Review Article

Applying precision medicine to unmet

clinical needs in psoriatic disease

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Abstract

Psoriatic disease is a heterogeneous condition that can affect peripheral and axial joints (arthritis), entheses, skin (psoriasis) and other structures. Over the past decade, considerable advances have been made both in our understanding of the pathogenesis of psoriatic disease (PsD) and in the treatment of its diverse manifestations. However, several major areas of continued unmet need in the care of patients with PsD have been identified. One of these areas is the prediction of poor outcome, notably radiographic outcome in patients with psoriatic arthritis, so that stratified medicine approaches can be taken; another is predicting response to the numerous current and emerging therapies for PsD, so that precision medicine can be applied to rapidly improve clinical outcome and reduce the risk of toxicity. In order to address these needs, novel approaches, including imaging, tissue analysis and the application of proteogenomic technologies, are proposed as methodological solutions that will assist the dissection of the critical immune-metabolic pathways in this complex disease. Learning from advances made in other inflammatory diseases, it is time to address these unmet needs in a multi-centre partnership aimed at improving short-term and long-term outcomes for patients with PsD.

Editor's Summary

In this Review, the authors discuss how new approaches, including imaging, tissue analysis and omics technologies, could be applied to identify patients with a poor prognosis and to predict response to treatment, thus enabling precision medicine and improving outcomes in psoriatic disease.

Key points

- Predicting outcome, in particular radiographic outcome, is a key unmet need in psoriatic arthritis (PsA), but although some individual markers seem promising, none has been validated in large clinical datasets.
- Several new treatments targeting different pathways in PsA have improved outcomes, but many patients have persistent disease; a precision medicine approach to treatment choice is required.
- Deep clinical phenotyping coupled with advances in imaging will help to better categorize patient status, an essential first step in the discovery of predictive biomarkers.
- Molecular phenotyping of well-characterized patients and associated liquid and/or tissue biosamples, is the next required step in trying to address these important areas of unmet need in PsA.

Introduction

Psoriatic disease (PsD) is the umbrella term used to describe the many ways in which a patient with psoriasis can be affected by their condition. Apart from the predominant skin and musculoskeletal features, comorbidities such as metabolic syndrome are very common and patients can have extra-musculoskeletal disease manifestations such as inflammatory bowel disease or uveitis[1]. The concept of PsD is valuable as it transcends the more usual medical specialty-driven approach to the assessment and treatment of patients with cutaneous psoriasis

(PsC) and psoriatic arthritis (PsA). At the same time, the use of the term PsD reinforces the realization that common inflammatory and metabolic pathways can be activated across diverse tissues and cells, including endothelial cells[2] and adipose tissue[3], as well as synovium and skin[4]. Approximately 2% of the UK population are affected by PsC, with 15–25% developing PsA over the course of their lifetime[5, 6]. Patients with PsA have varying prognoses, with radiographic erosions evident in 47% of cases 2 years after diagnosis[7] and 68% of cases 5 years after diagnosis[8]. Up to 40% of patients with PsA develop axial disease[1], and an estimated 5–8% develop the extreme phenotype of psoriatic arthritis mutilans (PAM)[9].

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Despite the many notable advances made in the last three decades that have improved our knowledge of the pathogenesis of PsD and have led to the identification of several novel therapeutic targets and treatments, there remain several areas of unmet need in the care of patients with PsD. These needs have been discussed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)[10, 11] and were also the subject of a 2019 scientific meeting held in Dublin, “New Frontiers in Psoriatic Disease”, which was attended by key opinion leaders in the field of PsD who are actively involved in clinical, translational and/or basic research. The purpose of the Dublin meeting, which importantly also included patients with PsD, was to review the three unmet needs identified by GRAPPA and to explore disruptive solutions, using emerging research techniques and strategies applied through global multi-centre research collaborations, in order to better understand the common inflammatory and metabolic pathways that are activated in PsD. In this Review, we focus on two of these areas of need. The first, which relates only to PsA, is the identification of patients with a poor prognosis as measured by the occurrence and progression of structural damage, thereby justifying earlier intensive treatment. The second is the identification of patients with PsD who will respond to treatment selected from ~~among~~ the numerous available and emerging therapies. These treatments include conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). The third area, the need for the early identification of

patients with PsC who will go on to develop PsA, was the subject of a separate review[12] and so is not discussed in detail here.

Pathobiology of psoriatic disease

The development of PsD occurs as a consequence of the interplay of an individual's phenotype and genotype, environmental triggers such as biomechanical or metabolic stress, local factors according to disease site (such as joints, skin, spine or entheses) and interaction with the innate and adaptive immune response, all of which combine to influence the clinical phenotypes that are observed. In Fig. 1, we propose a model for PsD pathogenesis. Primed antigen-presenting cells at sites such as the skin or enthesis engage with innate lymphoid cells and naive T cells, resulting in the local expansion of both type 1 (T helper 1 (T_H1) and type 1 $CD8^+$ (Tc1) cells) and type 17 (T_H17 and type 17 $CD8^+$ (Tc17) cells). The balance of effector T cell subsets (and stromal cells) at local sites, and the cytokine milieu that ensues, will influence not only the disease phenotype, but also structural outcomes and treatment response. Central to this proposed model is the idea that the interactions between antigen-presenting cells expressing different HLA alleles and/or haplotypes and the associated innate or T cell subsets are of critical importance[13], and could provide a mechanistic framework to address why only some cases of PsD progress to structural (bone) damage and why response to treatment is heterogeneous.

Fig. 1

Model of pathobiology of psoriatic disease according to disease phenotypes.

Distinct clinical phenotypes of psoriatic disease (PsD) occur as a consequence of genetic predisposition, environmental triggers (such as biomechanical or metabolic stress, infections and obesity), and local factors according to disease site (joints, skin, spine or entheses). Amplification of the IL-23–IL-17 axis is initiated via activation of innate cells in the skin, entheses and gastrointestinal tract, ultimately resulting in the expansion of $CD4^+$ and $CD8^+$ T helper 1 (T_H1) and T_H17 cells, which are expanded by IL-23 and IL-12 and produce TNF and IL-17. Different HLA alleles and/or haplotypes, T cell subsets and treatment response profiles are associated with different PsD phenotypes. Synovial-

predominant PsD is associated with *HLA-B*08:01:01*, *HLA-C*07:01:01* and haplotype HLA-B*08:01:01–HLA-C*07:01:01, $CD8^+$ engagement with T_H1 cells and responsiveness to TNF inhibition. Cutaneous-predominant PsD is associated with *HLA-B*57:01* and *HLA-C*06:02*, T_H1 cell-driven and responsive to IL-17 and IL-23 inhibition. Entheseal-predominant with or without axial disease, which is associated with the *HLA-B*27:05:02* allele, involves engagement of both T_H1 and T_H17 cells that produce both TNF and IL-17, and is responsive to TNF and IL-17 inhibition. Psoriatic arthritis mutilans (PAM) likely represents a combination of these host genetic factors and T cell interactions.

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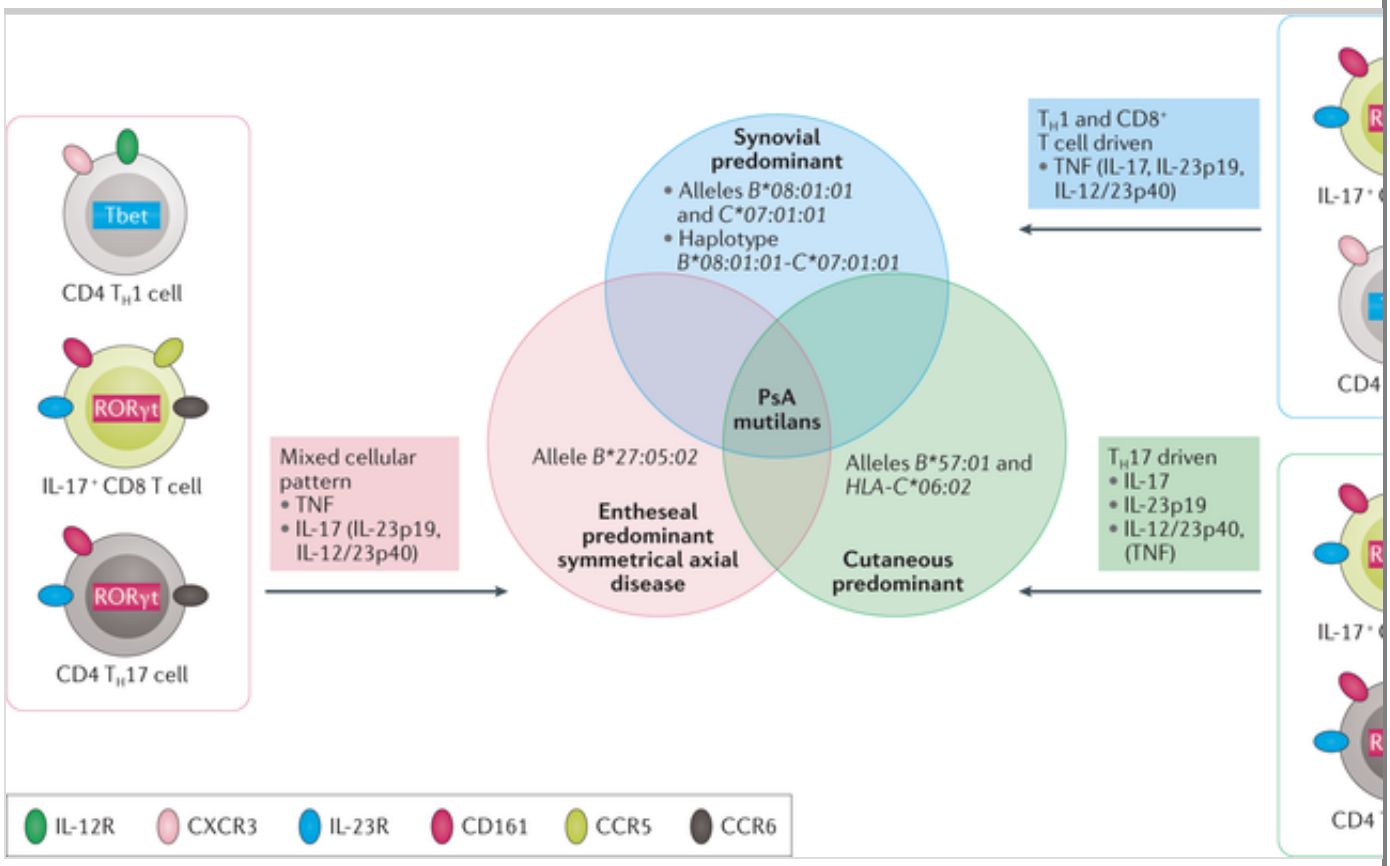


As summarized in Fig. 1, 'cutaneous-predominant PsD' is dominated by $CD8^+$ T cells (expressing the alleles *HLA-B*57:01* and *HLA-C*06:02*) interacting with T_H17 cells that are expanded by IL-23 and produce IL-17, which is reflected in the superiority of IL-17 and IL-23 blockade to TNF inhibition for this PsD phenotype. 'Synovial-predominant PsD' results from the interaction of $CD8^+$ T cells (expressing the alleles *HLA-B*08:01:01* and *HLA-C*07:01:01* and the haplotype *HLA-B*08:01:01–HLA-C*07:01:01*) and T_H1 $CD4^+$ T cell

engagement, resulting in synovitis that is responsive to TNF blockade and also IL-17 inhibition, whereas inhibition of the IL-12–IL-23 p40 subunit is less effective. 'Entheseal-predominant symmetrical axial disease' is propagated by $CD8^+$ T cells (expressing the allele *HLA-B*27:05:02*) engaging a mixed population of T_H1 and T_H17 cells; for this PsD phenotype, therapeutic inhibition of TNF and IL-17 is efficacious, although current data in ankylosing spondylitis (AS) demonstrate that targeting IL-23p19 or IL-12–IL-23p40 might be ineffective in axial disease. PAM, the most severe phenotype of PsD, could be the consequence of interaction between these three cellular pathways and genetic variants.

The mechanism by which specific HLA alleles and/or haplotypes lead to the expansion of type 1 and type 17 cells in PsD has not been fully elucidated, but might be attributable to the preferential presentation of arthritogenic and possibly microbial peptides[14], thus promoting clonal expansion of autoreactive T cells, as has been postulated in JIA[15]. Although previous studies failed to identify such autoreactive cells in PsD, despite marked clonality in the $CD8^+$ T cell population in particular[16], additional studies, perhaps focusing on subpopulations of $CD8^+$ T cells such as synovial IL-17^+CD7^+ tissue-resident memory cells[17], might help to elucidate if autoreactive T cells do indeed exist in PsD. Consistent with our model of PsD pathogenesis presented herein (Fig. 1), the conformational change in the HLA molecule, which results from amino acid changes, might then influence T cell receptor engagement and the downstream cytokine pathways that become activated. By better dissecting these critical pathways, including the coexisting molecular mediators and regulatory factors, we will improve our understanding of PsD pathobiology, in particular in relation to radiographic progression and treatment response.

It is clear that additional, non-HLA genetic variants are also associated with PsD. A 2015 study[18] identified two non-HLA variants more strongly associated with PsA than PsC; the first, rs12044149, was located near *IL23R* (encoding IL-23 receptor) and the second, rs9321623, near *TNFAIP3* (encoding A20). Both of these PsA-specific variants were independent of previously identified PsC-associated variants near *IL23R* and *TNFAIP3*. A 2017 study[19] provided further evidence of genetic differences between PsA and PsC, as an amino acid change resulting in the presence of an asparagine or serine residue at

position 97 of the HLA-B27 molecule increased PsA risk, but not PsC risk.

Unmet need: identifying poor prognosis

Structural damage and clinical outcome

The radiographic features of PsA differ from those observed in rheumatoid arthritis (RA). In PsA, as in RA, articular bone erosion is evident; however, other features are also observed in PsA, including osteoproliferation and osteolysis[1]. Patients with PsA are also prone to systemic trabecular bone loss, resulting in osteoporosis[20]. GRAPPA identified further understanding of the aetiopathogenesis of these joint and bone changes as a priority area of research, as this understanding will support the early identification, prediction and (possibly) prevention of radiographic progression and patients who will have poor and irreversible clinical outcomes[10, 11].

Currently, no cure exists for PsA; and long-term pharmacological and physical therapies are required to slow and/or halt the progression of disease and structural damage[21]. In 2002, the TNF inhibitor etanercept became the first biologic therapy to be licensed by the FDA for PsA[22]. In one study conducted in the pre-biologic era, almost one-third (27%) of patients with early PsA (<2 years since diagnosis) had peripheral radiographic erosion(s) at first presentation, progressing to 47% 2 years later[7]. Of note, although most randomized control trials (RCTs) of biologic therapies for PsA consistently demonstrate inhibition of peripheral joint radiographic progression, a small but noticeable proportion of patients develop marked structural damage, despite receiving biologic therapy. As measured by change in van der Heijde-modified total Sharp score, radiographic progression was noted in 8–15% of patients at 1 year in a study of secukinumab for PsA[23], 5–6% of patients at 48 weeks in a study of etanercept for PsA[24], and 29–39% of patients at 3 years in a study of ixekizumab for PsA[25].

Structural damage is related to poor function and disability, as measured by the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI)[9, 26], which has been shown to translate to increased health care utilization[27]. Levels of work disability and unemployment are high in patients with PsA (16–39% and 20–50%, respectively), and both have been associated with erosive

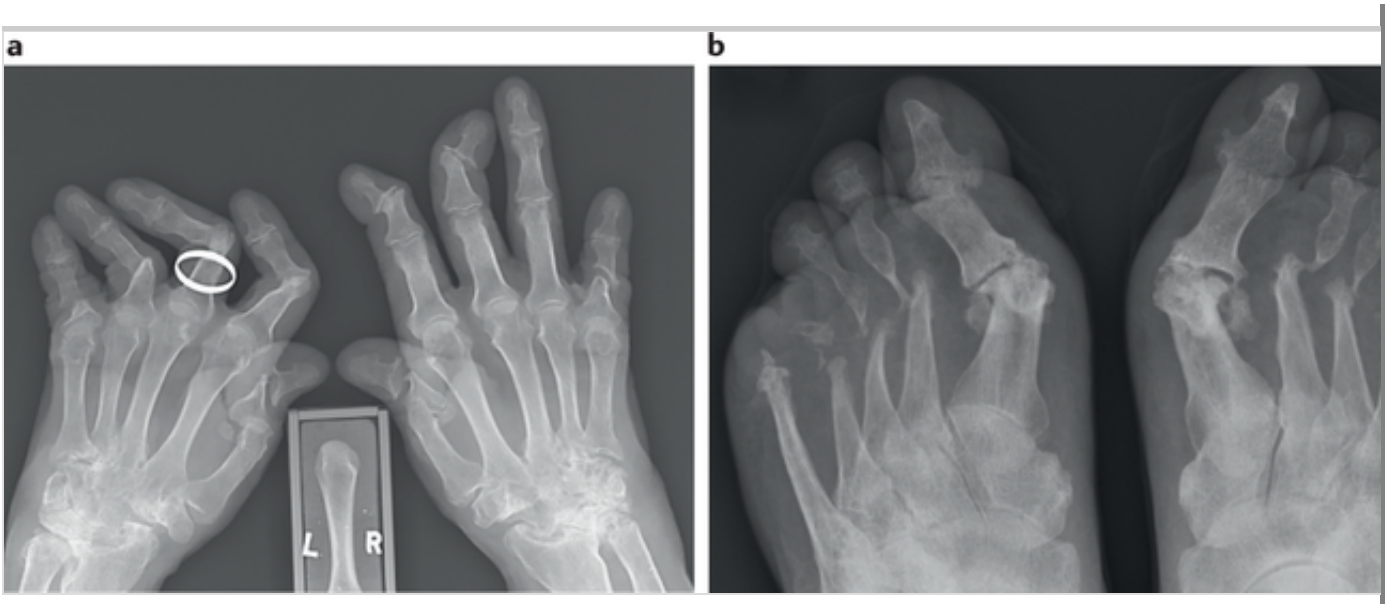
disease[28].

PAM, which exemplifies the extreme phenotype of structural damage observed in PsA, is characterized by severe erosion, osteolysis along the shaft of the phalanx and paradoxical osteoproliferation (Fig. 2), and is frequently associated with axial disease[9]. The identification of genetic and serum-soluble mediators of bone resorption and/or formation might elucidate the pathological mechanisms leading to PAM. However, PAM is difficult to identify and study, owing to its rarity and relatively short period of joint destruction followed by a protracted inactive phase[9]. Studies of PAM to date have been cross-sectional[29, 30, 31, 32, 33, 34, 35, 36, 37, 38], with fewer than 200 cases described in total and only one published longitudinal study[9]. Furthermore, no studies of pathological specimens from patients with PAM have been published; thus, the pathological differences between bony erosion, osteolysis and osteoproliferation in PAM are poorly understood. A further intriguing phenomenon is the co-occurrence of osteolysis and ankylosis within the same digit, which was evident in 12 of 35 (34%) PAM cases in the aforementioned longitudinal study[9]. Occasionally, osteolysis was seen to progress to joint ankylosis in the same joint, but more frequently joint space narrowing progressed to ankylosis. Within the constraints of its retrospective design, the same study observed that neither csDMARDs nor anti-TNF therapy prevented the onset of PAM[9].

Fig. 2

Structural sequelae of psoriatic arthritis mutilans.

a | Plain radiograph of the hand of a patient with psoriatic arthritis mutilans (PAM), demonstrating osteolysis, erosion and joint-space narrowing, resulting in loss of bone stock, shortened and deformed digits, and the characteristic ‘pencil-in-cup’ deformity affecting both thumbs. **b** | Plain radiograph of a different patient demonstrating PAM of both feet; the pencil-in-cup deformity has affected several toes and several phalanges have been entirely resorbed.



Assessment of structural damage

To date, end points of structural damage in clinical trials have been somewhat crude, relying on patient-reported outcomes, operator-dependent clinical examination and scoring of plain radiographs for assessment. Only in the last 5–10 years have more sophisticated modalities such as MRI and musculoskeletal ultrasonography been incorporated into clinical trials and academic studies, but often only in subsets of patients. Plain radiographs show structural damage once it has happened and is probably irreversible, rather than when the pathological processes are commencing or in progress. By contrast, bone marrow oedema revealed by MRI, soft-tissue hyperaemia visualized by power Doppler ultrasonography, and very early cortical or trabecular bony changes seen with high-resolution CT can indicate early structural changes. Tissue or serum-based molecular markers might be indicative of even earlier pathological activity, predictive of subsequent progression to structural damage and used to evaluate strategies to prevent damage and thus improve clinical outcomes.

In all RCTs showing that biologics (including anti-TNF[39], anti-IL-12–IL-23[40] and anti-IL-17[41, 42] agents) reduce structural progression in PsA, structural progression was measured by scoring plain radiographs. These scores quantify some, but not all, of the following domains to varying degrees: joint space narrowing, erosion, osteoproliferation, ankylosis, osteolysis, osteopaenia and periostitis[43]. Although radiographic scores might be used to demonstrate statistically significant differences between outcomes in active placebo groups

in an RCT, their usefulness is limited by a number of factors. For one, plain radiography has a low sensitivity to change at the individual joint level compared with higher-resolution cross-sectional imaging modalities such as MRI and micro-CT. Also, the high inter-rater and intra-rater variability of radiographic assessments contributes to mathematical noise, which limits statistical analysis, especially in longitudinal multi-centre studies. Perhaps most importantly, and as mentioned above, radiographs provide evidence of past pathological sequelae that are now irreversible, rather than necessarily currently active pathology. Despite these limitations, plain radiographs remain important, as the ability to assess irreversible structural damage is useful in itself. Furthermore, the application of MRI in PsA is yet to be fully validated, especially in terms of longitudinal scoring indices.

Predictors of structural damage

Clinical markers of poor outcome

A delay in the diagnosis of PsA results in a poorer prognosis. Even a 6-month delay from symptom onset to the first rheumatology assessment contributes to the development of peripheral joint erosions (OR 4.25) and poor physical function as measured by HAQ-DI (OR 2.2)[44]. Other factors that are associated with worse physical function include symptom duration of ≥1 year before diagnosis (OR 0.22), age >50 years at diagnosis (OR 0.27), female sex (OR 0.39), smoking (OR 0.23) and a history of anti-tumour necrosis factor (TNF) treatment (OR 0.63)[45]. Digits with dactylitis are also reportedly more likely than those without dactylitis to show radiographic progression (50% versus 38%)[46]. Other predictors of severe peripheral disease in PsA include female sex[45, 47], high concentrations of acute-phase proteins at diagnosis or during the disease course[8, 48, 49], polyarticular disease at presentation[47, 50, 51, 52] and the presence of nail psoriasis[53]. Despite showing promise, these clinical predictors have not been adequately validated and are not considered to be sufficiently discriminatory for use in clinical practice.

Genetic associations with joint damage

Relatively little is known about the genetic predictors of structural damage severity in PsA. Multivariable modelling of a cohort of 292 patients with PsA followed up for 14 years in Canada showed that *HLA-B27* in the presence of

HLA-DR7, and *HLA-DQw3* in the absence of *HLA-DR7*, predicted progression, as defined by the number of damaged joints[50]. In a cohort of 480 patients with PsA in the UK, carrying the *HLA-Cw6–HLA-DRB1*07* haplotype was associated with 41% fewer damaged joints[54], although variants of *HLA-Cw6* and *HLA-DRB1*07* were not independently associated with disease severity. Importantly, the latter finding was replicated for *HLA-Cw0602* in an independent cohort[55].

The presence of peripheral radiographic erosions has been associated with a polymorphism of *IL23R*[56], the *HLA-C*01:02:01* allele[57], the *HLA-B*27:05:02-HLA-C*01:02:01* haplotype[57], the IL-4 receptor gene (*IL4R*) I50V variant[58] and the genes encoding both TNF and lymphotoxin-α (formerly known as TNF-β)[59]. A study comparing 18 cases of PAM with 264 cases of PsA without PAM found a positive association between PAM and *HLA-C*02:02:02* (OR 3.1)[57]. Radiographic joint ankylosis was more likely to occur in patients with PsA carrying variants of *HLA-B*08:01:01*, *HLA-C*07:01:01* or *HLA-B*37:01:01* or the haplotypes *HLA-B*08:01:01–HLA-C*07:01:01* and *HLA-B*37:01:01–HLA-C*06:02:01*. The same study also found evidence that the character and severity of PsA phenotypes are determined at the genotype level[57]. In a larger study of 501 patients with PsA (59 of whom had PAM) in two cohorts, four *HLA* alleles (*B*27:05:02, B*35:01:01, C*06:02:01* and *C*15:02:01*) were independently and positively associated with PAM[60]. *HLA-C*06:02:01* was only associated with PAM when found in the presence of *HLA-B*08:01*, which itself was not associated with PAM. Multivariate regression models showed that when combined, these four alleles collectively accounted for a substantial proportion of the genetic susceptibility to PAM in patients with PsA.

Mediators of bone and cartilage destruction

The interactions between immune and bone cells that contribute to osteoproliferation, osteoporosis and bone and cartilage damage are central to the aetiopathogenesis of PsA, and are targets not only for therapeutic intervention but also for predicting which patients might develop substantial structural damage[61]. Bone remodelling is orchestrated by osteoblasts, osteocytes and osteoclasts, and regulated by hormones, cytokines and locally produced signalling molecules that are influenced by mechanical stimuli

(summarized in Fig. 3).

Fig. 3

Bone remodelling in PsA.

a | Immune bone cell interactions in psoriatic arthritis (PsA). Antigen-presenting cells (APCs; dendritic cells and monocytes), which might be presenting autoantigens, produce IL-23 (supported by IL-1β, IL-6 and TGFβ) to expand T helper 17 (T_H17) cells, and IL-12 to expand T_H1 cells. Pro-inflammatory cytokines increase expression of RANKL by mesenchymal stem cells (MSCs), and RANKL is also produced by activated fibroblast-like synoviocytes (FLS) and T_H17 cells. Increased expression of RANKL, along with macrophage colony-stimulating factor (M-CSF), drives osteoclastogenesis and subsequent bone resorption. Data for the effects of both IL-17 and TNF on osteoblastogenesis are mixed, as both of these cytokines can inhibit Wnt signalling but also inhibit the differentiation of MSCs into osteoblasts. IL-22 released by T_H17 cells is considered to promote osteoblast differentiation. **b** | Feedback loops identified in osteoimmunology of PsA. As summarized in panel **a**, pro-inflammatory cytokines are released by dendritic cells, monocytes and activated T cells, which in turn act on tissue-resident cells such as FLS, chondrocytes, osteocytes and osteoblasts to regulate bone metabolism. RANKL is upregulated (as shown in Fig. 3a) and binds RANK, thus driving osteoclastogenesis and bone resorption. Binding of RANKL to RANK is negatively regulated by osteoprotegerin (OPG), a soluble decoy for RANKL. Dickkopf-1 (Dkk-1) produced by activated FLS is a negative regulator of the Wnt signalling pathway and osteoblastogenesis. Sclerostin, produced by osteocytes, also negatively regulates bone formation. Cytokines and other mediators that positively or negatively influence the osteoimmunology of PsA are also integrated into this feedback loop. CSF-1R, colony-stimulating factor 1 receptor.

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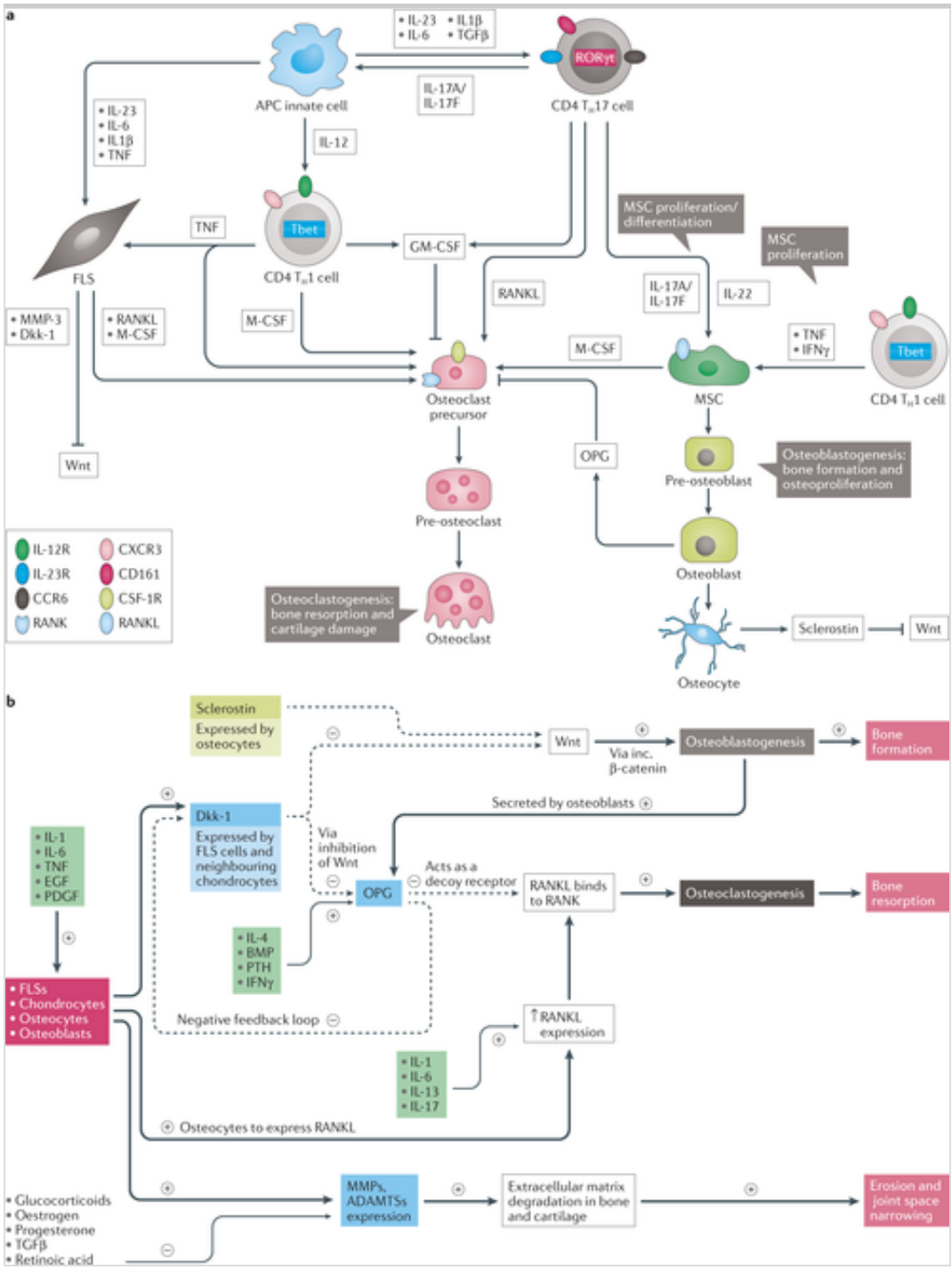


As summarized in Fig. 3a, osteoclasts are derived from haematopoietic stem cells of the monocyte lineage that are stimulated by macrophage colony-stimulating factor (M-CSF; from synovial mesenchymal cells and T_H1 cells), and are under the influence of RANKL signalling. RANKL (also known as TNF ligand superfamily member 11) is expressed in fibroblast-like synoviocytes and activated T cells (especially T_H17 cells) and RANKL levels are increased on mesenchymal stem cells (MSCs) by pro-inflammatory cytokines including IL-1,

IL-6 and TNF (Fig. 3). RANKL expression supports osteoclastogenesis, and inhibition of RANKL (by denosumab) reduces bone loss. Pro-inflammatory cytokines also directly activate osteoclast precursors, thus augmenting bone resorption; this process is negatively regulated by T_H2 cytokines such as IL-4, IL-10 and IL-13 and by T_H1 cytokines including IFN-γ and granulocyte–macrophage colony-stimulating factor (GM–CSF). IL-17 can upregulate RANK expression on osteoclast precursors and osteoclast differentiation; this process is negatively regulated by osteoprotegerin (OPG). The OPG produced by osteoblasts and stromal cells is a soluble decoy for the RANKL expressed in osteoblasts and stromal cells[62]. IL-17A itself can interact with stromal cells and macrophages, further perpetuating IL-1, IL-6 and TNF expression, thus providing a positive feedback loop for osteoclastogenesis. In patients with PsA, IL-17 antagonism has a positive effect on bone loss[41, 63]; a reduction in bone erosions is also seen following TNF inhibition[39, 64, 65, 66].

IL-23 indirectly promotes osteoclastogenesis via its ability to induce T_H17 cell differentiation, and also by inducing RANK expression on osteoclast precursors. Studies have also proposed that IL-23 inhibits osteoclastogenesis by inducing GM–CSF expression in T_H17 cells[67]. The net effect of IL-23, however, is probably influenced by IL-17 and RANKL expression, and PsA inhibition of IL-23 with ustekinumab reduces radiographic progression[40].

Dickkopf-related protein 1 (Dkk-1; produced by fibroblast-like synoviocytes) is a negative regulator of the Wnt signalling pathway that promotes osteoblastogenesis, but its blockade also reduces osteoclast numbers. TNF upregulates Dkk-1 and sclerostin expression, thereby inhibiting the Wnt pathway and thus new bone formation (Fig. 3b). There is compelling evidence that high levels of Dkk-1 expression contribute to the pathogenesis of erosive bone disorders such as PsA[68] and AS[69, 70, 71, 72, 73, 74, 75, 76], and that Dkk-1 is dysfunctional in both AS[69] and PsA[77]. It is possible that impaired binding of Dkk-1 to the Wnt co-receptor LRP6 results in negligible Dkk-1-mediated inhibition of the Wnt signalling pathway, and consequently in excess activity of bone-formation pathways[69]. In a mouse model of inflammatory arthritis, bone erosions in joints (measured by micro-CT and histopathology) resolved following administration of anti-Dkk-1 antibodies, even in the presence of active joint inflammation[78]. From these studies and those in other

models of inflammatory arthritides, Dkk-1 evidently has a dual action regulating both osteoblast and osteoclast function.

Pro-inflammatory cytokines such as IL-1, TNF, IL-6 and IL-17 induce the production of matrix metalloproteinases and aggrecanases (ADAMTS) by chondrocytes, fibroblast-like synoviocytes and neutrophils. These enzymes degrade the extracellular matrix of bone and cartilage, thereby contributing to erosions and joint-space narrowing (Fig. 3). Other serum-soluble proteins associated with radiographic damage in PsA are summarized in Table 1 and detailed extensively in a 2014 systematic review[68]. Notably, the extreme bone and cartilage changes associated with PAM compared with PsA do not seem to correlate with changes in levels of OPG, MMP-3, M-CSF or Dkk-1. However, it is very important to note that these proteins were probably not measured in PAM samples when the disease was in its active, destructive phase[77], illustrating the importance of longitudinal samples.

Table 1

Serum-soluble proteins tested for association with radiographic damage in PsA

Protein	Study design	Association with damage	Outcome measure	Ref.
Bone-related proteins				
OPG	Cross-sectional	OPG was associated with axial radiographic total severity (erosion, osteoproliferation, shiny corners, syndesmophytes, ankylosis) and osteoproliferation severity	PASRI	[77]
	Cross-sectional	OPG was not associated with peripheral radiographic damage (count or erosion) or radiographic sacroiliitis	Peripheral: modified Steinbrocker score. Axial: presence of at least unilateral grade 2 radiographic sacroiliitis	[86]
		MMP-3 was not associated with	Peripheral: modified Steinbrocker	

MMP-3	Cross-sectional	peripheral radiographic damage (count or erosion) or radiographic sacroiliitis	score. Axial: presence of at least unilateral grade 2 radiographic sacroiliitis	[86]
	Cross-sectional	MMP-3 was not associated with axial radiographic total severity (erosion, osteoproliferation, shiny corners, syndesmophytes, ankylosis) or osteoproliferation severity	PASRI	[77]
RANKL	Cross-sectional	RANKL correlated positively with radiographic erosion, joint-space narrowing and osteolysis scores	Sharp van der Heijde score modified for use in PsA. Number of joints in the hands and feet with pencil-in-cup deformities	[87]
	Cross-sectional	RANKL was not associated with peripheral radiographic damage (count or erosion) or radiographic sacroiliitis	Peripheral: modified Steinbrocker score. Axial: presence of at least unilateral grade 2 radiographic sacroiliitis	[86]
M-CSF	Cross-sectional	M-CSF positively correlated with radiographic erosion, joint-space narrowing and osteolysis scores	Sharp van der Heijde score modified for use in PsA. Number of joints in the hands and feet with pencil-in-cup deformities	[87]
	Cross-sectional	M-CSF was not associated with radiographic axial disease severity or osteoproliferation severity	PASRI	[77]
	Cross-	Dkk-1 was not associated with radiographic axial		

Dkk-1	sectional	disease severity or osteoproliferation severity	PASRI	[77]
Collagen-related proteins				
Serum type II collagen	Longitudinal	Serum type II collagen was associated with radiographic progression at 1 year after biologic therapy	Sharp van der Heijde score modified for use in PsA	[188]
	Cross-sectional	Serum type II collagen was not associated with peripheral radiographic damage (count or erosion) or radiographic sacroiliitis	Peripheral: modified Steinbrocker score. Axial: presence of at least unilateral grade 2 radiographic sacroiliitis	[86]
COMP	Cross-sectional	COMP was not associated with peripheral radiographic damage (count or erosion) or radiographic sacroiliitis	Peripheral: modified Steinbrocker score. Axial: presence of at least unilateral grade 2 radiographic sacroiliitis	[86]
Acute phase proteins				
A-SAA	Longitudinal[b]	Baseline levels of A-SAA were independently associated with 1-year radiographic progression	Modified Sharp–van der Heijde score	[189]
Serum calprotectin[a]	Cross-sectional	Serum concentration of calprotectin associated with presence of peripheral radiographic damage	Unknown	[190]
Protein S100-A12	Cross-sectional	Serum concentration of S100-A12 associated with presence of peripheral radiographic damage	Unknown	[190]
		hsCRP measurement	Peripheral: modified	

hsCRP	Cross-sectional	not associated with peripheral radiographic damage (count or erosion) or radiographic sacroiliitis	Steinbrocker score. Axial: presence of at least unilateral grade 2 radiographic sacroiliitis.	[86]
CRP	Longitudinal	Elevated CRP concentration at baseline was a strong independent predictor of radiographic progression	Modified total Sharp score	[49]
	Longitudinal[b]	Serum CRP concentration at baseline was not independently associated with 1-year radiographic progression	Modified Sharp–van der Heijde score	[189]
ESR	Longitudinal[b]	ESR at baseline was not independently associated with 1-year radiographic progression	Modified Sharp–van der Heijde score	[189]

A-SAA, acute-phase serum amyloid A; AS, ankylosing spondylitis; COMP, cartilage oligomeric matrix protein; CRP, C-reactive protein; DKK-1, Dickkopf 1; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity CRP; M-CSF, macrophage colony-stimulating factor; MMP-3, matrix metalloproteinase 3; OPG, osteoprotegerin; PASRI, Psoriatic Arthritis Spondylitis Radiology Index; PsA, psoriatic arthritis; RANKL, receptor activator of nuclear factor-κB ligand; TNFi, TNF inhibitor. [a]Comprises protein S100-A8 and protein S100-A9. [b]Protein measured at 0 and 3 months in patients in whom TNF inhibitor therapy was initiated.

Mediators of new bone formation

AS is the prototypical axial osteoproliferative disease. Axial PsA sits along the same axial osteoproliferative spectrum as, but usually has a lower magnitude of osteoproliferation[1]. Data for the role of IL-17 in osteoblastogenesis and new bone formation are conflicting. Some findings suggest that IL-17A actually downregulates genes of the Wnt pathway, thus suppressing osteoblastogenesis. However, human MSCs express IL-17RA and therefore IL-17 released by T_H17 cells could promote their differentiation to osteoblasts. The stage of

differentiation of osteoblast precursors could therefore determine whether IL-17A and/or IL-17F have a positive or negative effect on osteoblastogenesis. IL-22, produced by a variety of cell subsets including γδ T cells, T_H17, T_H22, T_c17 cells and ILC3, promoted the proliferation and migration of MSCs in in vitro studies[79], and might facilitate differentiation to osteoblasts[80]. By contrast, IL-23 is thought to have little effect on osteoblastogenesis[81].

There are data suggesting both positive and negative effects of TNF on osteoblastogenesis, and these effects can be influenced by the differentiation stage of responding cells (reviewed in Osta et al.[82]). TNF can induce Dkk-1 and sclerostin expression, thus inhibiting the Wnt pathway[78], or activate Smurf and antagonize the bone morphogenic protein 2 (BMP-2) pathway, thereby inhibiting osteoblastogenesis[83]. TNF can also, however, activate NF-κB and increase BMP-2 expression and thus promote osteoblastogenesis[84]. Evidence of the success of TNF antagonism in preventing new bone formation in AS has been derived mainly from observational studies[85], and robust studies quantifying the effect of TNF antagonism on osteoproliferation are not available for PsA.

In a cross-sectional study that included cases of mixed axial and peripheral PsA and peripheral-only PsA, radiographic progression was associated with changes in markers of osteoproliferation. OPG concentrations were lower (OR 0.20 per ng/ml increase) and Dkk-1 concentrations higher (OR 1.22 per ng/ml increase) in mixed axial and peripheral PsA compared with peripheral-only PsA[77]. OPG, Dkk-1, MMP-3 and M-CSF did not correlate significantly with quantitative axial radiographic severity or osteoproliferation severity in PsA[77]. In three other studies, no associations were found between radiographic sacroiliac osteoproliferation (sacroiliitis) and MMP-3, RANKL, OPG, BMP-2, BMP-4, BMP-6, cartilage oligomeric matrix protein or the type II collagen biomarkers C2C, C1-2C or CPII, with results being equivocal for Dkk-1 and M-CSF[86, 87, 88].

A stratified treatment approach based on markers of radiographic progression

Although several candidate biomarkers seem promising, none has yet been validated. The application of new ‘omic’ technologies and the identification, preliminary verification and validation of sensitive and specific biomarkers that

permit the early identification of patients with PsA that is likely to progress radiographically and functionally will represent important progress (as discussed in the section on the application of omic technologies, below). Such progress will provide tailored treatments to finely stratified risk groups within a precision-medicine approach in order to halt or prevent disease progression and disability and to design the optimal protocol for future interventional studies.

Unmet need: personalized treatment

Defining treatment success

Predicting which treatment will be efficacious for an individual patient or disease domain in PsD — that is, a precision medicine approach to treatment — would be extremely valuable for both patients and physicians. Linking patient pathotype to treatment response might also lead to a greater understanding of the disease aetiopathogenesis in an affected individual.

A range of therapeutic options is available for the treatment of PsA, including csDMARDs (such as methotrexate), bDMARDs and most recently tsDMARDs. The bDMARDs include five TNF inhibitors (plus their biosimilar counterparts) and three other classes of drugs targeting the IL-23–IL-17 axis, comprising antibodies blocking the common p40 subunit of IL-12 and IL-23, the p19 subunit of IL-23 and IL-17 or its receptor. tsDMARDs available for the treatment of PsA include phosphodiesterase type 4 (PDE4) inhibitors and Janus kinase (JAK) inhibitors.

In phase III clinical studies for PsA, the primary outcome or treatment success is often defined as achieving the American College of Rheumatology (ACR) criteria for 20% improvement (ACR20 response) at a defined time-point, often with 28-joint disease activity score (DAS28) as a secondary outcome measure. For skin manifestations, treatment success is usually defined as 75% improvement in psoriasis area and severity index score (PASI75 response). For PsA, ACR20 includes assessment of 68 joints for tenderness, 66 for swelling, patient's and physician's global assessment (scored 1–5 on a Likert scale), patient's assessment of pain (1–5 on a Likert scale), patient's HAQ, and C-reactive protein (CRP) concentration. Other indices such as minimal disease activity (MDA) and Disease Activity index for Psoriatic Arthritis have been

recommended as important outcomes in treat-to-target strategies[89]. There are five clinical domains in PsD that need to be taken into account when defining response criteria or even remission: synovitis, enthesitis, dactylitis, axial spondyloarthritis and psoriasis (affecting skin and/or nails)[90]. The challenge faced by researchers is that the factors governing aetiopathogenesis across these domains most likely differ, as well as the timing and completeness of response for each domain. For example, IL-17–IL-23 inhibition is extremely effective in PsC and has modest benefits for synovial and entheseal disease (see recent editorial in Siebert et al.[91]. and data below), whereas in a 2018 study IL-23p19 inhibition was not successful (as measured by ASAS40 response) in axial spondyloarthritis[92]. The GRAPPA Composite Exercise project endeavours to develop new composite measures in PsD and compare them with existing indices[93]; this project should help to define appropriate measures for the purposes of identifying biomarkers of success that could be appropriate for multiple domains of disease.

PsC is highly responsive to therapeutic inhibition of the IL-23–IL-17 axis, with PASI100 (indicating complete clearance) rates of 40–60% being achieved in RCTs. Unfortunately, similar levels of success have not been attained with either bDMARDs or tsDMARDs for musculoskeletal disease in PsA, as >40% of patients do not achieve the primary outcome measure of ACR20 response in RCTs. Approximately 30–40% or even less achieve more stringent responses such as MDA[94]. A comparative effectiveness study of adalimumab (a TNF inhibitor) and secukinumab (an IL-17 inhibitor) in anti-TNF-naive patients with PsA, using data from the FUTURE-2 RCT (secukinumab versus placebo; n = 299) and the ADEPT RCT (adalimumab versus placebo; n = 313), reported higher rates of ACR20 and ACR50 responses with secukinumab treatment than with adalimumab through 1 year[95]. However, the results of the EXCEED study, a head-to-head RCT comparing adalimumab and secukinumab, did not show the superiority of secukinumab over adalimumab for articular measures of PsA[96]. Whilst a head-to-head RCT of ixekizumab (IL-17 inhibitor) and adalimumab in patients with active PsA showed the superiority of ixekizumab over adalimumab for the achievement of a novel hybrid end point (comprising both ACR50 and PASI100 responses), subanalyses showed this outcome to be driven by the skin (PASI100) response, with no significant difference when comparing only articular (ACR50) response[97].

Even though an ACR20 response is achieved by the majority of patients participating in RCTs, many patients can still experience clinically meaningful morbidity, discordant skin and musculoskeletal response, and patients might cycle through a number of therapies before identifying a treatment that works well for them. The following sections provide an overview of predictors of treatment response in PsA and, on the basis of recent achievements in RA, outline future research directions.

Predicting treatment response

Table 2 summarizes genetic, serum-soluble and cellular factors that might be associated with treatment response in PsC and PsA, as measured by PASI for skin manifestations, by DAS28 and ACR20 for joint disease and by the patient-reported outcome measures EuroQol and HAQ-DI. These findings are discussed in more detail in the following section.

Table 2

Biomarkers predictive of treatment response in psoriatic disease

Biomarker	Main findings	Ref.
Genetic markers in PsC		
*HLA-C*06:02*	*HLA-C*06:02*-negative patients were more likely to respond to adalimumab than to ustekinumab, using PASI90 as the outcome measure, in a retrospective, multi-centre study (n = 1,326)	[98]
	Median PASI75 response rate following treatment with ustekinumab was higher in *HLA-C*06:02*-positive patients (92%) than in HLA-C*06:02 negative patients (67%) in a systematic review and meta-analysis (n = 1,048)	[99]
HLA-C	Rs10484554 in *HLA-C* was associated with good response to TNF inhibitors (adalimumab, etanercept, infliximab but no association was found for ustekinumab in a retrospective, single-centre study (n = 250) AQ6	[100]
	HLA-C genotypes were not predictive of response (PASI75) to treatment with etanercept or adalimumab in a retrospective, multi-centre study (n = 138)	[102]
	*HLA-Cw*06* or *HLA-Cw*01–HLA-B*46* status was not associated with PASI50 response to treatment with alefacept, efalizumab, etanercept or ustekinumab in a prospective, single-centre study (n = 102)	[101]

HLA-B/MICA, IL12B, ZNF816A, MAP3K1	Polymorphisms rs13437088 *(HLA-B/MICA*), rs96844 (*MAP3K1*), rs9304742 (*ZNF816A*) and rs2546890 (*IL12B*) were associated with PASI response to etanercept in a prospective, single-centre study ($n = 78$)	[103]
IVL, NFKBIA, ZNF816A, IL12B	Polymorphisms rs6661932 (*IVL*), rs2145623 (*NFKBIA*), rs9304742 (*ZNF816A*) and rs2546890 (*IL12B*) were associated with ASI75 response to adalimumab and infliximab in a prospective, single-centre study ($n = 95$)	[104]
PGLYR4, ZNF816A, CTNNA2, IL12B, MAP3K1, HLA-C	Polymorphisms in *PGLYR4, ZNF816A, CTNNA2, IL12B, MAP3K1* and *HLA-C* were associated with PASI75 response to TNF inhibitors (adalimumab, etanercept, infliximab) in a prospective, single-centre study ($n = 144$)	[105]
10 SNPs	10 SNPs (including rs11096957 in *TLR10)* were associated with PASI response to TNF inhibitors (adalimumab, infliximab) in a prospective, multi-centre study ($n = 65$)	[106]
Genetic markers in PsA		
TNFAIP3	Polymorphism in *TNFAIP3* and association with improvement in arthritis and quality of life following treatment with TNF inhibitors (adalimumab, etanercept, infliximab) in a prospective, single-centre study ($n = 20$)	[107]
TNF, IL6	*TNF*-308 A allele and the *IL6*-174 GG homozygous genotype are independent markers predicting survival of the first TNF inhibitor (adalimumab, etanercept, golimumab, infliximab) in patients with seronegative SpA, assessed using BASDAI and DAS28-EULAR, in a retrospective, multi-centre study ($n = 187$)	[108]
TNF	*TNF* +489 variant allele A was associated with PsA susceptibility, severity of clinical disease (measured by PASI, ACR responses), clinical parameters and responsiveness to etanercept in a prospective, single-centre study ($n = 57$)	[109]
Serum markers in PsC		
CRP	Baseline CRP concentration did not predict PASI75 response to treatment with tofacitinib in a prospective, multi-centre phase III study	[110]
	Reduction in CRP concentration following treatment with adalimumab correlated with percentage reduction in PASI, but baseline CRP concentration did not predict PASI response, in a prospective multi-centre study ($n = 152$)	[111]
hsCRP,	Likelihood of achieving PASI75 was associated with the extent of change in hs-CRP and ESR following etanercept	

fibrinogen, ESR	treatment, but not with baseline hs-CRP and ESR measurements, in a prospective single-centre study (n = 41)	[112]
Serum markers in PsA		
hsCRP	hsCRP value at baseline was a predictive factor of response to golimumab, defined as achievement of minimal disease activity, in a prospective single-centre study (n = 151)	[113]
CRP	Higher CRP and lower disability at baseline were independently associated with good therapeutic response (ACR50) to infliximab in a prospective multi-centre study (n = 69)	[114]
	Concomitant methotrexate and high concentration of CRP at baseline were associated with drug survival in PsA treated with TNF inhibition in a prospective, multi-centre study (n = 261)	[115]
IL-6	Serum IL-6 concentration at baseline did not differentiate between responders and non-responders to treatment with adalimumab, infliximab or ustekinumab, but correlated with DAS28-CRP responses and were lower in patients who achieved remission (DAS28-CRP < 2.3) than in those who did not in a prospective, single-centre study (n = 113) AQ7	[116]
IL-6, VEGF, YKL-40, MMP-3, aggrecan	Plasma concentrations of IL-6, VEGF, YKL-40 and MMP-3 decreased in clinical responders to adalimumab, etanercept and infliximab at 2 weeks, with persistent reductions in IL-6, VEGF, YKL-40 and MMP-3 at 3 years, in a prospective, single-centre study (n = 49)	[117]
MMP-3, COMP	Baseline level of MMP-3 and increase in serum COMP were independently associated with treatment response to adalimumab, etanercept, golimumab and infliximab, classified using SJC, TJC and PASI, in a prospective, single-centre study (n = 40); none of OPG, CPII, C2C, C1-2C, CS-846 or hsCRP were associated with treatment response	[118]
92 serum proteins	Pyridinoline, adiponectin, prostatic acid phosphate and factor VII were identified as a panel of markers with the potential to be predictive of ACR20 response to golimumab in a prospective, multi-centre study (n = 100)	[119]
C3 complement	Elevated levels of C3 at baseline were associated with non-response to adalimumab and etanercept in a prospective, single-centre study (n = 55)	[120]
Tissue markers in PsC		
	IL-20, IL-21 and p40 mRNA expression levels in lesional	

IL-20, IL-21, p40 mRNA	psoriatic skin were upregulated in non-responders compared with responders to ustekinumab in a prospective, single-centre study ($n = 18$)	[121]
MCP-1 protein	MCP-1 levels did not predict response to adalimumab, etanercept or efalizumab, although treatment with TNF inhibitors reduced MCP-1 plasma concentrations and expression in lesional skin, in a prospective, single-centre study ($n = 16$)	[122]
Tissue markers in PsA		
CD3 protein	Change in CD3 expression in the synovial sublining was greater in responders to anakinra or etanercept relative to non-responders in a prospective, single-centre study ($n = 25$); baseline $CD3^+$ T cell number was not predictive of treatment response	[123]
25 proteins	25 proteins were differentially expressed between good and poor responders to TNF inhibitor therapy in a prospective, multi-centre study ($n = 32$)	[124]
57 proteins	A panel of 57 proteins was predictive of response to treatment with adalimumab in a retrospective, single-centre study ($n = 10$)	[125]

ACR, American College of Rheumatology; CRP, C-reactive protein; DAS, disease activity score; hsCRP, high-sensitivity C-reactive protein; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SpA, spondyloarthritis; SJC, swollen joint; SNP, single nucleotide polymorphism; TJC, tender joint.

Factors associated with response

In PsC, three studies have identified an association between *HLA-C*06* status and treatment response. An evaluation of 1,326 patients in a national psoriasis registry revealed that *HLA-C*06:02*-negative patients were more likely to respond (using PASI90 as the outcome measure) to the TNF inhibitor adalimumab than the IL-12–IL-23 inhibitor ustekinumab[98]. Conversely, in a meta-analysis of 1,048 patients who achieved a PASI75 response at 6 months with ustekinumab treatment, 92% of *HLA-C*06:02*-positive patients achieved this outcome compared with 67% of *HLA-C*06:02*-negative patients[99]. In the third study, the rs10484554 polymorphism in *HLA-C* was associated with a good response to TNF inhibition, especially with adalimumab[100]. Other studies, however, have found no association between *HLA-C*06* status and PASI response to etanercept, ustekinumab, efalizumab (CD11a inhibitor) or

alefacept (LFA-3 fusion protein)[101, 102]. For other HLA loci, a polymorphism at rs13437088 (near *HLA-B* and *MICA*) has been associated with response to etanercept at 3 months in patients with moderate to severe psoriasis. Notably, *HLA-C*06* has not been linked with treatment response in PsA.

Non-HLA single-nucleotide polymorphisms (SNPs) have been investigated in PsC, including SNPs in the gene encoding the keratinocyte protein involucrin (*IVL*) (associated with PASI75 response to adalimumab and infliximab), *ZNF816A* (associated with response to adalimumab, infliximab and etanercept), *IL12B* (associated with response to etanercept) and *MAP3K1* (associated with PASI75 response to adalimumab and infliximab)[103, 104]. The same authors further evaluated 173 polymorphisms in 144 patients with moderate to severe psoriasis and showed an association with polymorphisms in *PGLYR4*, *ZNF816A*, *CTNNA2*, *IL12B*, *MAP3K1* and *HLA-C* and the PASI75 response to TNF inhibitor therapy at 3 months, and *IL12B* and *MAP3K1* at 6 months[105]. A genome-wide association study of 731,442 SNPs in 65 Asian patients with PsC (12 of whom had PsA) treated with adalimumab or infliximab found strong associations between treatment response and 10 of the SNPs evaluated[106], none of which were candidates characterized in the aforementioned studies[103, 104, 105]. Several SNPs were closely related to those identified in previous studies as exhibiting a potential association with response to TNF inhibitor therapy, most notably rs726501 and the gene *MAP3K1* (ref.[106]).

In PsA, polymorphisms in *TNFAIP3* have been correlated with an improvement in quality of life (as measured by European Quality of life Visual Analogue Scale (EQ−VAS)) after TNF inhibitor treatment[107]. Other SNPs associated with *TNF* have included the −308A allele, which predicts TNF inhibitor survival[108], and the +489 A allele, associated with responsiveness to etanercept[109]. The homozygous GG genotype of the −174G/C *IL6* promoter polymorphism was also associated with the survival of the first TNF inhibitor in patients with seronegative spondyloarthritis[108].

CRP is the most well-characterized serum predictor of responsiveness to treatment. In several studies CRP correlated with treatment response or bDMARD persistence in PsA, but not in PsC. In PsC, baseline CRP concentrations were not predictive of PASI responses to the JAK inhibitor tofacitinib[110], adalimumab[111] or etanercept[112], although the change in

CRP concentration from baseline did correlate with percentage change in PASI following treatment with adalimumab[111] or etanercept[112]. In PsA, baseline high-sensitivity CRP (hsCRP) measurement was predictive of achieving MDA after 6 months of golimumab treatment[113], and baseline CRP concentration was also associated with response to TNF blockade in two other PsA studies[114, 115]. Evidence for other serum markers is similarly equivocal. Among patients with PsA, baseline serum IL-6 concentrations failed to differentiate responders and non-responders to TNF inhibition as measured by DAS28 with CRP (DAS28-CRP), but were lower in patients who achieved DAS28-CRP <2.3 (ref.[116]). In another study, using DAS28 as the outcome measure, baseline concentrations of IL-6, VEGF and MMP-3 were higher in responders to TNF inhibition than in non-responders[117]. Baseline MMP-3 levels were independently associated with treatment response to TNF inhibition in patients with PsA; however, baseline hsCRP was not associated with response[118]. These studies highlight the challenges of trying to associate a limited number of proteins with response to treatments that target different pathways.

In an attempt to more effectively identify markers of clinical progression or therapeutic response, the GO-REVEAL study[119] examined 92 protein biomarkers in 100 patients with active PsA who were treated with golimumab at baseline, week 4 and week 14. Apolipoprotein C III, ENRAGE (S100A12), IL-16, myeloperoxidase, VEGF, pyridinoline, MMP-3, CRP, carcinoembryonic antigen, ICAM-1 and MIP-1α at baseline or week 4 were strongly associated with ACR20 and/or DAS28 response at week 14. Different combinations of markers including pyridinoline, adiponectin, PAP, factor VII, IL-16, SGOT, IgA and/or leptin were found to be predictive of ACR20, DAS28 or PASI75 response to golimumab treatment[119]. In another study evaluating erythrocyte sedimentation rate, CRP concentration and complement pathway components in patients with PsA, high baseline level of complement C3 was associated with non-response according to EULAR criteria[120].

Obtaining tissue samples in order to define treatment success has less commonly been utilized than blood sampling for a number of reasons, in particular, feasibility. However, two studies examined mRNA or protein expression in lesional skin from patients with PsC. In the first study, comparison of mRNA expression in 10 responders and 5 non-responders to ustekinumab,

IL20, IL21 and *p40* mRNA were upregulated in non-responders at baseline[121]. In the second study, baseline plasma levels of MCP-1 at baseline did not correlate with response to treatment, although levels of MCP-1 in plasma were moderately decreased and in lesional skin were robustly decreased by TNF inhibitor treatment[122].

In PsA, three studies have used synovial tissue analysis to evaluate treatment response. In one study, changes in CD3 expression in the synovial sub-lining layer following treatment with anakinra (an IL-1 receptor antagonist) and etanercept were greater in responders than in non-responders[123]. In another study, proteomic analysis of synovial tissue samples following anti-TNF treatment identified 25 proteins that were differentially expressed between 'good responders' and 'poor responders'[124]. In the third study, a targeted proteomics strategy (using multiple-reaction monitoring mass spectrometry) screened 57 proteins in synovial tissue samples from patients with PsA receiving biologic therapy; combined data from these 57 proteins predicted response to treatment, with a modest area under the curve of 0.76. Some of the predictive proteins included S100-A8, S100-A10, immunoglobulin κ constant, fibrinogen-α and γ, haptoglobin, annexin A1 and A2, collagen α-2, vitronectin and α-1-acid glycoprotein 1 (ref.[125]).

Factors influencing treatment success

Clinical trials of bDMARDs inform us that up to 40% of patients are primary non-responders to different classes of treatment. However, the phenomenon of secondary non-response is also well-recognized in patients with PsA, and up to 30% of patients will discontinue TNF inhibitor therapy at 1 year[126]. In RA, factors known to influence the risk of primary non-response include long disease duration, high disease activity and high BMI[127]. In PsA, a post hoc analysis of patients treated with abatacept revealed that baseline characteristics including CRP concentration, DAS28-CRP score, dactylitis and median number of erosions identified patients for whom abatacept was most likely to be effective[128]. Given the heterogeneity of the inflammatory arthritides, the composition of inflammatory infiltrates at the tissue level will probably be informative for stratifying patients and guiding treatment decisions, and is discussed later in this Review.

When evaluating the efficacy of monoclonal antibody bDMARDs, the structure of the antibody and the target molecule, the dose and dosing schedule, and the rate of receptor-mediated clearance need to be considered. Monitoring drug concentration and the development of anti-drug antibodies (ADAs) is likely to be very important. Traditionally, trough drug concentrations are measured but these measurements do not take into account drug levels in tissue, increased clearance owing to high cytokine burden or receptor loss following repeated dosing. A number of studies have evaluated drug levels and ADAs in the inflammatory arthritides. In a 2019 study, drug levels and ADAs were associated with disease activity in spondyloarthritis and RA, but did not predict response to treatment[129]. Adalimumab drug levels and ADAs have also been associated with change in DAS28 and inversely correlated with HAQ in PsA, with drug levels influenced by BMI[130]. Several studies have shown that low trough levels of TNF inhibitors increase the risk of developing ADAs, infusion reactions and loss of clinical efficacy (reviewed in Kalden and Schulze-Koops[127]) and the concomitant use of methotrexate potentially decreases the risk of developing ADA. In PsA, concomitant use of methotrexate has also proved beneficial in improving TNF inhibitor persistence[131].

Moving to precision medicine for PsD

Lessons learned from rheumatoid arthritis

The challenges associated with addressing unmet needs in PsD are evidently considerable and, in considering solution-driven strategies, evaluating the achievements of stratified medicine approaches being employed to address comparable unmet needs in other rheumatological diseases is perhaps useful. In North America, the Accelerating Medicines Partnership (AMP), involving the NIH, FDA, multiple industry partners and academic centres focusing on RA and systemic lupus erythematosus, has been particularly successful in agreeing and implementing standardized operating procedures for sample collection and storage, and scientific methodology for single-cell transcriptomics and whole-genome sequencing[132]. These developments have been critical to the successful involvement of multiple centres in AMP and, as a result, the output of the programme has been impressive[133, 134, 135], with the ensuing benefits to patients likely to be felt for some time to come. For example, high-dimensional analysis using mass cytometry has been used to identify a new

population of peripheral T helper cells that forms 25% of RA synovial T cells; these cells, which were characterized as PD-1^{hi}CXCR5^{-}CD4^{+}, displayed the ability to infiltrate inflamed tissues and to enhance local B cell antibody production and differentiation into plasma cells[136]. Data obtained from mass cytometry analyses[133] revealed the presence of CD27^{-}HLA-DR^{+} effector memory cells in RA peripheral blood, which were also found to be markedly increased in synovial fluid and tissue, have a T_H1 and cytotoxic profile, produce IFN-γ and granzyme A upon stimulation, and decreased in frequency in patients who responded to immunosuppressive therapy. Furthermore, microfluidic droplet technology and single-cell RNA sequencing (drop-Seq) were used to identify unique fibroblast subpopulations in dis-aggregated RA synovial tissue, thus providing the first 'atlas' of haematopoietic and fibroblast subpopulations from single-cell RNA-seq in autoimmune disease tissue[137]. Additional novel subsets of fibroblasts were identified from bulk transcriptomics of targeted subpopulations and single-cell transcriptomics[138], including a subset of CD34^{-} fibroblasts that were expanded threefold in patients with RA relative to those with osteoarthritis. These cells expressed podoplanin, THY1 and cadherin-11, were localized to the perivascular zone in inflamed synovium, secreted pro-inflammatory cytokines and were proliferative, with phenotypic characteristics of invasive cells. With high expression of RANKL and low expression of OPG, this fibroblast subset was hypothesized to be involved in osteoclastogenesis[138]. Thus, these approaches have identified pathogenic subsets that are increased at the site of disease as targets for immunotherapeutic intervention, enabled the further characterization of the unique pathobiology of RA, and also correlated changes in cellular phenotypes with treatment success.

There are other examples of large consortia exploring stratified medicine approaches in RA, such as Maximizing Therapeutic Utility in Rheumatoid Arthritis (MATURA) in the UK. The Pathobiology of Early Arthritis Cohort (PEAC) dataset forms part of the MATURA dataset, and has dissected gene expression signatures across synovial and blood compartments, and integrated deep phenotypic profiling in blood and synovial tissue[139]. It characterized transcriptional subgroups in synovium that were linked to three distinct pathotypes: pauci-immune, macrophage-rich diffuse-myeloid and lympho-myeloid pathotypes. Using bulk tissue and whole-blood RNA-seq, the authors identified an inflammatory synovial gene signature that correlated with clinical

response to initial drug therapy, and a poor prognosis subgroup with progressive structural damage[139]. The PEAC dataset has demonstrated elegantly the power of using synovial tissue and enabled the identification of high-risk patients. Using similar methodologies, the Stratification of Biologic Therapies for Rheumatoid Arthritis by Pathobiology study should (in future) provide further insights into whether identifying pathotypes proves successful in RA[140].

Current examples of precision medicine in PsA

Currently, few examples of precision medicine approaches in PsA are available. A 2019 study[141] presented the first precision medicine approach to treatment stratification with bDMARDs in PsA, using immunophenotyping of peripheral $CD4^+$ T cells to classify patients into four distinct groups: activated T_H1-dominant; activated T_H17-dominant; activated T_H1/T_H17-high; and activated T_H1/T_H17-low. Markers used in the phenotyping process included the T_H1 cell-associated chemokine receptor CXCR3, CCR6 for T_H17 cells, and HLA-DR and CD38 as markers of T cell activation. Treatment was stratified accordingly: ustekinumab was administered to T_H1-dominant patients; secukinumab to T_H17-dominant patients TNF inhibitors or secukinumab to T_H1/T_H17-high patients with major joint complaints and major skin complaints, respectively; and TNF inhibitors to T_H1/T_H17-low patients. At 6 months, patients treated according to this strategy ($n = 26$) achieved a rate of low disease activity higher than that achieved by patients who received standard treatment with bDMARDs ($n = 38$). Although this study was to our knowledge the first precision medicine study using immunophenotyping in PsA, the sample size was relatively small and participants were not randomized. However, it provides a potential starting point for such precision medicine strategies to be validated in larger cohorts of patients with PsA.

Approaches to addressing unmet needs

In this section we discuss existing and emerging approaches to addressing unmet needs in PsD, primarily identifying patients whose disease will progress and predicting response to treatment. In order to begin to address both heterogeneous radiographic outcomes and treatment responses in PsD, certain principles relating to the research approach need to be considered, which help to

ensure scientific rigour and reproducibility.

First, the scientific hypothesis should be clearly articulated. Without a clear, well-thought-out scientific question, the research approach will be driven in the wrong direction and unfortunately this is often only realized at the end of the process. Second, clinical cohorts need to be exceptionally well defined. Failure to include cohorts with sufficient and rigorous clinical phenotypic data to address the question being asked will either preclude the identification of the required patients (for example, those at risk of damage progression) or lead to inaccurate conclusions being drawn. Third, the definition of damage should take into account the imaging modality used, the reversibility of damage-related findings, the timing of the imaging study used and the known relationship between imaging finding and underlying pathology. Fourth, treatment response and non-response should be appropriately defined. For studies designed to discover signals in particular, it is best to use the most stringent response measure (for example, remission as defined by very low disease activity or Disease Activity index for Psoriatic Arthritis remission criteria)[142] to identify responders and to use failure to achieve an ACR20 response or worsening of disease as indicators of non-response. Lastly, the sensitivity and specificity of imaging technique or of the technological approach should be optimized and clearly stated, including where appropriate performance metrics such as area under the curve for receiver operator curves and values for false-negative and false-positive rates.

These research principles should be carefully considered when selecting the technologies and approaches summarized below.

Imaging

There is a need for higher-resolution imaging to detect very early changes that might progress in the absence of intervention and for imaging that differentiates early changes that might herald imminent structural damage, ongoing active damage and previous but now inactive damage.

Micro-CT

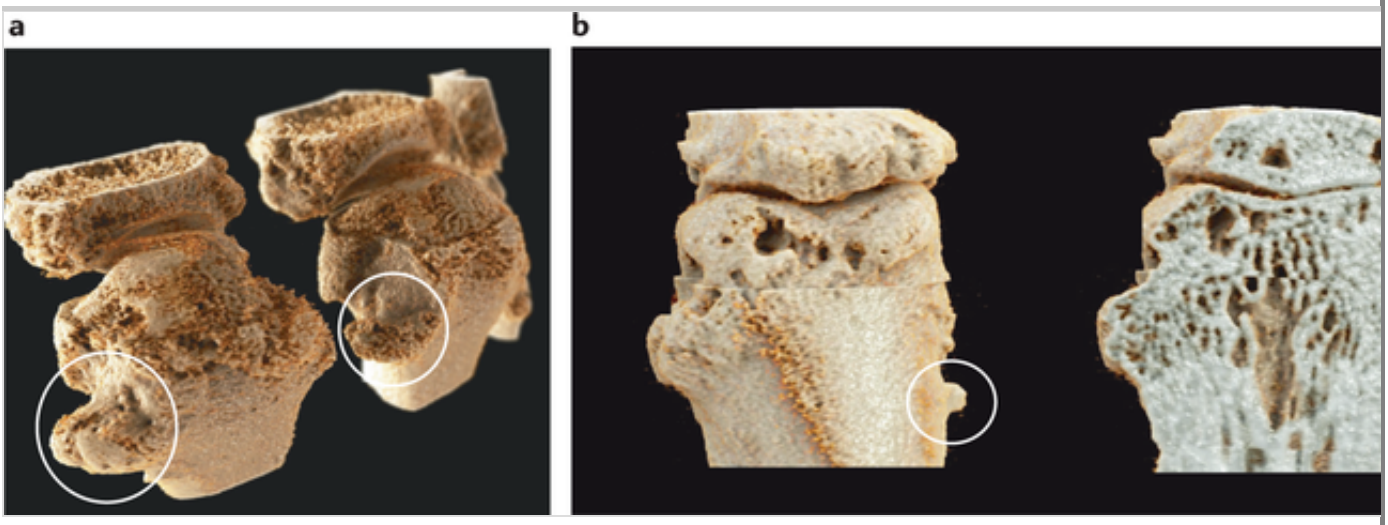
Micro-CT is an emerging modality that seems to be useful for detecting structural damage at an earlier stage and with greater sensitivity to change than

plain radiography. Enthesophytes typical of PsA are also more sensitively detected with micro-CT (illustrated in Fig. 4) than with MRI and plain radiographs[143]. Enthesophytes have been proposed as one of the earliest musculoskeletal manifestations in patients with PsC[144]. Candidate contributors to this process include PGE2, IL-23, IL-17, TNF, IL-22, Wnt proteins and bone morphogenic proteins. Adding credence to the biological plausibility of this model is the finding that enthesophytes do not progress in patients with PsA treated with anti-IL-17 therapy[145]. It has been proposed that mechanical strain could be a sufficient trigger of disease in individuals predisposed by their genetics and microbiome[146, 147]. Micro-CT has been shown to reliably differentiate the early metacarpophalangeal joint bone erosions in patients with PsA and RA by their size, morphology and topography of erosions[148].

Fig. 4

Micro-CT of small joints in psoriatic arthritis.

a | Image showing structural entheseal lesions (enthesophyte; circled) of the metacarpophalangeal joints in a patient with psoriatic arthritis. **b** | Image showing structural entheseal lesions (enthesophyte; circled) of the proximal interphalangeal joints in a patient with psoriatic arthritis (a different patient from that shown in panel **a**). All images courtesy of G. Schett and D. Simon, University of Erlangen, Germany, and K. Engle, Siemens Healthcare GmbH, Germany.



Despite the morbidity and mortality associated with osteoporotic fracture, the

monitoring of progressive trabecular bone loss is often overlooked in patients with PsA, both in clinical practice and in RCTs. The pivotal effects of IL-23 and IL-17 on both cortical bone and trabecular bone are increasingly understood, in part because of the use of micro-CT[149, 150].

Given the high spatial resolution of CT for cartilage and bone, dual-energy CT with iodine mapping might be a suitable method to detect early arthritis and/or tendinopathy, monitor for structural damage progression[151] and measure bone density with a lower ionizing radiation dose than contrast-enhanced CT.

Musculoskeletal ultrasonography

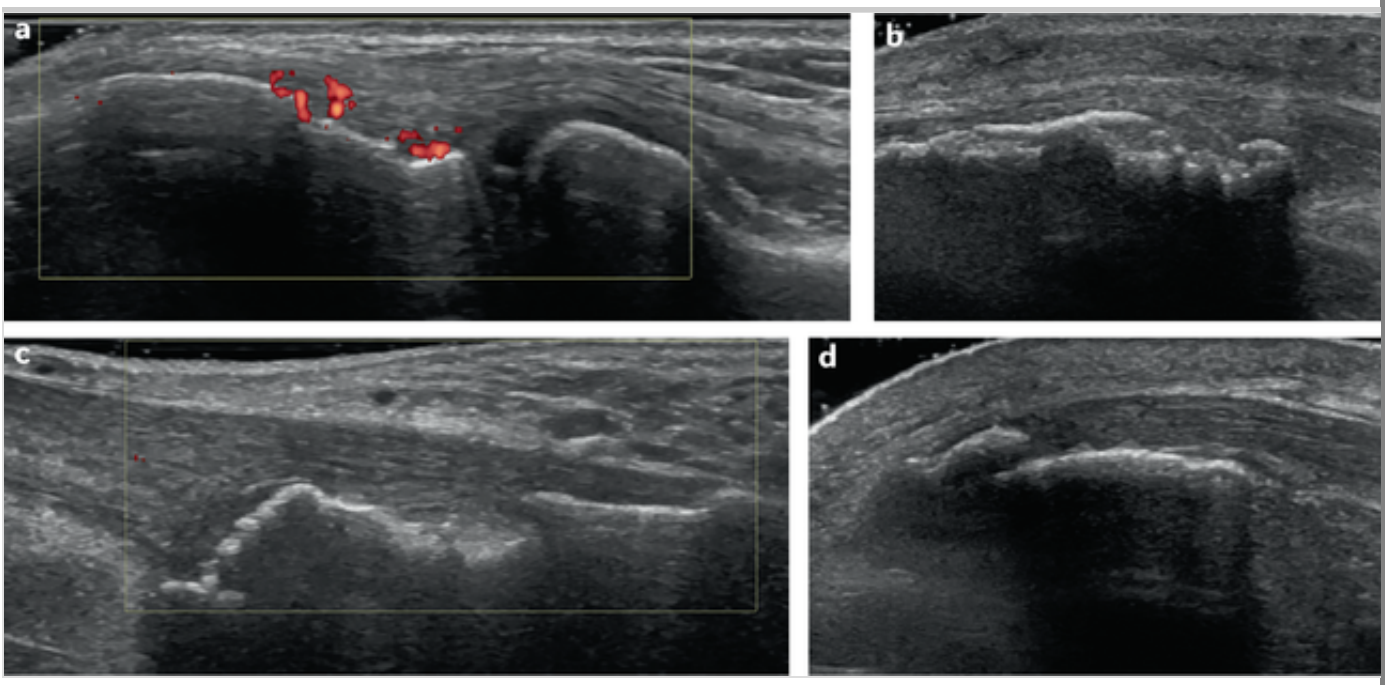
Unlike plain radiography and micro-CT, musculoskeletal ultrasonography can visualize several different structures and features of PsD, including synovial proliferation, effusion, enthesitis, tenosynovitis, tendinopathy, synovial–entheseal neovascularization, erosions, osteoproliferation, enthesophytes and even neovascularization at the nailbed (indicative of early synovial–entheseal complex inflammation), some of which are demonstrated in Fig. 5. Musculoskeletal ultrasonography is dynamic, and the advent of high-frequency probes has permitted high-resolution scanning of small, non-linear structures such as distal fingers, toes and tendons that might not be as well visualized using standard MRI. Musculoskeletal ultrasonography incorporating both grey-scale and power Doppler imaging can be used to detect and monitor disease activity in both the synovium and the enthesis.

Fig. 5

High-resolution musculoskeletal ultrasound in psoriatic arthritis.

a | Image of the elbow of a 22-year-old woman with symptomatic, recent-onset (<12 months) psoriatic arthritis (PsA), showing cortical irregularity, hypoechoic and thickened enthesis with power Doppler signal at the lateral humeral epicondyle. **b** | Image of the knee of a 53-year-old man with a 30-year history of PsA, showing erosion and hypoechoic left patella tendon insertion. **c** | Image of the lower right leg of a 53-year-old man (the same as in panel **b**) with a 30-year history of PsA, showing a hypoechoic, thickened right Achilles tendon with associated erosion, but without power Doppler signal. **d** | Image of the knee of a 67-year-old woman with a 20-year history of PsA, showing a thickened

hypoechoic patellar tendon and enthesophyte at its insertion. All images courtesy of M. Sapsford, Cambridge, UK.



The role of musculoskeletal ultrasonography in predicting outcome in PsA has not yet been established. The Ultrasound in Psoriatic Arthritis Treatment prospective multicentre observational cohort study of early PsA is underway, with the aim of comparing the value of clinical examination with and without ultrasonography for predicting the future attainment of MDA[152]. A 2019 review has shown that musculoskeletal ultrasonography and MRI can augment treat-to-target approaches in RCTs of PsA, particularly in terms of the detection of subclinical disease, joint involvement and pathology[153]. Another 2019 study has shown that musculoskeletal ultrasonography can better identify patients with PsC who require referral to a rheumatology specialist and probably have PsA than the patient-reported screening tools currently used in practice[154].

MRI

MRI offers several advantages over other imaging modalities, such as enhancement of inflammatory pathology with gadolinium or fat-suppressed sequences, which improves sensitivity for early pathology, higher inter-rater reliability, 3D reconstruction and increasing spatial resolution through the

advent of better coils. Scanning times have been reduced through the use of increasingly strong magnetic fields, thereby making whole-body or multiple-site scanning feasible. Given the variety of sites affected by PsA, including peripheral joints, axial skeleton, entheses and tendons, whole-body MRI could offer a more comprehensive and increasingly feasible method of identifying, quantifying and monitoring structural damage longitudinally. PsA-specific MRI indices, such as the Psoriatic Arthritis Magnetic Resonance Imaging Score[155], have been developed and are being increasingly used longitudinally in clinical trials. Notably, bone marrow oedema detected by MRI can herald the onset of irreversible structural damage[155].

PET combined with CT

PET-CT might contribute to the more detailed assessment of PsA. This imaging modality has been used to detect subclinical arthritis in patients with PsA and PsC[156], to assess disease activity in PsA[157] and might quantify and elucidate the pathogenesis of atherosclerotic and cardio-metabolic disease in PsD[158].

Tissue studies

The utility of newer imaging techniques such as ultrasonography, CT and micro-CT to guide biopsy of entheseal, synovial and fibrocartilage tissue could be particularly pertinent in the research of PsD immunobiology, as tissues local to the site of structural damage might better represent pathology than systemic blood. Moreover, the increasing availability of trained musculoskeletal sonographers could permit earlier and longitudinal use of ultrasonography, for both the detection of damaged sites and the sampling of local tissues for analysis.

Although technologies that enable high-dimensional single-cell analyses of synovial tissue have proved promising in RA, a number of factors require consideration when evaluating their use in PsD. First, is the synovium the appropriate tissue to evaluate the aetiopathogenesis of PsD and with which to investigate biomarkers of damage or predictors of response to treatment? A study comparing gene expression profiles in skin and synovial tissue samples from patients with PsD[4] revealed a stronger IL-17 gene signature in skin than in synovium, and equivalent TNF and IFN-γ gene signatures in both tissues.

This observation is consistent with IL-17 inhibition being more efficacious for skin relative to joint disease. Interestingly, PsD lesional skin and synovium from the same patient shared more common gene expression relative to comparing PsD synovial tissue with that of patients with other forms of arthritis such as RA, osteoarthritis and systemic lupus erythematosus. Second, the disease domains associated with PsD pose a challenge with respect to obtaining entheseal, spinal or bone tissues, which are commonly involved. In relation to entheseal disease, a 2019 study of normal human entheseal soft tissue and peri-entheseal bone taken from patients undergoing spinal surgery revealed the presence of a $CD14^+$ myeloid population able to produce IL-23, IL-1β, TNF and CCL20, which confirms the feasibility of this approach; although difficult to obtain, it would be interesting to evaluate whether these subsets are expanded in patients with PsD[159].

Obtained as part of the PEAC initiative in RA, preliminary data in early PsA have identified synovial tissue pathotypes similar to those in RA, although with a relative increase in the pauci-immune subset and a decrease in the lymphoid–myeloid subset[160]. Expression of genes related to neutrophil recruitment and enrichment, cell migration and cytoskeleton remodelling modules were upregulated in PsA compared with RA synovium.

Application of omic technologies

The last two decades have seen immense progress in the development and application of omic technologies, which has led to a greater understanding of the molecular events and biomarkers underlying heterogeneous disease phenotypes[161]. Concurrent advances in genomics, transcriptomics, epigenetics, proteomics and metabolomics have provided an unprecedented opportunity to decipher the clinical and functional heterogeneity of PsD so as to address the important unmet needs described above. Notably, the development of high-throughput and high-sensitivity protein identification and quantification approaches extending to single-cell proteomics[162, 163] and multi-omics[164, 165] are supporting the protein-centric molecular characterization of diseases including rheumatic diseases[164, 166]. Furthermore, the ability to analyse these changes at the single-cell level[167], made increasingly feasible by developments in techniques such as mass cytometry (also known as CyTof), now affords us the opportunity to investigate both cellular heterogeneity and

interactions between cells within tissues that are involved in the pathogenesis of PsD and that result in its diverse clinical manifestations. These advances have also led to the emergence of ‘proteogenomics’[168], in which genomic events, including SNPs, mutations, insertions, deletions and substitutions, can be analysed at the protein level to gain a better understanding of the mechanisms by which genomic and epigenetic events exert their influence on cellular events. Proteogenomic strategies[169, 170] have been applied initially in the field of cancer research[171, 172], in which the global sharing of proteogenomic data is anticipated to have a substantial influence on ‘precision oncology’[173]. We suggest that proteogenomics is now primed for application to PsD[168].

Combining multi-omic data presents substantial challenges but computational workflows and standards to integrate omics data are emerging[174, 175]. It is now reasonable to anticipate that these approaches will enable us to more precisely investigate and understand the complex interplay between diverse immune cells and subsets of macrophages[176, 177], fibroblasts[178, 179] and other tissue-resident cells that underlies the changes observed in multiple PsD domains (bone, synovium, skin and so on). The expectation is that this detailed molecular and mechanistic understanding will afford us the opportunity to target the main events and/or pathways of PsD and more effectively intervene therapeutically[165, 180].

Collaborations and initiatives

As demonstrated in the research and care of patients with RA, combining the skills of multiple academic units and industry partners might help to address important unmet needs in PsD. Such partnerships could pave the way towards more precise PsD diagnosis, classification and prognosis, with therapeutic targeting resulting in improved patient outcomes. To this end, the GRAPPA Collaborative Research Network (CRN) is seeking to determine the independent validity of several soluble biomarkers for predicting structural damage in patients with PsA receiving therapy[10]. In order to identify additional candidate biomarkers, initial studies of longitudinal serum samples and peripheral radiographs obtained during RCTs of ixekizumab[41, 181] and etanercept[24], will include discovery proteomics (liquid chromatography with tandem mass spectrometry) and an initial evaluation strategy using targeted proteomics with multiple-reaction monitoring mass spectrometry. Data will be

analysed using multivariate statistical methods, including elastic-net regularized linear regression. It is anticipated that this approach will elucidate a panel of biomarkers that might predict radiographic progression in PsA and that can then be validated in larger studies. The CRN has also been developing standardized procedures for the capture of patient-related data, the collection, storage and shipping of biosamples (including both liquid and tissue samples) and the scientific methodology that would be used in analysing these samples[10]. This initiative will enable collaborative project development within the CRN focusing initially on the collection of biosamples prior to treatment initiation.

One can also learn from the experiences of the AMP as well as the Human Protein Atlas, the Genotype-Tissue Expression project and the Human Cell Atlas consortium (HCA). These projects are truly collaborative and international and are open resources. The HCA, for example, will include a comprehensive analysis of skin, synovium, tendon, bone, enthesis and capsule, with plans to include the spine and sacroiliac joints. With the goal of mapping human cells in health, the HCA strategy combines single-cell molecular profiling of dissociated cells (and/or single-nucleus molecular profiling) with highly multiplexed spatial analysis of intact tissue.

Big data and artificial intelligence

It is increasingly recognized that extracting biological knowledge and clinically actionable information from large-scale omics datasets will require the application of machine learning[182] and other artificial intelligence methods[183]. These methods work most effectively on high-quality datasets and their strength increases proportionally with the size of the datasets to which they are applied. Artificial intelligence and machine-learning algorithms identify structures and associations within heterogeneous datasets. The diversity and varying quality of omics data combined with the complexity of data from the clinical assessment of patients presents considerable challenges. One such challenge is the need for methodologies to process, normalize, integrate and transform the data so as to enable the development of accurate predictive models[175, 184] capable of identifying novel biomarker signatures to improve clinical decision-making and thus transform precision medicine. Notably, and as an illustration, a longitudinal analysis that integrated transcriptomic, serum proteomic and immunophenotypic data and detailed clinical parameters from

well-characterized cohorts of untreated and treated patients with RA and healthy controls revealed molecular profiles that led to a greater understanding of the molecular and cellular systems associated with drug treatment and RA severity[185]. Both a EULAR task force[186] and the European Medicines Agency[187] have issued summary guides on the use of big data for rheumatic and musculoskeletal disease and for the regulation of new medicines.

Conclusions

In this Review, we have outlined some important unmet needs in PsD, notably predicting poor outcome and response to treatment. An improved understanding of PsD pathobiology will support the early identification of patients with a poor prognosis, which will enable the application of precision medicine in order to prevent disease progression and irreversible damage. To that end, existing and emerging approaches include the use of advanced imaging modalities and tissue analysis, and multi-omics approaches will need to be employed. Given the important advances being made in these areas, the time is certainly right to apply these technologies, ideally through collaborative partnerships, to unravel the heterogeneous phenotype of PsD and improve outcomes for patients.

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Author contributions

All of the authors contributed to researching data for the article, made substantial contributions to discussion of the content, writing the manuscript and reviewing and/or editing the manuscript before submission.

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