 2015 [119]	150	APLT *vs* PBO	24 and 40 weeks	Serum	IL-8, TNF-α, IL-6, MIP-1β, MCP-1, ferritin IL-17, IL-23, IL-10 and IL-1 receptor antagonists
Ademowo *et al.* [120]	18 (Discovery) and 7 (Validation)	ABT and ADA	6 months	Synovial tissue	Novel and significant out of 57-S100-A8, IGKC, HP, ANAX2, COL1A2, PRELP, COF1, FGA, KER and F13A
Van Mens *et al.* 2018 [121]	20 SpA (13 PsA)	SEC	12 weeks	Synovial tissue and serum	MMP-3, IL-17A, CRP

ABT: abatacept; ADA: adalimumab; ANAX2: annexin A2; APOC3: apolipoprotein C III; APLT: apremilast; CEA: carcinoembryonic antigen; COF1: cofilin; COL1A2: collagen alpha-2; ENRAGE: S100A12; F13A: coagulation factor X111A; FGA: fibrinogen-α; GOL: golimumab; HP: haptoglobin; ICAM1: intercellular adhesion molecule 1; IGKC: Ig kappa chain C; IFX: infliximab; KER: keratin; MCP-1: monocyte chemotactic protein; MIP1A: macrophage inflammatory protein 1α; MIA: melanoma inhibitory activity; PBO: placebo; PRELP: prolargin; PYD: pyridinoline; SEC: secukinumab; TNFi: anti-TNF biologic; YKL-40; chitinase-3-like protein 1.

on biologic treatment and complementing the more detailed data from imaging with proteomic analysis. Additionally, synergism between predictive proteome work in PsA and PsO will be vital [123]. The ever-expanding capabilities from omic technology, including metabolomics and the subcategory of lipidomics [124], are also exciting areas of discovery.

Tissue biomarkers predictive of treatment response

A study looking at response to TNFi treatment in the synovial tissue of PsA patients showed a differential proteomics response between good and poor responders [125]. Another landmark study from Dublin developed a panel of 57 proteins from synovial tissue samples to predict response to treatment [120]. MRM technology was then utilized to validate the panel in 18 patients treated with adalimumab, and the panel was then examined in a cohort of patients treated with abatacept (a T cell co-stimulation inhibitor) when its potential use in PsA was being investigated. A number of novel key discriminating proteins (including S-100A8) were deemed to be the most predictive. These findings need to be validated in studies with larger cohorts and standardization of biomarker work across sites. Alternative sites for potentially investigating proteomics response include skin samples [126].

A recent study, linking proteomic sources, looked at IL-17i and its impact on inflammatory markers. It included a small cohort of PsA patients in whom secukinumab treatment decreased the CRP, and the ESR and MMP-3 production in clinical responders. SM analysis demonstrated a significant decrease in expression of mRNA for IL-6, IL-17A, MMP-3 and CCL20 [121]. A summary of predictive proteomic biomarker work is outlined in Table 3 [108–110, 112, 117–121].

Future research agenda

First, we need to establish which composite disease scores most accurately reflect disease activity and response to therapy, and then validate imaging tools in US and MRI that assess polyarthritis, enthesitis and axial disease. We can then investigate the utility of imaging to predict response to therapy and complement clinical and imaging data with omic technology to produce robust predictive laboratory panels.

Conclusion

There is a paucity of data to guide decision making when choosing which biologic therapy is most effective for the heterogeneous PsA patient group. With ever-increasing treatment options, we need to identify which medications can target which domains of disease more effectively. There is an awareness that traditional outcome measures in inflammatory arthritis studies do not reflect the complexity of PsA. This has been demonstrated by the development of composite clinical and imaging scoring systems that fail to adequately delineate PsA pathology by not distinguishing PsA from other causes of pain. As newer treatments emerge, it is an opportune time to assess response to the various forms of biologics.

Imaging, in particular US and MRI, can help us to better stratify patients and assess disease activity. Enthesitis is a hallmark of PsA that merits more detailed evaluation. Research has shown sustained resolution of clinical enthesitis compared with placebo in those PsA patients treated with IL-17 inhibitors, ustekinumab and TNFi. There is no published study assessing US enthesitis and its response to IL-17 inhibitors, and no research comparing the effects of the two different classes of biologic treatment on either clinical or radiological enthesitis.

Biomarker discovery research may eventually deliver stratified medicine in PsA, but this needs careful integration with imaging-defined pathology. Once we have established the definite clinical phenotype indicated by imaging of the synovium and the entheses, we can complement this data with biomarker work. We can then make informed decisions on our biologic choices or revert to chronic pain management.

Funding: This paper is published as part of a supplement supported by a grant from UCB Pharma.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

No new data were generated or analysed in support of this research.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis 2005;64(Suppl 2):ii14–7.

2 Coates LC, Gossec L, Ramiro S *et al.* New GRAPPA and EULAR recommendations for the management of psoriatic arthritis. Rheumatology 2017;56:1251–3.

3 Coates LC, Navarro-Coy N, Brown SR *et al.* The TICOPA protocol (tight control of psoriatic arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis. BMC Musculoskelet Disord 2013;14:101.

4 McGonagle D, Hermann KGA, Tan AL. Differentiation between osteoarthritis and psoriatic arthritis:

implications for pathogenesis and treatment in the biologic therapy era. Rheumatology 2015;54:29–38.

5 Iannone F, Nivuori M, Fornaro M *et al.* Comorbid fibromyalgia impairs the effectiveness of biologic drugs in patients with psoriatic arthritis. Rheumatology 2020; 59:1599–606.

6 McArdle A, Pennington S, FitzGerald O. Clinical features of psoriatic arthritis: a comprehensive review of unmet clinical needs. Clin Rev Allergy Immunol 2018; 55:271–94.

7 Hammer HB, Jensen Hansen IM, Järvinen P *et al.* Swollen, but not tender joints, are independently associated with ultrasound synovitis: results from a longitudinal observational study of patients with established rheumatoid arthritis. Ann Rheum Dis 2019; 78:1179–85.

8 Kondo Y, Suzuki K, Inoue Y *et al.* Significant association between joint ultrasonographic parameters and synovial inflammatory factors in rheumatoid arthritis. Arthritis Res Ther 2019;21:14.

9 Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. Arthritis Care Res 2010;62:965–9.

10 Helliwell PS, FitzGerald O, Fransen J *et al.* The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). Ann Rheum Dis 2013;72:986–91.

11 Smolen JS, Schoels M, Aletaha D. Disease activity and response assessment in psoriatic arthritis using the Disease Activity index for PSoriatic Arthritis (DAPSA). A brief review. Clin Exp Rheumatol 2015;33: S48–50.

12 Ritchlin CT, Kavanaugh A, Gladman DD *et al.*; Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Treatment recommendations for psoriatic arthritis. Ann Rheum Dis 2009;68:1387–94.

13 Tucker L, Helliwell P, Coates L; GRACE Collaboration. O13 Which composite measure best reflects disease activity and predicts treatment change in psoriatic arthritis? Rheumatology 2021; Advance Access published 26 April 2021, doi: 10.1093/rheumatology/keab246.012

14 Coates LC, Helliwell PS. Psoriatic arthritis: state of the art review. Clin Med J R Coll Physicians London 2017; 17:65–70.

15 Mease PJ, McInnes IB, Strand V *et al.* Clinical characteristics and disease activity in psoriatic arthritis patients with dactylitis or enthesitis: results from Corrona registry. Arthritis Care Res 2020;40:1021–8.

16 Polachek A, Cook R, Chandran V, Gladman DD, Eder L. The association between sonographic enthesitis and radiographic damage in psoriatic arthritis. Arthritis Res Ther 2017;19:189.

17 Baskan B, Oten E, Sivas F *et al.* The relationship between vitamin D, vertebral deformity and quality of life in psoriatic arthritis. Acta Reumatol Port 2016;41: 350–8.

18 Jacques P, Lambrecht S, Verheugen E *et al.* Proof of concept: enthesitis and new bone formation in spondyloarthritis are driven by mechanical strain and stromal cells. Ann Rheum Dis 2014;73:437–45.

19 Zabotti A, Bandinelli F, Batticciotto A *et al.*; on behalf of the Musculoskeletal Ultrasound Study Group of the Italian Society of Rheumatology. Musculoskeletal ultrasonography for psoriatic arthritis and psoriasis patients: a systematic literature review. Rheumatology 2017;56:1518–32.

20 Macchioni P, Salvarani C, Possemato N *et al.* Ultrasonographic and clinical assessment of peripheral enthesitis in patients with psoriatic arthritis, psoriasis, and fibromyalgia syndrome: the ULISSE study. J Rheumatol 2019;46:904–11.

21 Sakkas LI, Alexiou I, Simopoulou T, Vlychou M. Enthesitis in psoriatic arthritis. Semin Arthritis Rheum 2013;43:325–34.

22 Mease PJ. Measures of psoriatic arthritis: Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). Arthritis Care Res 2011;63(Suppl 11): S64–85.

23 Kaeley GS, Eder L, Aydin SZ, Gutierrez M, Bakewell C. Enthesitis: a hallmark of psoriatic arthritis. Semin Arthritis Rheum 2018;48:263–73.

24 Singh JA, Guyatt G, Ogdie A *et al.* Special article: 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. Arthritis Rheumatol 2019;71:5–32.

25 Gossec L, Baraliakos X, Kerschbaumer A *et al.* EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020;79:700–12.

26 Maneiro JR, Souto A, Salgado E, Mera A, Gomez-Reino JJ. Predictors of response to TNF antagonists in patients with ankylosing spondylitis and psoriatic arthritis: systematic review and meta-analysis. RMD Open 2015;1:e000017.

27 Eder L, Thavaneswaran A, Chandran V, Cook RJ, Gladman DD. Obesity is associated with a lower probability of achieving sustained minimal disease activity state among patients with psoriatic arthritis. Ann Rheum Dis 2015;74:813–7.

28 Theander E, Husmark T, Alenius GM *et al.* Early psoriatic arthritis: short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). Ann Rheum Dis 2014;73:407–13.

29 Saber TP, Ng CT, Renard G *et al.* Remission in psoriatic arthritis: is it possible and how can it be predicted? Arthritis Res Ther 2010;12:R94.

30 Mease PJ, Kavanaugh A, Coates LC *et al.* Prediction and benefits of minimal disease activity in patients with psoriatic arthritis and active skin disease in the ADEPT trial. RMD Open 2017;3:e000415.

31 Fabbroni M, Cantarini L, Caso F *et al.* Drug retention rates and treatment discontinuation among anti-TNF-α agents in psoriatic arthritis and ankylosing spondylitis in clinical practice. Mediators Inflamm 2014;2014: 862969.

32 Iannone F, Lopriore S, Bucci R *et al.* Two-year survival rates of anti-TNF-α therapy in psoriatic arthritis (PsA) patients with either polyarticular or oligoarticular PsA. Scand J Rheumatol 2015;44:192–9.

33 Bonafede M, Fox KM, Watson C, Princic N, Gandra SR. Treatment patterns in the first year after initiating tumor necrosis factor blockers in real-world settings. Adv Ther 2012;29:664–74.

34 Glintborg B, Østergaard M, Dreyer L *et al.* Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor α therapy: results from the nationwide Danish DANBIO registry. Arthritis Rheum 2011;63: 382–90.

35 Costa L, Perricone C, Chimenti MS *et al.* Switching between biological treatments in psoriatic arthritis: a review of the evidence. Drugs R D 2017;17:509–22.

36 Gladman D, Rigby W, Azevedo VF *et al.* Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. N Engl J Med 2017;377: 1525–36.

37 Mease PJ, Smolen JS, Behrens F *et al.*; SPIRIT H2H Study Group. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. Ann Rheum Dis 2020;79:123–31.

38 McInnes IB, Behrens F, Mease PJ *et al.* Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet (London) 2020;395:1496–505.

39 Strober B, Krueger J, Magnolo N, *et al*. Bimekizumab versus Ustekinumab efficacy across subgroups of patients with moderate to severe plaque psoriasis: results from the multicenter, randomized, double-blinded phase 3 BE VIVID trial. Ski J Cutan Med 2021;doi:10.25251/skin.5.supp.16.

40 Warren R, Blauvelt A, Bagel J, *et al.* Bimekizumab efficacy and safety versus adalimumab in patients with moderate to severe plaque psoriasis: results from a multicenter, randomized, double-blinded active comparator-controlled phase 3 trial (BE SURE). Ski J Cutan Med 2021;doi:10.25251/skin.5.supp.15.

41 Ritchlin CT, Kavanaugh A, Merola JF, *et al.* Bimekizumab in patients with active psoriatic arthritis: results from a 48-week, randomised, double-blind, placebo-controlled, dose-ranging phase 2b trial. Lancet 2020;395:427–40.

42 Reich K, Armstrong AW, Foley P *et al.* Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol 2017;76:418–31.

43 Papp KA, Blauvelt A, Bukhalo M *et al*. Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis. N Engl J Med 2017;376:1551–60.

44 Reich K, Armstrong AW, Langley RG *et al.* Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. Lancet 2019; 394:831–9.

45 Mease PJ, McInnes IB, Tam LS *et al*. Comparative effectiveness of guselkumab in psoriatic arthritis: results from systematic literature review and network meta-analysis. Rheumatol 2021;60:2109–21.

46 Diels J, Thilakarathne P, Schubert A, Hassan F, Peterson S, Noel W. AB0556 comparing efficacy of guselkumab versus ustekinumab in patients with psoriasis arthritis: an adjusted comparison using individual patient data from discover 1&2 and psummit trials. Ann Rheum Dis 2021;doi:10.1136/annrheumdis-2021-eular.2595.

47 Araujo EG, Englbrecht M, Hoepken S *et al.* OP0217 Ustekinumab is superior to TNF inhibitor treatment in resolving enthesitis in PSA patients with active enthesitis—results from the Enthesial CLearance In PSoriatic Arthritis (ECLIPSA) study. Ann Rheum Dis 2017;76:142.

48 Sudoł-Szopińska I, Matuszewska G, Kwiatkowska B, Pracoń G. Diagnostic imaging of psoriatic arthritis. Part I: etiopathogenesis, classifications and radiographic features. J Ultrason 2016;16:65–77.

49 Jadon DR, Sengupta R, Nightingale A *et al.* Axial Disease in Psoriatic Arthritis study: defining the clinical and radiographic phenotype of psoriatic spondyloarthritis. Ann Rheum Dis 2017;76:701–7.

50 Benjamin M, Rufai A, Ralphs JR. The mechanism of formation of bony spurs (enthesophytes) in the Achilles tendon. Arthritis Rheum 2000;43:576.

51 Olivieri I, Scarano E, Padula A, Giasi V, Priolo F. Dactylitis, a term for different digit diseases. Scand J Rheumatol 2006;35:333–40.

52 Glinatsi D, Bird P, Gandjbakhch F *et al.* Validation of the OMERACT Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) for the hand and foot in a randomized placebo-controlled trial. J Rheumatol 2015; 42:2473–9.

53 Oostveen JCM, Prevo RL, Den Boer JA, Van De Laar MAFJ. Early detection of sacroiliitis on magnetic resonance imaging and subsequent development of sacroiliitis on plain radiography. A prospective, longitudinal study. J Rheumatol 1999;26:1953–8.

54 Anandarajah AP, Ory P, Salonen D *et al.* Effect of adalimumab on joint disease: features of patients with psoriatic arthritis detected by magnetic resonance imaging. Ann Rheum Dis 2010;69:206–9.

55 Anandarajah AP, Schwarz EM, Totterman S *et al.* The effect of etanercept on osteoclast precursor frequency and enhancing bone marrow oedema in patients with psoriatic arthritis. Ann Rheum Dis 2008; 67:296–301.

56 Marzo-Ortega H, McGonagle D, Rhodes LA *et al.* Efficacy of infliximab on MRI-determined bone oedema in psoriatic arthritis. Ann Rheum Dis 2007;66:778–81.

57 Kampylafka E, d'Oliveira I, Linz C *et al.* Resolution of synovitis and arrest of catabolic and anabolic bone changes in patients with psoriatic arthritis by IL-17A blockade with secukinumab: results from the prospective PSARTROS study. Arthritis Res Ther 2018;20:153.

58 Song IH, Hermann KG, Haibel H *et al.* Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. Ann Rheum Dis 2011;70: 590–6.

59 Krabbe S, Østergaard M, Eshed I *et al.* Whole-body magnetic resonance imaging in axial spondyloarthritis: reduction of sacroiliac, spinal, and entheseal inflammation in a placebo-controlled trial of adalimumab. J Rheumatol 2018;45:621–9.

60 Mathew AJ, Krabbe S, Eshed I *et al.* The OMERACT MRI in enthesitis initiative: definitions of key pathologies, suggested MRI sequences, and a novel heel enthesitis scoring system. J Rheumatol 2019;46: 1232–8.

61 Terslev L, Naredo E, Iagnocco A *et al.*; Outcome Measures in Rheumatology Ultrasound Task Force. Defining enthesitis in spondyloarthritis by ultrasound: results of a Delphi process and of a reliability reading exercise. Arthritis Care Res 2014;66:741–8.

62 Schmoldt A, Benthe HF, Haberland G. Atlas of the OMERACT Heel Enthesitis MRI Scoring System (HEMRIS). RMD Open 1975;24:1639–41.

63 De Miguel E, Cobo T, Muñoz-Femández S *et al.* Validity of enthesis ultrasound assessment in spondyloarthropathy. Ann Rheum Dis 2009;68:169–74.

64 Balint PV, Kane D, Wilson H, McInnes IB, Sturrock RD. Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. Ann Rheum Dis 2002;61: 905–10.

65 Balint PV, Terslev L, Aegerter P *et al.*; OMERACT Ultrasound Task Force Members. Reliability of a consensus-based ultrasound definition and scoring for enthesitis in spondyloarthritis and psoriatic arthritis: an OMERACT US initiative. Ann Rheum Dis 2018;77: 1730–5.

66 Tom S, Zhong Y, Cook R, Aydin SZ *et al.* Development of a preliminary ultrasonographic enthesitis score in psoriatic arthritis—GRAPPA ultrasound working group. J Rheumatol 2019;46:384–90.

67 Ficjan A, Husic R, Gretler J *et al.* Ultrasound composite scores for the assessment of inflammatory and structural pathologies in Psoriatic Arthritis (PsASon-Score). Arthritis Res Ther 2014;16:476.

68 Backhaus M, Ohrndorf S, Kellner H *et al.* Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: a pilot project. Arthritis Rheum 2009;61:1194–201.

69 Schäfer VS, Fleck M, Kellner H *et al.* Evaluation of the novel ultrasound score for large joints in psoriatic arthritis and ankylosing spondylitis: six month experience in daily clinical practice. BMC Musculoskelet Disord 2013;14:358.

70 Østergaard M, Eder L, Christiansen SN, Kaeley GS. Imaging in the diagnosis and management of peripheral psoriatic arthritis—the clinical utility of magnetic resonance imaging and ultrasonography. Best Pract Res Clin Rheumatol 2016;30:624–37.

71 Maksymowych WP, Lambert RGW, Østergaard M *et al.* MRI lesions in the sacroiliac joints of patients with spondyloarthritis: an update of definitions and validation by the ASAS MRI working group. Ann Rheum Dis 2019;78:1550–8.

72 Maksymowych WP, Inman RD, Salonen D *et al.* Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. Arthritis Rheum 2005;53:703–9.

73 Althoff CE, Sieper J, Song IH *et al.* Active inflammation and structural change in early active axial spondyloarthritis as detected by whole-body MRI. Ann Rheum Dis 2013;72:967–73.

74 Kehl AS, Corr M, Weisman MH. Enthesitis: new insights into pathogenesis, diagnostic modalities, and treatment. Arthritis Rheumatol 2016;68:312–22.

75 Alivernini S, Tolusso B, Petricca L *et al.* Synovial features of patients with rheumatoid arthritis and psoriatic arthritis in clinical and ultrasound remission differ under anti-TNF therapy: a clue to interpret different chances of relapse after clinical remission? Ann Rheum Dis 2017;76:1228–36.

76 Bosch P, Husic R, Ficjan A *et al.* Evaluating current definitions of low disease activity in psoriatic arthritis using ultrasound. Rheumatology 2019;58:2212–20.

77 Dubash SR, De Marco G, Wakefield RJ *et al.* Ultrasound imaging in psoriatic arthritis: what have we learnt in the last five years? Front Med 2020;7:487.

78 Fiorenza A, Bonitta G, Gerratana E *et al.* Assessment of enthesis in patients with psoriatic arthritis and fibromyalgia using clinical examination and ultrasound. Clin Exp Rheumatol 2020;38(Suppl 123):31–9.

79 Polachek A, Furer V, Zureik M *et al.* The role of ultrasound for the assessment of psoriatic arthritis patients with fibromyalgia—interim analysis [abstract]. Arthritis Rheumatol 2019;71(Suppl 10):abstract no. 2472. https://acrabstracts.org/abstract/the-role-of-ultrasound-for-the-assessment-of-psoriatic-arthritis-patients-with-fibromyalgia-interim-analysis/ (7 December 2020, date last accessed).

80 Ceccarelli F, Lucchetti R, Perricone C *et al.* Musculoskeletal ultrasound in monitoring response to apremilast in psoriatic arthritis patients: results from a longitudinal study. Clin Rheumatol 2019;38:3145–51.

81 Højgaard P, Ellegaard K, Nielsen SM *et al.* Pain mechanisms and ultrasonic inflammatory activity as prognostic factors in patients with psoriatic arthritis: a prospective cohort study. Arthritis Care Res 2019;71: 798–810.

82 Acquacalda E, Albert C, Montaudie H *et al.* Ultrasound study of entheses in psoriasis patients with or without musculoskeletal symptoms: a prospective study. Joint Bone Spine 2015;82:267–71.

83 Lehtinen A, Leirisalo-Repo M, Taavitsainen M. Persistence of enthesopathic changes in patients with spondylarthropathy during a 6-month follow-up. Clin Exp Rheumatol 1995;13:733–6.

84 Genc H, Duyur Cakit B, Nacir B *et al.* The effects of sulfasalazine treatment on enthesal abnormalities of inflammatory rheumatic diseases. Clin Rheumatol 2007; 26:1104–10.

85 Ruta S, Acosta Felquer ML, Rosa J *et al.* Responsiveness to therapy change of a global ultrasound assessment in spondyloarthritis patients. Clin Rheumatol 2015;34:125–32.

86 Hu Z, Xu M, Wang Q *et al.* Colour Doppler ultrasonography can be used to detect the changes of sacroiliitis and peripheral enthesitis in patients with ankylosing spondylitis during adalimumab treatment. Clin Exp Rheumatol 2015;33:844–50.

87 Mouterde G, Aegerter P, Correas J-M, Breban M, D'Agostino M-A. Value of contrast-enhanced ultrasonography for the detection and quantification of enthesitis vascularization in patients with spondyloarthritis. Arthritis Care Res (Hoboken) 2014;66:131–8.

88 Janta I, Martínez-Estupiñán L, Valor L *et al.* Comparison between full and tapered dosages of biologic therapies in psoriatic arthritis patients: clinical and ultrasound assessment. Clin Rheumatol 2015;34: 935–42.

89 Hartung W, Nigg A, Strunk J, Wolff B. Clinical assessment and ultrasonography in the follow-up of enthesitis in patients with spondyloarthritis: a multicenter ultrasound study in daily clinical practice. Open Access Rheumatol Res Rev 2018;10:161–9.

90 Naredo E, Batlle-Gualda E, García-Vivar ML *et al.* Power Doppler ultrasonography assessment of entheses in spondyloarthropathies: response to therapy of entheseal abnormalities. J Rheumatol 2010;37: 2110–7.

91 Savage L, Goodfield M, Horton L *et al.* Regression of peripheral subclinical enthesopathy in therapy-naïve patients treated with Ustekinumab for moderate-to-severe chronic plaque psoriasis. Arthritis Rheumatol 2019;71:626–31.

92 Gutierrez M, Di geso L, Salaffi F *et al.* Development of a preliminary US power Doppler composite score for monitoring treatment in PsA. Rheumatology 2012;51: 1261–8.

93 Acosta-Felquer ML, Ruta S, Rosa J *et al.* Ultrasound entheseal abnormalities at the distal interphalangeal joints and clinical nail involvement in patients with psoriasis and psoriatic arthritis, supporting the nail-enthesitis theory. Semin Arthritis Rheum 2017;47: 338–42.

94 Aydin SZ, Castillo-Gallego C, Ash ZR *et al.* Ultrasonographic assessment of nail in psoriatic disease shows a link between onychopathy and distal interphalangeal joint extensor tendon enthesopathy. Dermatology 2012;225:231–5.

95 Ash ZR, Tinazzi I, Gallego CC *et al.* Psoriasis patients with nail disease have a greater magnitude of underlying systemic subclinical enthesopathy than those with normal nails. Ann Rheum Dis 2012;71:553–6.

96 Canzoni M, Piga M, Zabotti A *et al.* Clinical and ultrasonographic predictors for achieving minimal disease activity in patients with psoriatic arthritis: the UPSTREAM (Ultrasound in PSoriatic arthritis TREAtMent) prospective observational study protocol. BMJ Open 2018;8:e021942.

97 Atkinson AJ, Colburn WA, DeGruttola VG *et al.* Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89–95.

98 Tejasvi T, Stuart PE, Chandran V *et al. TNFAIP3* gene polymorphisms are associated with response to TNF blockade in psoriasis. J Invest Dermatol 2012;132: 593–600.

99 Garg AV, Gaffen SL. IL-17 signaling and A20, a balancing act. Cell Cycle 2013;12:3459–60.

100 Seitz M, Wirthmüller U, Möller B, Villiger PM. The -308 tumour necrosis factor-α gene polymorphism predicts therapeutic response to TNFα-blockers in rheumatoid arthritis and spondyloarthritis patients. Rheumatology 2007;46:93–6.

101 Murdaca G, Gulli R, Spanò F *et al.* TNF-α gene polymorphisms: association with disease susceptibility and response to anti-TNF-α treatment in psoriatic arthritis. J Invest Dermatol 2014;134: 2503–9.

102 Morales-Lara MJ, Cañete JD, Torres-Moreno D *et al.* Effects of polymorphisms in *TRAILR1* and *TNFR1A* on the response to anti-TNF therapies in patients with rheumatoid and psoriatic arthritis. Joint Bone Spine 2012;79:591–6.

103 Ramírez J, Fernández-Sueiro JL, López-Mejías R *et al. FCGR2A*/*CD32A* and *FCGR3A*/*CD16A* variants and EULAR response to tumor necrosis factor-α blockers in psoriatic arthritis: a longitudinal study with 6 months of followup. J Rheumatol 2012;39:1035–41.

104 Di Meglio P, Di Cesare A, Laggner U *et al.* The IL23R R381Q gene variant protects against immune-mediated diseases by impairing IL-23-induced Th17 effector response in humans. PLoS One 2011;6:e17160.

105 Batalla A, Coto E, Gómez J *et al. IL17RA* gene variants and anti-TNF response among psoriasis patients. Pharmacogenomics J 2018;18:76–80.

106 Mcardle A, Qasim Butt A, Szentpetery A *et al.* Developing clinically relevant biomarkers in inflammatory arthritis: a multiplatform approach for serum candidate protein discovery. Proteomics Clin Appl 2016;10:691–8.

107 Gold L, Ayers D, Bertino J *et al.* Aptamer-based multiplexed proteomic technology for biomarker discovery. PLoS One 2010;5:e15004.

108 Tak PP, van Kuijk AWR, Degroot J *et al.* Soluble biomarkers of cartilage and bone metabolism in early proof of concept trials in psoriatic arthritis: effects of adalimumab versus placebo. PLoS One 2010;5:e12556.

109 Chandran V, Shen H, Pollock RA *et al.* Soluble biomarkers associated with response to treatment with tumor necrosis factor inhibitors in psoriatic arthritis. J Rheumatol 2013;40:866–71.

110 Cauza E, Hanusch-Enserer U, Frischmuth K *et al.* Short-term infliximab therapy improves symptoms of psoriatic arthritis and decreases concentrations of cartilage oligomeric matrix protein. J Clin Pharm Ther 2006;31:149–52.

111 Grazio S, Razdorov G, Erjavec I *et al.* Differential expression of proteins with heparin affinity in patients with rheumatoid and psoriatic arthritis: a preliminary study. Clin Exp Rheumatol 2013;31:665–71.

112 Hellman U, Engström-Laurent A, Larsson A, Lindqvist U. Hyaluronan concentration and molecular mass in psoriatic arthritis: biomarkers of disease severity, resistance to treatment, and outcome. Scand J Rheumatol 2019;48:284–93.

113 Sherlock JP, Joyce-Shaikh B, Turner SP *et al.* IL-23 induces spondyloarthropathy by acting on ROR-γt$^+$ CD3$^+$ CD4$^-$ CD8$^-$ entheseal resident T cells. Nat Med 2012;18:1069–76.

114 Reveille JD. Genetics of spondyloarthritis—beyond the MHC. Nat Rev Rheumatol 2012;8:296–304.

115 Benham H, Rehaume LM, Hasnain SZ *et al.* Interleukin-23 mediates the intestinal response to microbial β-1,3-glucan and the development of spondyloarthritis pathology in SKG mice. Arthritis Rheumatol 2014;66:1755–67.

116 De Wilde K, Martens A, Lambrecht S *et al.* A20 inhibition of STAT1 expression in myeloid cells: a novel endogenous regulatory mechanism preventing development of enthesitis. Ann Rheum Dis 2017;76:585–92.

117 Wagner CL, Visvanathan S, Elashoff M *et al.* Markers of inflammation and bone remodelling associated with improvement in clinical response measures in psoriatic arthritis patients treated with golimumab. Ann Rheum Dis 2013;72:83–8.

118 Pedersen SJ, Hetland ML, Sørensen IJ *et al.* Circulating levels of interleukin-6, vascular endothelial growth factor, YKL-40, matrix metalloproteinase-3, and total aggrecan in spondyloarthritis patients during 3 years of treatment with TNFα inhibitors. Clin Rheumatol 2010;29:1301–9.

119 Schafer PH, Chen P, Fang L, Wang A, Chopra R. The pharmacodynamic impact of apremilast, an oral phosphodiesterase 4 inhibitor, on circulating levels of inflammatory biomarkers in patients with psoriatic arthritis: substudy results from a phase III, randomized, placebo-controlled trial (PALACE 1). J Immunol Res 2015;2015:906349.

120 Ademowo OS, Hernandez B, Collins E *et al.* Discovery and confirmation of a protein biomarker panel with potential to predict response to biological therapy in psoriatic arthritis. Ann Rheum Dis 2016;75:234–41.

121 Van Mens LJJ, Sande MGH, Menegatti S *et al.* Brief report: interleukin-17 blockade with secukinumab in peripheral spondyloarthritis impacts synovial immunopathology without compromising systemic immune responses. Arthritis Rheumatol 2018;70:1994–2002.

122 Visvanathan S, Rahman MU, Keystone E *et al.* Association of serum markers with improvement in clinical response measures after treatment with golimumab in patients with active rheumatoid arthritis despite receiving methotrexate: results from the GO-FORWARD study. Arthritis Res Ther 2010;12:R211.

123 Xu M, Deng J, Xu K *et al.* In-depth serum proteomics reveals biomarkers of psoriasis severity and response to traditional Chinese medicine. Theranostics 2019;9:2475–88.

124 Coras R, Kavanaugh A, Boyd T *et al.* Pro- and anti-inflammatory eicosanoids in psoriatic arthritis. Metabolomics 2019;15:65.

125 Collins ES, Butt AQ, Gibson DS *et al.* A clinically based protein discovery strategy to identify potential biomarkers of response to anti-TNF-α treatment of psoriatic arthritis. Proteomics Clin Appl 2016;10:645–62.

126 Cretu D, Liang K, Saraon P *et al.* Quantitative tandem mass-spectrometry of skin tissue reveals putative psoriatic arthritis biomarkers. Clin Proteomics 2015;12:1.