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Perspective

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# Delineating inflammatory from non-inflammatory mechanisms for therapy optimization in psoriatic arthritis

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## Abstract

Psoriatic arthritis (PsA) is anatomically much more heterogeneous than rheumatoid arthritis, as, beyond synovitis, it often also involves enthesitis, peritendinitis, tenosynovitis, osteitis and periostitis. This heterogeneity currently precludes a gold standard for objectively defining resolution of inflammation following treatment, with enthesitis posing a particular challenge. Despite these difficulties, we apply lessons learned from rheumatoid arthritis to describe how patients with PsA and an inadequate response to therapy can be designated within two patient subgroups, characterized by persistent inflammatory PsA (PIPsA) and non-inflammatory PsA (NIPsA), respectively. The NIPsA phenotype is defined by the lack of ongoing joint inflammation, as confirmed through clinical assessment and imaging, along with normalized inflammatory marker levels. NIPsA might be associated with obesity, biomechanical-related pain, osteoarthritis, fibromyalgia, secondary post-inflammatory damage and central pain mechanisms. In this article, we frame PsA composite outcomes measures in relationship to the PIPsA and NIPsA phenotypes and propose that this approach might help to minimize unnecessary or ineffective cycling of PsA therapy in patients who acquire dominant non-inflammatory mechanisms and might also inform future trial design.

## Sections



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## Key points

- For optimal management of patients with psoriatic arthritis (PsA) and an inadequate response to treatment (particularly in cases that are difficult to treat or refractory), we propose two main disease subcategories: persistent inflammatory PsA (PIPsA) and non-inflammatory PsA (NIPsA).
- Despite the complexity of PsA in terms of the structures involved (enthesis, synovium, tendons, para-tendinous soft tissue and bone), the best clinical feature for the routine recognition of genuine inflammatory arthritis is joint swelling (synovitis or dactylitis), which can be confirmed by ultrasonography (PIPsA phenotype).
- In symptomatic patients with persistent pain and high composite scores, but without objective clinical signs of inflammation, the absence of 'active' inflammation on ultrasonography suggests a NIPsA phenotype that is likely to be associated with comorbidities, such as obesity and osteoarthritis; however, distinguishing 'pure' and less common isolated entheseal phenotypes remains challenging for this less common clinical phenotype.
- The exhaustion of therapeutic options define treatment-refractory PsA; however, it is recognized that non-response, as measured by composite outcomes, might involve non-inflammatory components, highlighting the need for imaging.
- Accurate characterization of the PIPsA phenotype will facilitate clinical trials, including combinations of advanced therapies using existing composite outcomes for PsA.

## Introduction

The success of biological disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) in rheumatology for both rheumatoid arthritis (RA) and psoriatic arthritis (PsA) has revolutionized the management and even resulted in dose optimization or tapering strategies as key features in disease management[1,2]. Despite these therapeutic advances, there has been increasing recognition of patients with inflammatory arthritis that is non-responsive or refractory to treatment, initially in RA and later in PsA[3–7].

Patients with RA who have been exposed to multiple DMARDs without apparent benefit are variously designated as having 'difficult-to-treat', 'treatment-resistant' or 'refractory' RA[4,6]. We previously suggested that patients with RA in whom all available classes of drug have failed could be designated as having 'poly-refractory RA', as there are no therapeutic options left[8]. In RA, the 'difficult-to-treat' terminology is the best agreed term and defines individuals with signs of active disease in whom at least two bDMARD or tsDMARD classes have failed following conventional DMARDs[4]. The 'difficult-to-treat' terminology as articulated for RA was also used in PsA, with 'difficult-to-treat' PsA having been suggested to also represent failure of at least one conventional DMARD and two bDMARD or tsDMARD classes[3,9] (Table 1). An attempt has also been made to differentiate 'difficult-to-treat' PsA from 'treatment-resistant' PsA driven by comorbidities (also defined as 'complex-to-manage' PsA, abbreviated to C2M PsA)[9,10]. However, universal agreement on these definitions is still lacking.

In this article, we propose that patients with PsA and an inadequate response to therapy, starting with patients who are unresponsive to conventional DMARDs and extending to individuals with 'difficult-to-treat' PsA and refractory PsA (in whom treatments from all available classes have failed) can be classified into two distinct disease subgroups: a subgroup with a persistent inflammatory PsA (PIPsA) phenotype, which is marked by active joint inflammation (typically clinically manifesting as joint swelling) and confirmed on imaging; and a subgroup with non-inflammatory PsA (NIPsA) phenotype, which is often linked to comorbidities such as obesity and osteoarthritis (OA). In addition, we discuss potential mechanisms underlying these phenotypes, as well as considerations for treatment strategies and trial design.

## Inadequate therapy responses in PsA

A Northern European registry study of over 10,000 patients demonstrated that patients with PsA who received more than four bDMARDs or tsDMARDs — that is, patients representing an approximation for a refractory or near-refractory state — have a very low likelihood of achieving remission as assessed using the Disease Activity in Psoriatic Arthritis (DAPSA) score, with number needed to treat of 63 (ref. 11). In such patients, differentiation between inflammatory (that is PIPsA-associated) and non-inflammatory (that is NIPsA-associated) mechanisms, is vital to prevent futile therapy cycling and ensure optimal PsA management in the real-world setting.

Multiple treatment failures make it essential to identify the underlying mechanisms driving inadequate responses to therapy. Several patients with PsA who are cycling through bDMARDs or tsDMARDs show little objective evidence of joint inflammation. International registries data, observational studies and clinical trials reveal that only 10% to 40% of patients with PsA achieve remission[12–14] despite very low rates of radiographic disease progression. Hence, a failure to differentiate between PsA associated with traceable inflammatory mechanisms (that is, PIPsA) versus PsA where non-inflammatory mechanisms might be in place (that is, NIPsA) might explain why a large population of patients with PsA do not achieve remission or low disease activity. The existing burden of apparent treatment failure in PsA has shifted the focus from Minimal Disease Activity (MDA) or DAPSA remission onto 'Patient Acceptable Symptom State'[15,16], which we propose should be assessed through the perspective of both inflammatory and non-inflammatory mechanisms to optimize treatment strategies. At first glance, our newly suggested term NIPsA might appear to be contradictory, as the term 'arthritis' inherently implies the presence of inflammation. However, chronic inflammatory conditions, including PsA, often progress through an initial inflammatory phase to post-inflammatory phases. The latter may be characterized by secondary OA and joint malalignment, both of which involve pain sensitization mechanisms and are, thus, painful. Differentiating between disease phases presents a clinical challenge, as purely inflammatory or non-inflammatory states are rarely observed, not only in PsA but also in conditions such as RA, and overlapping mechanisms frequently coexist[17].

Outside of rheumatology, similar dynamics between pro-inflammatory and post-inflammatory disease states are observed. For instance, in multiple sclerosis, patients with severe disability are unlikely to respond to therapy if inflammation is no longer active, as evidenced by negative MRI scans[18,19]. Similarly, validated composite outcome measures in PsA, such as DAPSA, Psoriatic Arthritis Disease Activity Score (PASDAS) and MDA, encompass patients with treatment-resistant disease. Such apparent resistance, which emerges from the clinimetric indices, might stem not from active inflammation

**Table 1 | Psoriatic arthritis phenotypes: terms and definitions**

| | |
|---|---|
| **Difficult to treat PsA** (*clinical classification*) | Patients with active disease in whom at least two different lines of biologic or targeted synthetic therapy and at least one conventional DMARD have failed |
| **Refractory PsA** (*clinical classification*) | Failure owing to treatment inefficacy or intolerance, or treatment exclusion based on contraindications, for at least one drug of each advanced therapy (biologic or targeted synthetic DMARDs) licensed for PsA. This criterion applies to patients with active disease as determined by a validated composite outcome measure |
| **Persistent inflammatory PsA** (*clinical and imaging classification*) | Patients with active disease with imaging evidence of ongoing inflammation (based on ultrasonography or MRI), despite undergoing at least one recommended therapy from any single DMARD class (either conventional or biologic and targeted synthetic DMARDs) |
| **Non-inflammatory PsA** (*clinical and imaging classification*) | Patients with active disease without imaging evidence of ongoing inflammation (based on ultrasonography or MRI), despite undergoing at least one recommended therapy from any single DMARD class (either conventional or biologic and targeted synthetic DMARDs) |
| **Active disease** (*clinical classification*) | Ongoing peripheral and/or axial musculoskeletal symptoms. Conventionally characterized by a DAPSA score >14 or an alternative validated outcome measure and ASDAS ≥2.1 for isolated spinal symptoms |

ASDAS, Ankylosing Spondylitis Disease Activity Score; DAPSA score, Disease Activity in Psoriatic Arthritis score; PsA, psoriatic arthritis.

at the time of assessment but rather from the residual damage inflicted by prior inflammation.

To avoid confusion and the implication that such patients with high composite scores are no longer considered to have PsA, it is more accurate to describe the mechanisms driving their symptoms as non-inflammatory or representative of a NIPsA phenotype. This terminology provides a nuanced perspective on their condition, acknowledging its complexity while maintaining the validity of their diagnosis.

## Anatomical challenges in PsA

The heterogeneity of musculoskeletal involvement in PsA, including synovitis, osteitis, enthesitis, peritendinitis and periostitis, complicates the detection and definition of PsA with inadequate response to treatement[20,21]. Isolated axial disease or peripheral enthesitis without adjacent synovio-entheseal involvement are rare manifestations but important to recognize in order to avoid misdiagnoses and inappropriate therapeutic approaches (Fig. 1). Furthermore, it is acknowledged that the persistence of pain and joint tenderness in the absence of joint swelling and of elevated C-reactive protein (CRP) levels are more likely to be reported in PsA than in RA, owing to the entheseal and extracapsular centric inflammation in PsA[22] (Fig. 1). Such PsA cases might represent immunologically driven refractory disease that is difficult to demonstrate objectively[20,23–25]. The pathological variability of the affected tissues, combined with the challenges in assessing enthesitis, makes distinguishing between inflammatory and non-inflammatory mechanisms more challenging than RA (Fig. 1). In particular, the correlation between entheseal tenderness and imaging findings varies according to the studies from poor to suboptimal, hence a gold standard test is lacking[26–28]. However, similar to RA, PsA is most commonly characterized by joint swelling, and the presence or absence of this clinical lesion is also a key parameter for the delineation between inflammatory and non-inflammatory mechanisms in PsA.

## Lessons from refractory RA

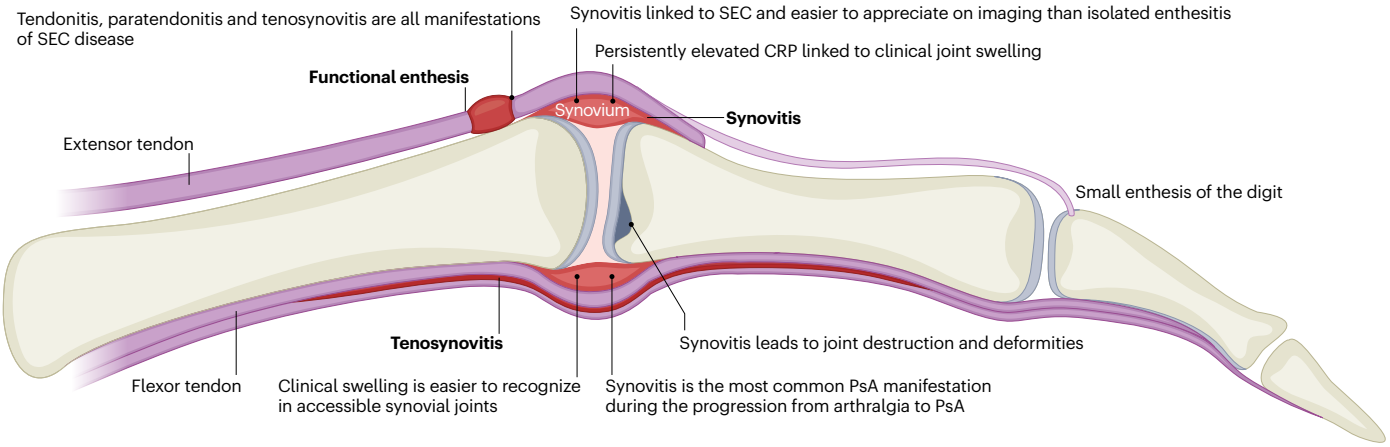
Lessons learned from refractory RA can help to better understand inflammatory mechanisms in PsA patients with inadequate response to therapy. We previously proposed two major subdivisions for the clinical assessment of RA towards switching DMARD class and especially switching across bDMARDs or tsDMARDs: non-inflammatory refractory RA (NIRRA) and persistent inflammatory refractory RA (PIRRA)[8,17]. The NIRRA group, as designated by the absence of ultrasonographic power Doppler changes in clinically swollen joints correlated more strongly with obesity, OA and fibromyalgia, as well as with lower CRP and lower SJC compared with the PIRRA group, with NIRRA representing 40% of total refractory RA cases[8]. The primacy of synovitis and secondary nature of erosion in RA is well established, as is the control of joint inflammation towards structural damage prevention[2,29]. RA-associated synovitis is readily evaluable using ultrasonography in clinically accessible locations and furthermore[30], there is a clear link between synovial inflammation and bone erosion — a key prognostic surrogate in RA.

Compared with RA, erosive disease is less prevalent and disease progression is slower in PsA, with only a subset of patients experiencing substantial radiographic progression[31,32]. However, analogous to RA, baseline radiographic erosive damage, raised CRP levels and persistent synovitis are also major risk factors for PsA progression[31,33–35], underscoring the key importance of synovitis and outcomes in PsA. Damage in PsA also includes post-inflammatory lesions including both juxta-articular and entheseal new bone formation in both the peripheral and axial skeleton[21,36], but at the population level persistent inflammatory disease is mostly readily recognized in relation to joint swelling associated with synovitis.

## Recognizing the PIPsA landscape

PIPsA refers to cases where patients continue to show active disease with clear imaging evidence of ongoing inflammation, such as through ultrasonography or MRI, despite having received at least one recommended therapy from a DMARD class, including conventional, biologic, or targeted synthetic options (Table 1). The temporal concept referenced with 'persistent' in the PIPsA classification is important and refers to a lack of reduction in disease activity by at least 50% within 3 months or not reaching the treatment target within 6 months, in accordance with the treat-to-target approach and the European Alliance of Associations for Rheumatology (EULAR) recommendation on PsA treatment[1].

Both animal studies and human imaging analyses suggest that initial PsA involvement is entheseal and includes the synovio-entheseal complex (SEC) structure, and this explains the focal joint swelling (Fig. 1a) or entire digital swelling (dactylitis)[24,37–40]. Dactylitis encompasses most of the primary lesions of psoriatic finger involvement, ranging from tenosynovitis and subcutaneous edema (also called pseudotenosynovitis), which are characteristic of the acute phases, to articular synovitis and erosions observed in the chronic phases (Fig. 1a). Indeed, apart from the rare pure axial PsA phenotypes or isolated peripheral entheseal phenotypes, persistent swelling is clearly linked to PsA clinical expression, progression joint erosion, destruction and joint deformity (Fig. 1). Accordingly, the concept of NIRRA and PIRRA relating to objective evidence of synovitis in RA may be


a
Tendonitis, paratendonitis and tenosynovitis are all manifestations of SEC disease
Synovitis linked to SEC and easier to appreciate on imaging than isolated enthesitis
Persistently elevated CRP linked to clinical joint swelling
Functional enthesis
Synovium
Synovitis
Extensor tendon
Small enthesis of the digit
Tenosynovitis
Synovitis leads to joint destruction and deformities
Flexor tendon
Clinical swelling is easier to recognize in accessible synovial joints
Synovitis is the most common PsA manifestation during the progression from arthralgia to PsA

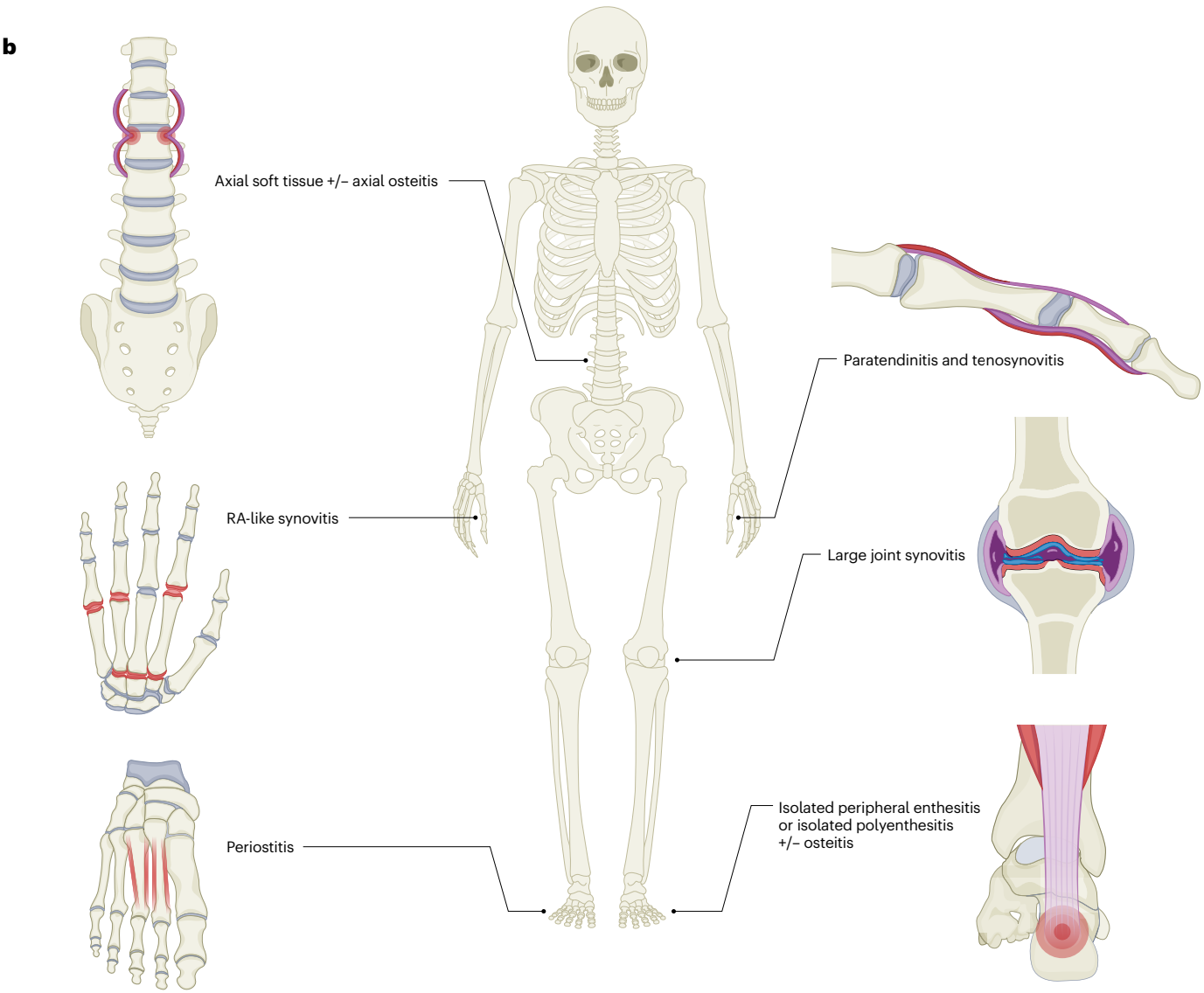

b
Axial soft tissue +/– axial osteitis
Paratendinitis and tenosynovitis
RA-like synovitis
Large joint synovitis
Periostitis
Isolated peripheral enthesitis or isolated polyenthesitis +/– osteitis

**Fig. 1 | The complexity of psoriatic arthritis-related joint disease.** **a**, The central role of synovitis in psoriatic arthritis (PsA) and its various clinical implications are highlighted towards defining imaging and possibly tissue assessment as the gold standard for exclusion of non-inflammatory PsA (NIPsA) phenotypes. Synovitis is the most common manifestation of early PsA in patients with arthralgia follow-up. Synovitis linked with the synovio-entheseal complex (SEC) is easier to detect than enthesitis alone, with synovitis often acting as a 'smoking gun' for other pathology. Clinically, synovitis is easy to recognize owing to visible joint swelling and can be confirmed through imaging techniques. Persistent raised C-reactive protein (CRP) levels in trials, indicating a non-response, are linked to joint swelling. Additionally, synovitis contributes to joint destruction and deformity like those observed in rheumatoid arthritis (RA) and is associated with PsA-related erosion and outcomes. **b**, The pathological tissue heterogeneity of musculoskeletal pathological involvement in PsA-related joint disease, and the associated difficulty in objectively measuring joint target tissues, complicates the detection and definition of refractory PsA. PsA involvements include not only synovitis but also osteitis, enthesitis, peritendinitis, and periostitis of both the peripheral and axial skeleton. At the population level, isolated axial disease and isolated peripheral enthesitis without adjacent synovio-entheseal soft-tissue involvement are uncommon PsA manifestations. Ultrasonography can be used to identify inflammatory changes in all soft-tissue structures that are affected in PsA, including the synovial cavities and bursae, tenosynovial structures and adjacent soft tissues, enabling the diagnosis of PsA with inadequate response to treatment.

broadly applicable to PsA patients with inadequate response to therapy where joint synovitis is often central to the patient outcomes[8]. Hence, most NIPsA and PIPsA phenotypes can be clinically gleaned from joint tenderness and swelling, as documented by ultrasonography (Fig. 2).

Assessing enthesitis, peritendinitis, periostitis and osteitis is comparatively more challenging than evaluating clinical joint swelling that is often associated with joint cavity synovitis and effusion[1,41] (Fig. 1b). When clinically accessible, entheseal structures are, unlike the synovium, relatively avascular and, although painful or tender, might not display ultrasonographic changes. In addition, whereas the association between joint synovitis and structural damage has been well established, especially in RA, the link between the involvement of peri-articular structures (such as peritendinitis), which are commonly seen in PsA, and structural damage is less defined. Results from the phase IIIb ACHILLES randomized controlled trial, where secukinumab for peripheral enthesitis showed statistically significant improvements over the placebo only in the retrocalcaneal bursitis component of the SEC structure, thus highlight the utility of synovitis evaluation in a primary entheseal pathology[42,43]. These findings suggest that the synovial component of the SEC is more responsive to change, which is why we will focus on this SEC component in PIPsA phenotype definitions — even when enthesitis is the specific lesion under evaluation[44–48].

### Importance of objective measurement of joint inflammation

PsA-related oligoarthritis and PsA-polyarthritis (the latter defined by the presence of at least five swollen joints, which is considered a poor prognostic factor according to EULAR recommendations[1]) are readily evaluable in the clinic, and the presence or absence of synovitis or peritendinitis can be easily detected using ultrasonography (Fig. 2). Dactylitis is included in the EULAR recommendations for polyarthritis owing to the presence of synovitis and has a poor prognosis for the association with radiographic damage, especially when more than one finger or toe are affected[1,39].

Compared with joint swelling with evidence of active inflammation on imaging, PIPsA phenotypes with isolated entheseal involvement are substantially more challenging to objectively assess, especially in patients with persistent inflammatory enthesitis symptoms despite treatment[49]. Also, the persistence of pain in a particular enthesis might be related to mechanical enthesopathies or non-inflammatory pain mechanisms triggered after an inflammatory process, or a combination of both[20,24,50,51]. In this scenario, detection of entheseal tenderness during the physical examination would not be sufficient to define a PIPsA phenotype. The same limitation applies to the axial disease, where the inflammatory and non-inflammatory mechanisms are both likely to impact the same patient, sometimes simultaneously. In patients with axial symptomatic PsA, and especially in HLA-B27-negative individuals, MRI is often negative despite the presence of inflammation[52]. Thus, although collectively there might be imaging "blind spots" for the detection of both isolated peripheral entheseal and axial inflammation, joint or digit swelling appearing at physical examination in patients with inadequate response to therapy can still be an indicator of a PIPsA phenotype, hence the suggested focus on swelling that is likely to be linked to SEC disease (Fig. 1).

### Ultrasonography for defining PIPsA and NIPsA

Despite the challenges posed by the heterogeneity of the structures involved, especially when compared with RA, imaging has potentially a key role in defining PIPsA and NIPsA phenotypes. In patients with elevated disease activity scores and joint swelling (which is the best surrogate for joint inflammation in PsA), the presence of 'active' inflammation on ultrasonography should be used for confirming the PIPsA phenotype, especially in doubtful cases, as in the presence of obesity or joint deformities[45,46,53]. In a patient with a confirmed PIPsA phenotype, imaging can also help to identify the specific anatomical site involved (for example, in the case of a mini-enthesitis of the digit)[45,54,55]. In addition, ultrasonography has the potential to detect PsA-independent factors that promote persistent inflammation, such as concomitant crystal arthritis[44,56,57]. In patients with joint tenderness but without any clinical evidence of inflammation, for example, in those with no joint swelling and normal CRP levels[58–62], in whom a NIPsA is suspected, imaging, and particularly ultrasonography, can be used to exclude the presence of SEC inflammation[63]. Furthermore, although isolated enthesitis (that is, enthesitis without joint or tendon manifestations) is uncommon in patients with PsA, the detection of an entheseal power Doppler signal, with or without other indicators of 'active' entheseal inflammation (such as hypoechoic areas or entheseal thickening[47,64]) or structural damage (such as bone erosions) — especially at the Achilles enthesis, might indicate an entheseal PIPsA phenotype. Whereas ultrasonography is an affordable and accessible approach to assessing synovitis in PsA it is still not able to detect peri-entheseal osteitis. Therefore, in patients with ongoing features of inflammatory pain, an MRI scan should be considered for further evaluation if ultrasonography findings are negative.

## Potential pathogenetic mechanisms in PIPsA

The immunopathogenesis of PIPsA is poorly understood, as few studies have so far focused on treatment-refractory PsA. Genome-Wide Association Studies (GWAS), as well as results from translational studies

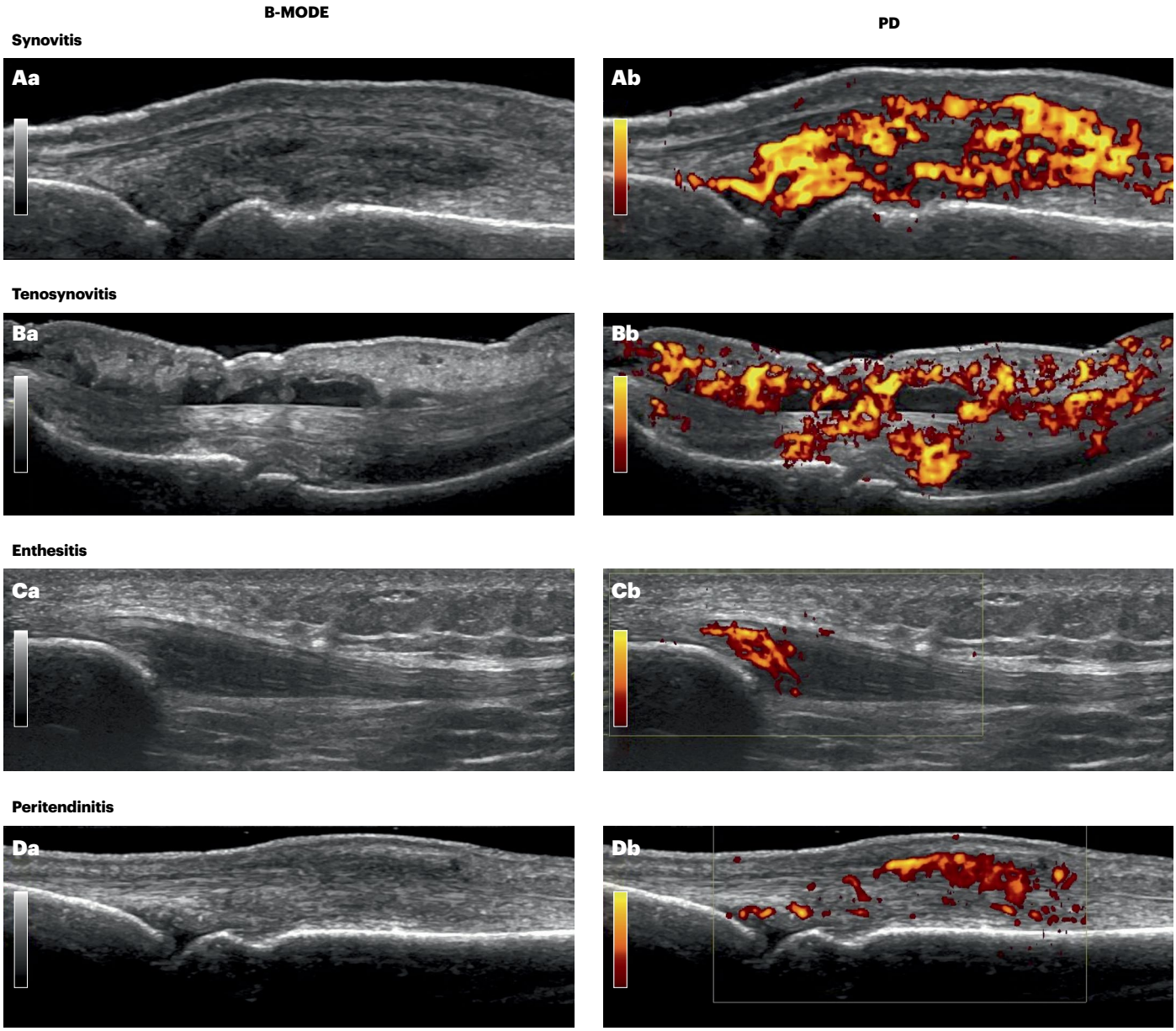



**Fig. 2 | Imaging peripheral inflammation in psoriatic arthritis.** In rheumatoid arthritis (RA), the persistent inflammatory refractory RA (PIRRA) phenotype is based on the presence of joint synovitis, as determined in B-mode, as synovial hypertrophy (Aa) and concomitant power Doppler (PD) changes (Ab). Likewise, in psoriatic arthritis (PsA), synovitis is a central disease component to the persistent inflammatory PsA (PIPsA) phenotype. However, given the synovio-entheseal complex (SEC) centricity of disease, other lesions, including tenosynovitis (Ba and Bb), enthesitis (Ca and Cb) and peritendinitis (Da and Db), should be evaluated in a patient with an inadequate response to therapy.

testing inhibitors of the tumour necrosis factor (TNF), interleukin-23 (IL-23) and IL-17 pathways strongly incriminate the IL-23–IL-17 axis and the NF-κB–TNF pathways in PsA pathogenesis[65], but there are very limited data on the contribution of these pathways to treatment-refractory disease. Also, the MHC-1 associations beyond HLA-B27 in PsA, as well as mechanistic studies using patient-derived samples or humanized mouse models of PsA all point to a key role for $CD8^+$ T cells and their associated cytokines[66–68].

As the PIPsA phenotype is likely to arise in patients previously exposed to TNF, IL-17 or IL-23 inhibition, and in cases where drug compliance and the absence of neutralizing antibodies are confirmed, genetic associations might help to explain PIPsA immunopathogenesis. In fact, genetic variants affecting many cytokine pathways including those downstream of IL-1, IL-4 or IL-13 and IL-6 have emerged from GWAS[69]. The reverse translational immunology studies investigating a role for these cytokines in refractory PsA are rudimentary, but

case series of refractory PsA responding to IL-6 inhibition have been reported[70]. Furthermore, the use of IL-4- or IL-13-blocking strategies for eczema is associated with the development of both psoriasis and PsA, implicating type 2 cytokine dysregulation in the induction of PsA[71]. GWAS have also linked genetic variants of the type 1 interferon and JAK–STAT pathways with PsA. Accordingly, it will be interesting to see how many patients in whom JAK pathway inhibition has failed have a PIPsA phenotype. Other potential molecular mechanisms leading to PIPsA might include rare monogenic forms of PsA, especially in younger patients, epigenetic modifications and somatic mutations, but this is largely speculative owing to the paucity of data. Synovial biopsies from patients with a defined PIPsA phenotype might help to dissect the immunopathogenesis of non-response to two or more classes of therapy in PsA[72,73].

### Potential mechanisms in NIPsA

Evidence supporting the concept that the NIPsA phenotype is common comes from evaluations of patients with PsA 12 months after initiating a first anti-TNF therapy, which showed that almost 40% reported unacceptable pain and that nearly two-thirds of this remaining pain load was attributed to a pain pattern indicative of a non-inflammatory mechanism (defined as refractory pain in that study)[74]. The refractory pain was defined as a combination of pain of >40 mm on the visual analogue scale, a CRP value of below 10 mg/l and fewer than one swollen joint[74]. More swollen joints and higher global assessment at the start of anti-TNF therapy were associated with a significantly lower risk of 12-month refractory pain, suggesting that patients with higher initial inflammation might be less prone to present with unresolved pain indicative of a non-inflammatory mechanism later on[75].

One of the most interesting research areas in difficult-to-treat or refractory PsA, as defined by composite outcome measures, is the exploration of pain persistence mechanisms that are not directly mediated by active inflammation. The International Association for the Study of Pain has developed definitions for three general categories of pain: nociceptive, neuropathic and nociplastic[76]. These types of pain can occur simultaneously, increasing both the severity and the interference of the overall pain experience[77]. In patients with NIPsA, persistence of disease activity assessed using traditional composite scores is likely to be mediated by nociplastic and neuropathic pain mechanisms, rather than nociceptive mechanisms[78]. Accurately and reliably characterizing these complex types of pain is crucial for customizing appropriate treatment strategies and enhancing patient outcomes. Even when inflammation is clinically controlled, patients with chronic arthritis still experience pain and this residual pain appears to be more pronounced in PsA than in RA[79].

In patients with a NIPsA phenotype it is also important to exclude any recurrent, short-duration, inflammatory flares that have subsided prior to clinical assessment, as these might warrant therapy switching. Using a statistical methodology known as mediation analysis, various DMARDs have been assessed for pain reduction resulting from inflammation and neuroinflammation control versus a direct pain-relieving effect, as some DMARDs might act directly on the nervous system as neuromodulatory agents[77,80].

Local and systemic inflammation might contribute to nociplastic pain, and detecting systemic inflammation can be challenging, especially in PsA, where systemic inflammation levels are frequently low[81]. Neuroinflammation has been associated with a specific inflammatory pattern in PsA, that involves IL-23 and IL-17 signalling, the JAK–STAT pathway, TNF and IL-6 cytokines, although the field is still rudimentary compared with knowledge about central pain mechanisms and how these impact neural connectivity in RA[81]. Disentangling the NIPsA phenotype will also facilitate research into how pro-inflammatory cytokines might contribute to pain via neuropathic pain mechanisms in nerves and dorsal root ganglia and also in nociplastic pain mechanisms in the central nervous system.

## Composite outcomes through the NIPsA and PIPsA lens

Contemporary composite outcomes represent the mainstay of disease activity and response assessment in PsA and mainly include DAPSA, Disease Activity Score 28 and MDA[82–84] (Fig. 3). There are important variations in the frequency of remission status according to the definition used, varying between 13.1% (very low disease activity) to 42.1% (Disease Activity Score 28), depending on the score used, and this indicates that achieving remission in PsA might be unattainable for many patients[12]. There has been a shift towards a more patient-centred disease perspective with increased adoption of patient-reported outcomes[85]. Given the multifaceted nature of pain in chronic PsA, we believe that a more formal differentiation between PIPsA and NIPsA components might not only benefit patients, but also help physicians and the pharmaceutical industry to better charter novel therapy development courses. We propose that the non-inflammatory and persistent inflammatory aspects of PsA composite outcomes can be set out along a continuum of inflammatory to non-inflammatory features and a dissociation between these features will help to quickly delineate PIPsA or NIPsA phenotypes (Fig. 3).

In composite PsA indices, pain has a substantial impact on the total score as, for example, in MDA, 3 out of 7 components are patient-reported outcomes (pain visual analogue scale, patient global assessment and health assessment questionnaire), 2 out of 7 components are related to tenderness in joints and entheses, although not necessarily indicating inflammation, and only two MDA components are associated with objective signs of inflammation (PASI and swollen joints). The proportion of subjective measures in those scores partly explains discrepancies in reported responses to bDMARDs or tsDMARDs, where a PASI90 response is generally expected in over 80% of treated patients with psoriasis[86], whereas an MDA response is expected in only 30–40% of patients treated for PsA[29,87] (Fig. 3). This disparity certainly reflects the complexity of PsA, with possible involvement of multiple domains (joints, entheses, axial), but failure to achieve MDA might be mediated independently of PsA-driven inflammation with a strong NIPsA component. Thus, the persistence of inflammation in a patient with PsA showing inadequate response to therapy ideally requires investigation of the inflammation in all potential domains, before concluding by classifying them under a NIPsA phenotype.

With respect to enthesitis, a high number of tender entheseal points, is more suggestive of widespread pain syndromes than genuine inflammatory disease[58,59,88]. Improvement in SJC and CRP values, for example, alongside dramatic concurrent improvements in other composite outcome measure components, attests to the utility of composite outcome measures in capturing excellent clinical responses. By contrast improvement in joint swelling, psoriasis and CRP but not composite outcome measure components is more likely to indicate a NIPsA phenotype (Fig. 3). Accordingly, we propose that a focus on the NIPsA and PIPsA phenotype with objective measurement of the most measurable PsA lesion, that is, synovitis, is key to avoiding futile or erroneous switching of therapy and for dissecting disease mechanisms (Fig. 3).

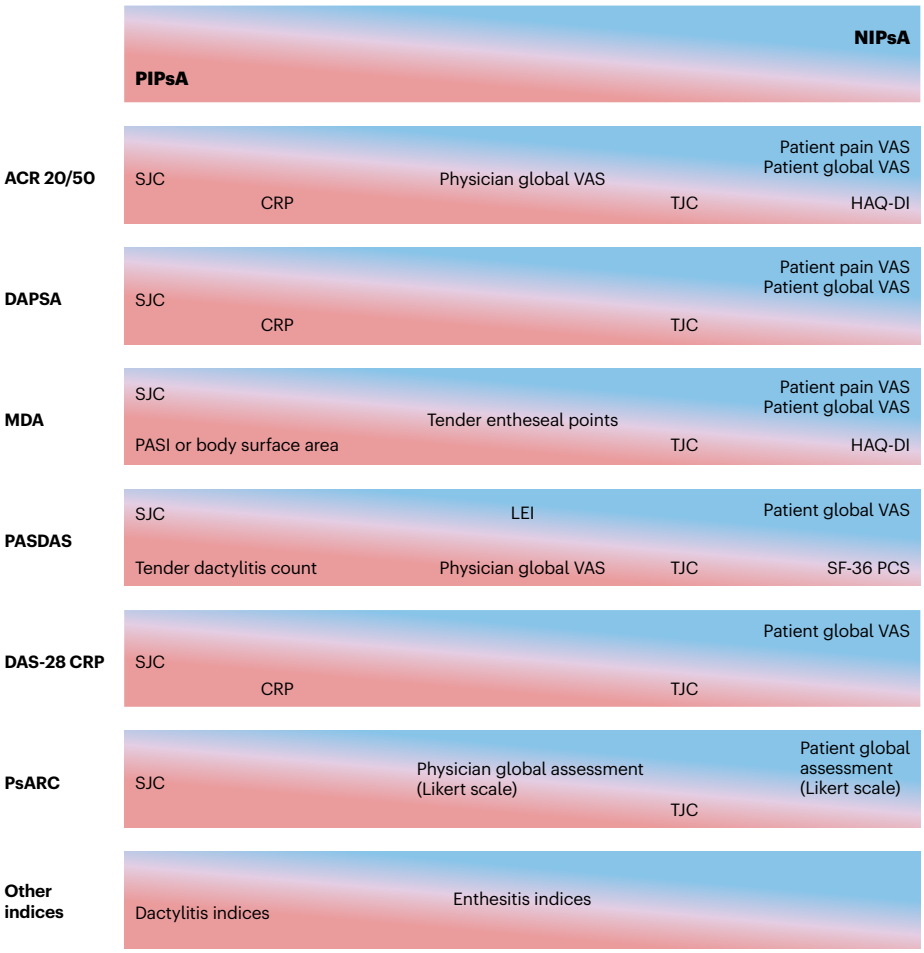



**Fig. 3 | Evaluating psoriatic arthritis through the perspective of composite outcomes.** Psoriatic arthritis (PsA) is a clinically defined multidomain disease, typically assessed using composite outcomes. Some composite outcome components might strongly align with non-inflammatory PsA (NIPsA) and others with persistent inflammatory PsA (PIPsA) phenotypes. Common composite outcome measures, including American College of Rheumatology 20 (ACR20)[123] and ACR50 (ref. 123), are used in clinical trials. In addition, Disease Activity in Psoriatic Arthritis (DAPSA) score[124], minimal disease activity (MDA)[82], Psoriatic Arthritis Disease Activity Score (PASDAS)[125], Disease Activity Score 28 (DAS28)[126] and Psoriatic Arthritis Response Criteria (PsARC)[127,128] are also used regularly in the clinic. Here, we display how certain domains, including swollen joint count (SJC), dactylitis resolution, C-reactive protein (CRP) and Psoriasis Area Severity Index (PASI), are strongly aligned with PIPsA immune mechanisms, whereas other domains, including patient visual analogue scale (VAS) pain and global assessment, are aligned more closely with NIPsA and are likely to inflate composite outcomes via the non-inflammatory component of the disease. Unfortunately, outcome domains, such as enthesitis, or the cardinal lesion, are difficult to measure objectively and align more closely with the NIPsA rather than the PIPsA concept. Isolated high patient-reported outcome measures with resolution of joint swelling, CRP normalization (if elevated initially) and substantial skin improvement or clearance point towards NIPsA mechanisms. HAQ-DI, Health Assessment Questionnaire-Disability Index; SF-36 PCS, Short Form 36 Physical Component Summary; TJC, tender joint count.

## Comorbidity factors in refractory PsA

Various comorbidities, including obesity, depression, fibromyalgia and concomitant or secondary post-inflammatory OA, might affect the development of NIPsA phenotypes and thus contribute to reduced PsA therapy responses and an apparent refractory PsA phenotype[5,10,89]. The link between obesity and persistent inflammatory or non-inflammatory phenotypes might be much more complex in PsA than in RA, as obesity is a risk factor for PsA development[90,91], with weight loss being associated with non-progression to PsA and with improved efficacy of biological therapy[92]. Furthermore, obesity is linked to an increased rate of subclinical entheseal sonographic abnormalities in healthy people, thus complicating the interpretation of imaging in PsA[20,27,93]. In addition, increased skeletal stress in obesity might also contribute to the Koebner phenomenon, biomechanical-related pain, or physical stress-related enthesitis, which is well described in animal models[20,94]. Thus, mechanical enthesopathies in obesity and inflammatory enthesitis pose a particular challenge in defining immune or non-immune disease mechanisms, with the likelihood of both mechanisms being integrated or overlapping. In terms of comorbidity, such as obesity, PsA sits at the boundary between inflammatory and metabolic rheumatism with the frequent co-occurrence of gout[95]. In patients with PIPsA, the presence of monosodium urate crystals might promote the persistence of synovial inflammation through mechanisms that differ from those observed in PsA[95]. Concomitant gout or calcium pyrophosphate deposition disease might also contribute to refractory RA, especially in seronegative disease[96,97]. Concomitant gout should be evaluated in the PIPsA phenotype and treated with urate-lowering therapy if confirmed or suspected.

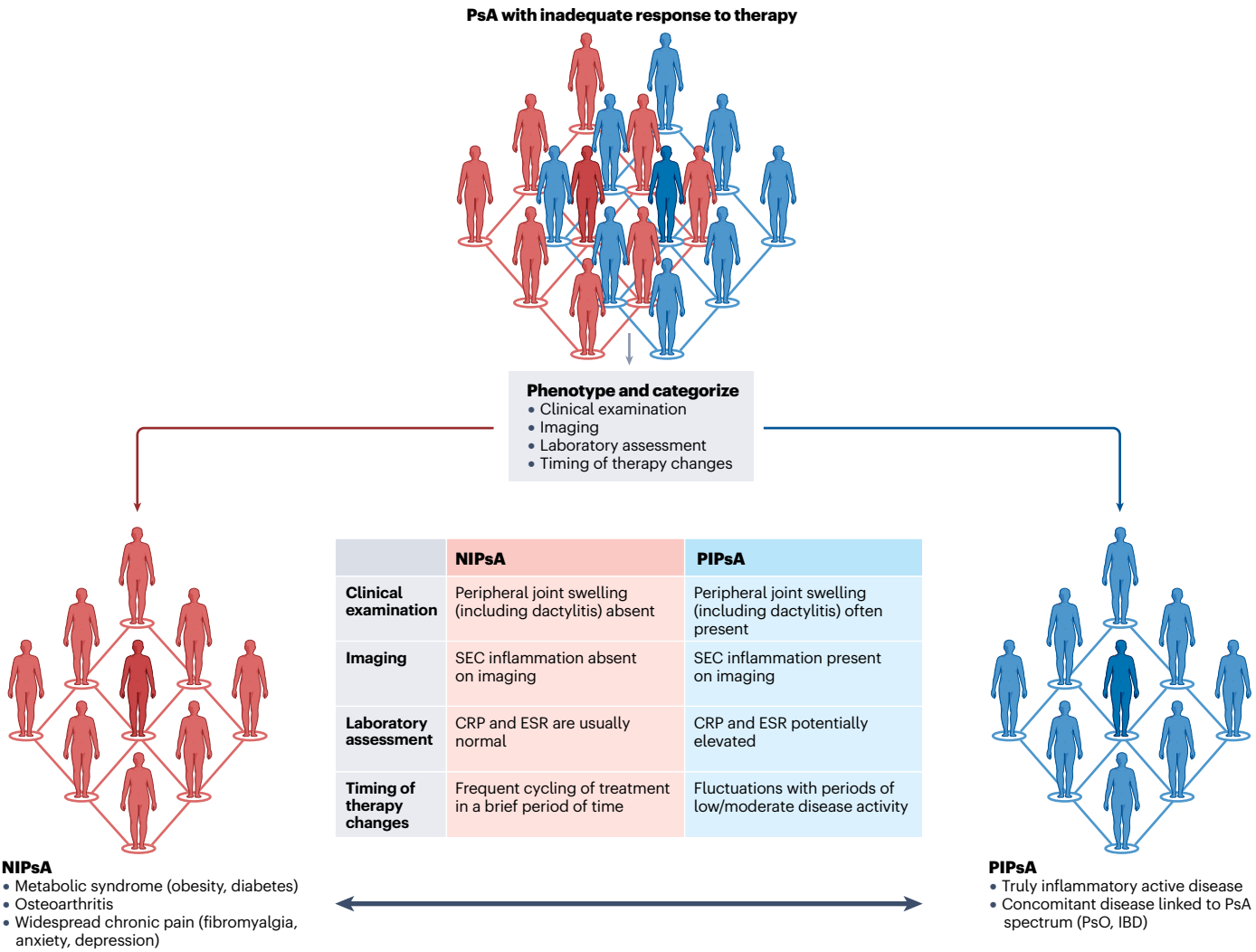
## Other considerations on NIPsA and PIPsA

The lack of a "gold-standard" histological confirmation, tissue inaccessibility, difficulty visualizing painful entheseal structures and the usually modest inflammatory responses make the differentiation between a persistent inflammatory and a non-inflammatory phenotype more challenging in PsA than in RA. Also, some manifestations of PsA, such as axial disease, show a disconnect between symptoms and imaging, as asymptomatic new bone formation is sometimes detected. Clearly, such silent lesions do not warrant therapy unless it is considered that there is a risk of inflammation-driven extensive spinal fusion, something that has not been addressed to date. Not being able to objectively distinguish NIPsA from PIPsA mechanisms in such cases thus shifts the option more towards drug cycling or a trial of therapy to support a PIPsA phenotype.

### Treating PsA with extra-articular inflammatory manifestations

Patients with PsA often have extra-articular inflammatory manifestations, including anterior uveitis, inflammatory bowel disease (IBD) and psoriasis, and therapy selection for PsA is usually based on ability to treat these associated extra-articular manifestations, if present[41,87,98–100]. However, the coexistence of articular and extra-articular involvement is certainly an element that might complicate treatment and promote a PIPsA pattern (Fig. 4) or limit therapy options, for example, in the case of patients with PsA and IBD, where the IL-17 inhibitor should be avoided[101,102]. An asynchronous response, when, for example, cutaneous involvement but not joint involvement might respond to treatment, or the persistence of activity at the extra-articular level, as in the case of IBD, can contribute to the persistence of disease activity at the articular level and impact patients' function and quality of life, even in the absence of joint disease[85,103].

Although RA is associated with some extra-articular or extra-synovial features that might render disease more 'complex to manage', we did not find these to be major considerations in our refractory RA cohort[8]. Other non-articular features, including interstitial lung disease[104,105] and vasculitis[106], might contribute to difficult-to-treat RA, but in our cohort of 1600 patients on biologic drugs these were relatively uncommon[8]. The term C2M-PsA, emphasizing the potential influence of comorbidities in influencing disease treatment and outcomes, has recently been introduced for PsA but this did not include any criteria for stratification into inflammatory and non-inflammatory




| | NIPsA | PIPsA |
|---|---|---|
| **Clinical examination** | Peripheral joint swelling (including dactylitis) absent | Peripheral joint swelling (including dactylitis) often present |
| **Imaging** | SEC inflammation absent on imaging | SEC inflammation present on imaging |
| **Laboratory assessment** | CRP and ESR are usually normal | CRP and ESR potentially elevated |
| **Timing of therapy changes** | Frequent cycling of treatment in a brief period of time | Fluctuations with periods of low/moderate disease activity |

**Fig. 4 | Stratification of patients with psoriatic arthritis who respond inadequately to therapy.** This figure illustrates the categorization of psoriatic arthritis (PsA) into two distinct phenotypes: non-inflammatory PsA (NIPsA) and persistent inflammatory PsA (PIPsA). Patients with PsA can be classified into one of these two phenotypes based on their clinical features, imaging features, timing of treatment responses and laboratory examinations. Patients with NIPsA do not exhibit objective inflammation but have other conditions contributing to their symptoms, such as osteoarthritis and fibromyalgia. These patients often have obesity or diabetes as well. By contrast, PIPsA is defined by continuous objective inflammatory activity including joint swelling, raised C-reactive protein (CRP) levels and imaging abnormalities indicative of active disease. The figure highlights the main features and differences between these two phenotypes, showing that although they are distinct, they can be interchangeable over time in a single patient, as their conditions evolve. ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; PsO, psoriasis; SEC, synovio-entheseal complex.

mechanisms[9,107]. Given the relative safety of the IL-23 and IL-17 targeting monoclonal antibody therapies, management is potentially more straightforward in complex cases.

In RA, the presence of OA is unsurprisingly associated with a NIRRA phenotype[8]. However, the influence of OA on refractory PsA phenotypes might be much more complex, as some forms of OA and PsA share similar features, including distal interphalangeal joint and cervical spine involvement that can complicate both diagnosis evaluation of the response to therapy[108,109]. The processes of joint degeneration and remodelling, which are typical of OA, and of inflammation, which is usually linked to PsA, are often considered to be distinct; nevertheless, the psoriatic phenotype might influence the underlying OA, making it more inflammatory in nature and responsive to systemic treatment, especially in the early, inflammatory, disease phase. This opens up the possibility that OA as a comorbidity might frequently promote a NIPsA phenotype[110,111] but also generate an initial PIPsA phenotype.

Finally, clinicians need to consider sex-related differences in the context of difficult-to-treat and refractory[112] PsA. Observational studies investigating the effectiveness of bDMARDs consistently report that women have poorer treatment outcomes and lower drug persistence rates than men[113,114], and that this is primarily due to higher levels of pain, fatigue and worse quality of life. By contrast, men with PsA often exhibit more severe radiographic structural damage in both axial and peripheral joints, as well as greater progression of this damage, than women[115,116]. This highlights the necessity of gaining a deeper understanding of the mechanisms behind arthritis pain and how the mechanisms that promote PIPsA and NIPsA may be sex- and gender-related[117,118].

### Implications for clinical trials designs

The selection of patients with a PIPsA phenotype, based on the presence of joint swelling with imaging-confirmed synovitis, is likely to increase the chances of success for any inflammation-targeting interventions, including the combination of bDMARDs and tsDMARDs. Conversely, excluding the NIPsA phenotype from the trial landscape might help to minimize inconsistencies in the next phase of trials in PsA (Fig. 4). Combinations of bDMARDs and tsDMARDs have the potential for improved disease control but are currently underutilized in PsA and in rheumatic and musculoskeletal diseases in general[119–122]. Data from the VEGA trial in IBD suggests that combination therapy with the IL-23 inhibitor guselkumab and the TNF inhibitor golimumab might be more effective for ulcerative colitis than therapy with either drug alone[123]. A similar trial in PsA is comparing guselkumab in combination with golimumab, versus guselkumab or golimumab alone in patients with an inadequate response to TNF inhibitors alone (NCT05071664). Whereas the IBD combination trial includes objective colonoscopic and histological confirmation of intestinal inflammation, the PsA trials lack objective confirmation of joint inflammation. These differences could have disappointing translational consequences. Nevertheless, the preliminary case series in PsA and spondyloarthritis support the use of bDMARD and tsDMARDs in combination or as add-on therapies in disease settings[119,121], and the implementation of a strategy for improved patient stratification might help to deliver promising results.

## Conclusions

In this article, we have pragmatically extrapolated the similarities between 'difficult-to-treat' and refractory RA and PsA, with a focus on synovial and soft-tissue inflammation, and delineate the PIPsA and NIPsA phenotypes for patient stratification. In the absence of reliable serum biomarkers that predict responses to advanced therapies for PsA, we propose a focus on imaging, and particularly the use of ultrasonography, to identify clinically accessible inflamed structures at the peripheral skeleton and disentangle the PIPsA phenotype from the NIPsA phenotype. We next propose that new biological therapy strategies, including combination therapy strategies, should be focussed on patients with a PIPsA phenotype. Ultimately, this will help to optimize use of biological therapy and identify truly refractory PIPsA. Furthermore, a formal focus on the NIPsA phenotypes will facilitate new research avenues in patients without any objectively detectable ongoing inflammation who still experience disabling pain, and this dichotomy will be important for targeting central pain mechanisms.

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A.Z., S.Z.A., A.D.M. and D.M. conceived the main concepts and equally described the newly suggested terminology. A.Z., S.Z.A., P.D., A.D.M. and D.M. contributed to writing. A.Z., A.D.M. and D.M. revised the final version of the manuscript.

## Competing interests
The authors have no competing interests to declare.

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