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

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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 it 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

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
Defining and predicting PsA using imaging and biomarkers

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, comorbidities, and drug cost and safety profile. There is little evidence guiding choice 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 entheses (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 enthesal 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 enthesal 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
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.

**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           | X          | X           | X          |
| Skin                          |         |             |            |             | X          |
| Enthesitis                    | X       | X           |            | X           |            |
| Dactylitis                    |         |             |            |             | X          |
| Axial disease                 |         |             |            |             | X          |
| CRP                           | X       | X           |            |             |            |
| HAQ                           |         |             |            |             | 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.).
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].

**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.
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, 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 features of 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].

**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.

**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 utilising 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 (≥18 out of 136) has been shown to have sensitivity (83.3%) and specificity (82.8%) for SpA diagnosis [63].
| PsA phenotype            | Definition as per OMERACT                                      | US                                                                 | MRI                                                                 |
|-------------------------|----------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------|
| Enthesitis dominant     | Hypoechogenicity, increased thickness of tendon insertion,      | Intratendin/infracia hypersignal, peri tendon/perifascia hypoechogenic signal, bone marrow oedema, bursitis, tendon/fascia thickening, enthesophyte and bone erosion [61] |
|                         | calcifications, enthesophytes, erosions and Doppler signal at   |                                                                      |                                                                     |
|                         | the enthesis ≤2 mm near the bony cortex [61]                   |                                                                      |                                                                     |
| PsA/SpA score examples/joints included | MASEI [63]—(6) at, pf, ppt, ppt, pt and tt | HEMRIS [62]: pf and at                                              |                                                                     |
|                         | GUESS [64]—(5) at, pf, ppt, pt                              |                                                                      |                                                                     |
|                         | OMERACT US [65] WG (4) le, at, pt, ppt                       |                                                                      |                                                                     |
|                         | GRAPPA US [66] WG—(6) ppt, dop, at, le, ss and pf            |                                                                      |                                                                     |
| Polyarthritis           | Synovitis: presence of a hypoechoic synovial hypertrophy       | 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 peritendinitis, tendonitis and tendinopathy. |
|                         | 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         |                                                                      |                                                                     |
| PsA score examples; joints included | PsASon13/22 [67]—specific for PsA; hand MCP/PIP/DIP, feet MTP/DIP, large joints and 4 entheses | PsAMRIS [70] MCP/PPIP/DIP joints on the 2nd to 5th fingers         |                                                                     |
|                         | 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   |                                                                      |                                                                     |
| Axial dominant          | Activity changes—bone marrow oedema, capsulitis, joint space  | Structural damage changes—erosion, fat lesion, fat metaplasia in an erosion cavity, sclerosis, ankylosis and non-bridging bone bud |                                                                     |
|                         | enhancement, inflammation at an erosion, enthesitis, joint    |                                                                      |                                                                     |
|                         | space fluid                                                  |                                                                      |                                                                     |
| SpA spine and SI joint score examples | N/A                                                           | SPARCC MRI index [72], Berlin MRI score [73]                          |                                                                     |
Studies have been performed assessing TNFi, DMARD or NSAID response on US enthesitis in SpA \[82–90\]. These have shown US enthesal 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 enthesal 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, enthesal 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,
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 TNF-α, 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               | ≤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       | APOC3, ENRAGE, IL-16, VEGF, PYD, MMP-3, MPO CRP, CEA, ICAM1, MP1A |
| Wagner et al. 2013 [117] | 100          | GOL vs PBO         | 4 and 14 weeks | Serum                | IL-8, TNF-α, IL-6, MIP-1β, MCP-1, ferritin IL-17, IL-23, IL-10 and IL-1 receptor antagonists |
| Schafer et al. 2015 [119] | 150          | APLT vs PBO        | 24 and 40 weeks | Serum                | Novel and significant out of 57-S100-A8, IGKC, HP, ANAX2, COL1A2, PRELP, COF1, FGA, KER and F13A |
| Ademowo et al. [120]   | 18 (Discovery) and 7 (Validation) | ABT and ADA | 6 months | Synovial tissue | MMP-3, IL-17A, CRP |
| 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 opportunite 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.

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**Data availability statement**

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

**Supplementary data**

Supplementary data are available at Rheumatology online.

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