State of the art and novel treatments in psoriatic arthritis

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Abstract

Psoriatic arthritis (PsA) is a heterogeneous, immune-mediated inflammatory disease characterised by multidomain clinical involvement, including peripheral arthritis, enthesitis, axial disease, dactylitis, and skin and nail manifestations, alongside a substantial burden of comorbidity. Over the recent decades, therapeutic options for PsA have expanded, with the introduction of multiple biologic and targeted compounds targeting tumour necrosis factor, the IL-23/IL-17 axis, and Janus kinase signalling. These advances have improved outcomes for many patients; however, incomplete responses, domain-specific refractory disease, treatment intolerance, and loss of efficacy remain common. In addition, current treatment strategies are largely reactive, reflecting limited ability to predict treatment response or align immune mechanism with clinical phenotype. This review summarises the current PsA treatment landscape and its limitations, and examines emerging therapeutic directions that aim to address disease heterogeneity and unmet need. These include combinatorial and sequential treatment strategies, next-generation biologics and oral agents, immunometabolic modulation, selective targeting of pathogenic immune cell populations and upstream inflammatory, immune tolerance–based approaches. It is with hope that these developments highlight a shift from incremental therapeutic expansion towards a integrated, targeted and ultimately, more informed treatment approach.

Keywords: Psoriatic arthritis; targeted therapy; biologics; Janus kinase inhibitors; IL-17; IL-23; precision medicine; immunometabolism; combination therapy

1.0 Psoriatic arthritis: clinical complexity and evolving therapeutic expectations

Psoriatic arthritis (PsA) is a heterogeneous, immune-mediated inflammatory arthritis that affects approximately one third of individuals with psoriasis (PsO)[1]. The disease encompasses multiple clinical domains, including peripheral arthritis, enthesitis, dactylitis, axial involvement, and skin and nail disease, each of which may vary in severity and dominance over time[2]. Beyond musculoskeletal and cutaneous manifestations, PsA is associated with a substantial burden of cardiometabolic, hepatic, and psychological comorbidity, contributing to impaired quality of life and adverse long-term health outcomes[3]. The adoption of treat-to-target strategies incorporating composite indices such as the Disease Activity Index for Psoriatic Arthritis (DAPSA) and Minimal Disease Activity (MDA) has improved disease monitoring and outcomes in routine care[4,5]. However, many patients continue to experience incomplete responses, domain-specific refractory manifestations, frequent treatment switching, or progressive structural damage despite apparent control of peripheral joint inflammation[6,7].

Advances in mechanistic understanding over the past two decades have clarified key aspects of PsA pathophysiology. Inflammation is thought to arise predominantly within the synovio-entheseal compartment, where mechanical stress intersects with dysregulated innate and adaptive immune responses[8]. Central to this process is activation of the IL-23/IL-17 axis and tumour necrosis factor (TNF) signalling, with downstream effects mediated in part through multiple JAK-STAT pathways[9]. Tissue-resident immune populations, including innate lymphoid cells, γδ T cells, and macrophages, contribute to the persistence of local cytokine production and chronic inflammation[10,11]. One of the main differentiators of PsA from other inflammatory arthritides is that bone pathology reflects the coexistence of osteitis and erosive damage alongside aberrant new bone formation. This, at least in part, helps explain the variable translatability of therapeutic approaches developed for rheumatoid arthritis (RA).

The therapeutic landscape for PsA has expanded substantially, evolving from conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) to a broad range of targeted therapies. Approved treatments across classes now include phosphodiesterase (PDE)-4 inhibitors, TNF inhibitors, IL-12/23 blockade, selective IL-23 p19 inhibitors; IL-17A and IL-17A/F inhibitors; and Janus kinase (JAK) inhibitors (**Table 1**). These advances have translated into meaningful improvements in clinical outcomes, including higher rates of remission or low disease activity, improved skin clearance, and gains in physical function. Nonetheless, important therapeutic limitations persist. Treatment discontinuation and

switching remain common due to secondary loss of efficacy, adverse events, or misalignment with patient preferences relating to route of administration and dosing frequency[12-14]. Moreover, treatment responses are often domain-specific, with enthesitis, axial disease, and prevention of structural progression continuing to represent areas of unmet need[10]. Despite increasingly sophisticated treatment algorithms, clinical decision-making in PsA often remains reactive rather than predictive, reflecting the absence of robust tools to match immune mechanism to clinical phenotype.

Therapeutic decision-making is further complicated by safety considerations and comorbidity profiles. Recognised risks, such as mucocutaneous candidiasis associated with IL-17 pathway inhibition, class-wide regulatory warnings limiting the use of JAK inhibitors in selected populations, and the need to account for coexisting conditions including inflammatory bowel disease or uveitis, constrain optimal treatment selection and sequencing in routine practice[15,16]. In addition, patients who are obese often have lower treatment efficacy which presents further treatment considerations[17]. As a result, expanding the number of available agents within existing mechanistic classes has not fully addressed the biological and clinical heterogeneity inherent to PsA.

Keeping these factors in mind, there is therefore a clear rationale for continued innovation beyond incremental additions to established therapeutic categories. This review therefore aims to examine why further advances are required at the current stage of the PsA treatment landscape and considers where emerging strategies may offer meaningful progress. It provides a high-level overview of developments in more selective intracellular signalling modulation, novel biological approaches, and immune pathways that remain insufficiently targeted by approved therapies.

2.0 Current therapeutic paradigms and their limitations

Currently, there are over a dozen treatments for PsA approved globally, with treatments mainly focusing on biologics, with the use of some oral therapies, where appropriate. The discovery and validation of targeting the IL-23/IL-17 pathway with treatments such as secukinumab, ixekizumab, ustekinumab and guselkumab, has offered a paradigm shift in the treatment of PsA, with meaningful treatment outcomes demonstrated in both trial and real-world settings[18-20]. Across pivotal IL-17 and IL-23 trials, high-level efficacy in skin and peripheral joint endpoints contrasts with more modest and variable effects on enthesitis, dactylitis, axial symptoms, and radiographic progression[18,21]. Rates of ACR50/70 responses, minimal disease activity (MDA) and sustained remission remain well below those seen for skin clearance, and real-world cohorts consistently report primary non-response, secondary loss of efficacy, and frequent switching[22]. The lack of robust outcomes in some domains

through IL-23/Th17 targeted therapies suggests that underlying PsA disease biology extends beyond canonical Th17 signalling.

3.0 Pushing beyond monotherapy: combinatorial and sequential treatment strategies

Experience across immune-mediated inflammatory diseases increasingly suggests that durable disease control may be limited by strategies that rely on single-mechanism intervention. In conditions such as inflammatory bowel disease (IBD) and hidradenitis suppurativa (HS), recognition of biological redundancy, compartmentalised inflammation, and adaptive immune escape has prompted renewed interest in combination and sequential treatment paradigms. A combinatorial approach to treatment in ulcerative colitis (UC) was studied in the phase II VEGA trial, examining short-term combination induction with the TNF inhibitor golimumab and an IL-23 p19 inhibitor guselkumab, followed by IL-23 monotherapy, compared with either agent alone[23]. Combination therapy achieved higher rates of clinical response and endoscopic improvement at week 12, supporting the notion that temporally defined dual targeting can deepen early disease control in UC.

By contrast, PsA remains at an earlier stage of evaluation for combinatorial approaches. Use to date has been confined to patients with difficult to control disease, however, there are few publications within the area and no appropriately designed trials, with most reports being case series. In the UK, a survey of 16 BritPACT-affiliated rheumatology centres, provided insight into real-world use of combinatorial treatment approaches. The survey revealed that only a small number of heavily pre-treated patients received combination therapy, yet most achieved remission or low disease activity with sustained treatment persistence and no serious adverse events reported, contrasting with other small series that identified higher discontinuation rates due to infection[24]. Supporting this, a Spanish multicenter study of dual targeted therapy in refractory PsA and SpA reported that, over a median exposure of approximately 15 months, nearly 70% of patients achieved major clinical improvement and over half reached remission or low disease activity, despite extensive prior biologic failure. Importantly, treatment persistence was high, with only four serious adverse events observed across 39 combinations, suggesting a potentially favourable benefit–risk profile in carefully selected, heavily pre-treated patients[25]. Combination therapy is also being explored in the phase II AFFINITY trial, which is evaluating treatment with guselkumab and golimumab compared with guselkumab monotherapy in patients with active PsA and inadequate response to prior TNF inhibition. Results from the trial are not presently available. Overall, these findings there position combinatorial therapy as a biologically rational, but currently under-evidenced approach, supporting the need for prospective, controlled studies to define appropriate patient selection, sequencing, and long-term safety before broader clinical adoption.

From an immunological perspective in PsA, targeting multiple inflammatory mediators may help overcome domain efficacy barriers, as well as the inherent heterogeneity seen within the disease. Distinct, yet overlapping immune processes drive peripheral synovitis, enthesitis, axial involvement, and cutaneous disease, with varying contributions from both adaptive and innate pathways across a range of tissues and disease stages[10,26,27]. Monotherapy directed at a single cytokine or signalling pathway may therefore suppress dominant pathways while leaving parallel or compensatory mechanisms intact contributing to incomplete, discordant and ultimately pathological immunological responses[28,29]. Therefore combination or sequential strategies are best viewed not necessarily as strictly ‘additive’ or ‘cumulative’ immunosuppression, but as a means of aligning therapeutic intervention with the heterogenous immunobiology of PsA, particularly in patients whose disease spans multiple domains or has proven refractory to monotherapy alone.

4.0 Next-generation biologics and novel oral agents

Sonelokimab is a novel, subcutaneously administered, trivalent nanobodyI engineered to simultaneously bind IL-17A and IL-17F with high affinity, while incorporating an albumin-binding domain to enhance systemic persistence and tissue penetration relative to conventional IgG monoclonal antibodies[30,31]. Nanobodies are single-domain antibody fragments derived from heavy-chain-only antibodies, with a smaller molecular weight that may facilitate access to dense or poorly vascularised sites of inflammation and enable modular, multispecific designs not feasible with larger antibody formats[32]. In the global, randomised, double-blind, placebo-controlled Phase II ARGO trial in patients with active PsA, sonelokimab met its primary endpoint at Week 12, with both 60 mg and 120 mg induction regimens achieving ACR50 response rates of approximately 46% compared with 20 % with placebo[31], showing similar outcomes to the BE COMPLETE phase 3 trial with bimekizumab. Sonelokimab also demonstrated high response rates across key secondary outcomes, including ACR20 responses (72-78 % vs approximately 38 % with placebo) and PASI90 skin responses in patients with PsO. In addition, treatment also produced substantial proportions of patients achieving high-threshold composite outcomes such as ACR70 + PASI100 and MDA by Week 24. The safety profile was consistent with IL-17 pathway inhibition, with the most frequently reported adverse events being mild-to-moderate nasopharyngitis, upper respiratory tract infection, injection-site erythema, headache, and a small number of oral candidiasis cases. The study did not identify any new or unexpected safety signals, and serious events such IBD and major adverse cardiovascular events were not noted during the treatment period. The blockade of IL-17A/F using a nanobody such as sonelokimab, may deliver rapid, multidomain clinical benefit in PsA. Sonelokimab is currently being examined in two Phase 3 trials, with one focusing on biologic-naive PsA patients and including evaluation of radiographic progression (IZAR-1), and the other

focusing on TNF-IR patients whilst also being the first trial to include risankizumab as an active reference arm (IZAR-2)[33].

Izokibep (ABY-035) is a novel IL-17A–targeting therapeutic that is designed as a small protein scaffold rather than a conventional monoclonal antibody, aimed to enhance tissue penetration while maintaining high neutralising potency. In a randomised, double-blind, placebo-controlled phase 2 study in patients with active PsA, izokibep demonstrated rapid, statistically significant, and clinically meaningful improvements across multiple disease domains, including peripheral arthritis, skin disease, enthesitis, and dactylitis, with responses evident as early as two weeks and sustained through 46 weeks at the higher dose. The therapy was generally well tolerated, with a safety profile consistent with IL-17 pathway inhibition and no unexpected safety signals, supporting izokibep as a differentiated IL-17A inhibitor with the potential to address difficult-to-treat manifestations of PsA.

Currently approved oral therapies for PsA are limited and are frequently associated with tolerability challenges, most notably gastrointestinal adverse events with phosphodiesterase-4 inhibition, such as nausea and diarrhoea observed with apremilast [34,35]. Janus kinase (JAK) inhibitors provide broader immunomodulatory efficacy but are accompanied by safety considerations, including increased risks of serious infections, venous thromboembolism, and major adverse cardiovascular events in selected patient populations, meaning careful patient selection and ongoing monitoring is necessary[16]. There is therefore a significant unmet need for tolerable and efficacious oral therapies in PsA, as evidenced by two-thirds of patients preferring oral treatment over injectables[36].

Icotrokinra (JNJ-77242113) is a novel, targeted oral peptide that selectively binds the IL-23 receptor, inhibiting signalling through a mechanistically differentiated, intracellular approach. Unlike currently approved biologic IL-23 inhibitors, which neutralise the p19 subunit extracellularly, icotrokinra is designed to modulate IL-23 receptor signalling directly, preserving pathway specificity while avoiding broader immune suppression. Its clinical efficacy and safety in PsA are being evaluated in the ongoing Phase III ICONIC-PsA programme, comprising two large, multicentre, randomised, double-blind, placebo-controlled trials in biologic-naive (ICONIC-PsA 1) and biologic-experienced (ICONIC-PsA 2) patients with active disease[37]. In both studies, the primary endpoint is the proportion of patients achieving an ACR20 response at Week 16, with secondary endpoints including ACR50/70 repsonses, PASI75/90/100, resolution of enthesitis and dactylitis, MDA, physical function, fatigue, and health-related quality of life. While efficacy data are not yet available, the scale, design, and endpoint selection of the ICONIC-PsA programme underscore the ambition to position selective oral IL-23 inhibition as a potential next-generation oral option capable of delivering multidomain efficacy.

Zasocitinib (TAK-279) is an investigational allosteric TYK2 inhibitor being developed as an oral therapy to suppress IL-23–driven inflammatory signalling while avoiding inhibition of JAK1/2/3, based on its high TYK2 selectivity. In plaque PsO, Takeda has recently reported positive topline results from two pivotal Phase 3 LATITUDE studies, with once-daily zasocitinib meeting co-primary endpoints (sPGA 0/1 and PASI75 at week 16) and achieving high levels of skin clearance (including PASI90 and PASI100), with a safety profile described as consistent with prior studies. Importantly for PsA, zasocitinib is also being advanced in Phase 3 trials (including biologic-naive and mixed prior biologic exposure populations), positioning it as a potential oral option targeting the IL-23/TYK2 axis[38]. Previous efforts to block TYK2, namely deucravacitinib, have proved largely underwhelming in PsA, with relatively low response rates measured by MDA[34].

If successful, these therapies may help address the persistent unmet need for well-tolerated, efficacious oral therapies in PsA, aligning therapeutic performance more closely with patient preference for oral treatment. However, their efficacy must near-match injectables to offer a meaningful place in the treatment landscape.

5.0 Emerging mechanistic directions in psoriatic arthritis treatment

Beyond optimisation of existing agents and treatment strategies, a focus of therapeutic innovation in PsA is being shaped by deeper interrogation of disease biology at the levels of metabolism, immune cell identity, upstream inflammatory regulation, and establishment of immune tolerance. Although refinement of established cytokine targets remains a valid therapeutic approach, this reflects a shift towards modifying the cellular drivers that sustain chronic inflammation, domain discordance, and treatment resistance. In the following sections, we outline key emerging mechanistic directions currently under investigation, including immunometabolic modulation, potential for selective reprogramming of pathogenic immune cell populations, targeting of upstream inflammatory amplifiers, and cellular-based strategies aimed at restoring immune regulation.

5.1 Reprogramming pathogenic immune cell populations

Despite the expansion of therapies targeting shared inflammatory pathways, these approaches largely focus on downstream cytokine signalling. As a result, they do not directly address upstream drivers of immune dysregulation, clonal persistence, or tissue-specific immune imprinting that may underpin disease chronicity in PsA and other inflammatory arthritides. This has prompted interest in strategies that move beyond cytokine neutralisation toward more directed and selective modulation of the immune repertoire itself.

Recently, the approach of targeting pathogenic T cells and subsequent depletion has offered therapeutic promise in treating ankylosing spondylitis (AS). The study aimed to target TRBV9+ (Vβ9+) T cells using seniprutug (BCD-180), a cytotoxic anti-TRBV9 monoclonal antibody, prompted by prior identification of an HLA-B27-associated CD8+ TCRβ CDR3 motif enriched in peripheral blood and synovial compartments, and the subsequent mapping of cognate HLA-B27–presented epitopes[39]. Treating a single patient, the authors demonstrated significant depletion of TRBV9+ T cells, accompanied by disappearance of the disease-associated CDR3 motif, with clinical remission achieved within three months after longstanding anti-TNF exposure. Remission was maintained over four years with intermittent re-dosing, with relapse coinciding with re-emergence of the pathogenic motif and rapid clinical improvement after repeat administration of the depleting antibody. Although this is a very small initial study and in AS, it bears relevance to PsA. Firstly, selective depletion of a defined T cell subset offers a potential therapeutic approach, rather than previous efforts of broad cytokine blockade. Secondly, the underlying TRBV9-associated CD8+ TCRβ motif has been reported across HLA-B*27-associated spondyloarthropathies, including PsA, which raises the possibility that a proportion of PsA patients may be driven by similarly tractable, antigen-linked clonal expansion. Indeed, data exist suggesting that PsA may be driven by CD8 clonal expansion[71]. Recently, the results of the phase 2 trial have been reported, demonstrating statistically significant superiority over placebo across multiple efficacy endpoints in patients with active AS, alongside acceptable tolerability and low immunogenicity[40].

Further support for selective targeting of pathogenic T-cell subsets comes from recent preclinical data presented on IMT-380, a first-in-class, fully human anti-CD161 monoclonal antibody. CD161-expressing T cells exhibit a highly pro-inflammatory phenotype, producing IL-17A, IFN-γ, IL-22, TNF and GM-CSF, and are enriched in inflamed tissues across autoimmune diseases. In preclinical models, selective depletion of CD161+ T cells reduced inflammatory cytokine production and improved disease severity, including significant improvements in psoriasis-like skin inflammation in non-human primates[41].

These findings suggest that selective targeting of pathogenic immune cell populations may offer a complementary strategy to cytokine inhibition in PsA. While clearly preliminary, and in another closely related disease, such an approach raise the possibility of addressing disease chronicity at the level of ‘antigenic sin’ rather than downstream inflammation.

5.2 Targeting upstream mediators of inflammation

There has been renewed interest in identifying upstream regulators that integrate immune activation with tissue-specific responses and may contribute to the persistence, rather than initiation, of chronic inflammation.

Tumour necrosis factor-like ligand 1A (TL1A, also known as TNFSF15) has emerged as one such potential target[42]. TL1A signals through death receptor 3 (DR3) and is expressed at sites of tissue inflammation, where it amplifies effector T-cell responses, supports survival of activated lymphocytes, and influences stromal and fibroblast cell behaviour [42]. Unlike canonical effector cytokines, TL1A appears to function as an immune checkpoint-like amplifier, potentiating downstream pathways including TNF and IL-17 signalling rather than acting in isolation[43]. The majority of data exploring the therapeutic targeting of TL1A has arisen from IBD, which has shown a strong genetic association, as well as high expression of TL1A in diseased tissue[44]. TL1A has also been shown to play a key role in fibrosis, with fibrotic effects thought to act in both an inflammation-dependent and independent manner[45]. Several TL1A-targeting monoclonal antibodies are now in mid- to late-stage clinical development in IBD. The most advanced programme is tulisokibart (MK-7240), which has demonstrated clinical and endoscopic efficacy in phase II studies in ulcerative colitis and Crohn's disease and has progressed into phase III development across both indications[46,47]. Other TL1A-directed antibodies, including PF-06480605, have completed phase I and II evaluation in IBD populations, providing additional human safety and proof-of-mechanism data[48]. Although no trials are currently publicly announced in PsA, mechanistically, targeting TL1A in PsA may be attractive as TL1A-DR3 signalling has been demonstrated in psoriatic and synovial tissues and linked to effector T-cell amplification and stromal activation[10]. These processes are particularly relevant to difficult-to-treat domains such as enthesitis and structural progression in PsA.

5.3 Immune reset strategies: cellular and tolerance-based therapies

Beyond use of biologics, the potential application of cellular-based therapies has been explored across a range of rheumatological conditions, including RA and PsA. These approaches have mainly centered around using adoptive transfer or expansion of regulatory T cells (Treg) and infusion of tolerogenic dendritic cells (DCs), although largely remain conceptual in nature[49.50].

Studies have shown that FoxP3^{+} Tregs accumulate in inflamed joints in individuals with PsA, and fail to control inflammation[51]. Studies have shown that synovial Tregs in PsA exhibit functional instability, co-expressing IL-17A and RORγt, giving them Th17-like features, rather than exerting traditional immunosuppressive actions[52]. Such findings underscore the rationale for therapies to boost stable, suppressive Tregs or an opportunity to correct their phenotype.

Although adoptive transfers of Tregs have been undertaken in RA, there are no current studies that have been published examining adoptive transfer in PsA. However, a Phase I/II open-label study in PsA patients examined low-dose IL-2 therapy, in addition to standard of care, to

selectively expand endogenous Tregs[53]. The trial showed that circulating Treg counts increased, and patients experienced a rapid reduction in joint symptoms and arthritis scores, suggesting that expansion of endogenous Tregs with IL-2 may offer a potential approach to treat some PsA patients.

Tolerogenic DCs are a functionally specialised subset of DCs engineered to promote antigen-specific immune tolerance rather than effector T-cell activation, primarily through low expression of co-stimulatory molecules, production of immunoregulatory cytokines such as IL-10, and induction or expansion of regulatory T cells[54,55]. Tolerogenic DCs have been explored to induce antigen tolerance in PsA. The most significant clinical trial to date examining this approach was the AuToDeCRA study, which tested autologous tolerogenic DC therapy in patients with RA or PsA with active knee synovitis[50]. Patient monocytes were differentiated into tolerogenic DCs, using well established protocols by exposing them to IL-10 and other mediators, and "loaded" with autoantigens from the patient's synovial fluid. The DCs were then injected intra-articularly into the inflamed knee, with dose escalated to $1x10^7$ cells per injection. Although the study demonstrated this was in principal a safe approach, with no serious adverse events reported, efficacy was limited with only a few patients achieving symptom remission in the injected joint. Although the study provided important proof of concept for antigen-specific immune modulation in PsA, the logistical complexity, cost of manufacture, and modest efficacy observed to date represent significant barriers to broader clinical translation, particularly in publicly funded healthcare systems.

6.0 Targeting comorbidities: immunometabolic modulation as a disease modifier

The association between chronic inflammation, obesity, and metabolic dysfunction is well established[56]. Adipose tissue is increasingly recognised as playing an active 'immunometabolic' role, capable of sustaining a state of low-grade systemic inflammation through the secretion of mediators such as TNF, IL-6, leptin, and adiponectin[56]. Further compounding this, in the context of PsA, is that obesity is a recognised risk factor for disease development and is thought to contribute, at least in part, through increased exposure to pro-inflammatory signalling pathways[57]. Higher body mass index (BMI) has been consistently associated with poorer treatment outcomes, including a reduced likelihood of achieving MDA[58-60], while weight reduction has been linked to improvements in disease activity in some studies, including the use of bariatric surgery[61].

Despite this, lifestyle-based weight loss interventions are variably effective and frequently difficult to sustain over the long term, both in PsA patients and in other patient groups[62,57]. The recent emergence of pharmacological therapies for obesity, including glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide, and dual incretin agonists such as tirzepatide, has substantially altered the metabolic treatment landscape[63,64]. Randomised clinical trials in populations without

inflammatory arthritis have demonstrated sustained weight reductions exceeding 20% in selected patients, versus 2% in placebo-treated patients[64]. Beyond their metabolic effects, incretin-based therapies have been shown to modulate inflammatory pathways, raising interest in their potential relevance to immune-mediated inflammatory diseases[65]. The potential positive effects from GLP-1 treatment in inflammatory disorders are hypothesised to be two-fold. Firstly, as discussed already, GLP-1-based therapies may confer indirect benefit through sustained weight loss and improvement in metabolic dysfunction, reducing adipose-driven low-grade systemic inflammation that is associated with poorer disease control in PsA[57]. Secondly, beyond metabolic effects, GLP-1 receptor signalling has been shown to influence inflammatory pathways, with experimental evidence of effects on immune cell activation and cytokine production[65]. Together, these indirect and potentially direct mechanisms provide a biologically plausible rationale for evaluating incretin-based therapies in inflammatory-mediated diseases, such as PsA.

Early observational data have begun to explore these possible connections. Retrospective analyses and exploratory studies have reported associations between GLP-1 receptor agonist use and reduced disease flares or improved joint-related outcomes in RA, alongside symptomatic improvement in PsA[66,67]. Analyses of large real-world datasets have further suggested a lower incidence IBD among individuals with obesity or type 2 diabetes treated with GLP-1-based therapies[68]. While these findings are hypothesis-generating and subject to confounding, they provide a biologically plausible signal, that has warranted further exploration.

Recently published data from the Phase 3b TOGETHER-PsA trial provide the first interventional evidence that pharmacological targeting of obesity can meaningfully augment biologic efficacy in PsA[69]. In patients with PsA and obesity or overweight, combination therapy with ixekizumab and tirzepatide resulted in significantly superior outcomes compared with ixekizumab alone. At Week 36, 31.7% of patients receiving combination therapy achieved both an ACR50 response and ≥10% weight loss, compared with 0.8% of those receiving ixekizumab monotherapy ($p<0.001$). A key secondary endpoint demonstrated a 64% relative increase in ACR50 response alone (33.5% vs 20.4%, $p<0.05$). Notably, over 60% of participants had high baseline disease activity and prior exposure to advanced therapies, underscoring the refractory nature of the study population.

A pragmatic randomised study is currently registered (ClinicalTrials.gov; NCT07111494) to assess the impact of GLP-1 receptor agonist therapy in patients with PsA and co-existing obesity and/or type 2 diabetes. The trial compares pharmacological metabolic intervention with standard non-pharmacological management over a defined follow-up period. Although not designed as a disease-modifying study, it aims to explore whether

sustained weight loss and metabolic improvement are associated with changes in PsA disease activity and patient-reported outcomes.

These findings move the concept of metabolic inflammation from association to potential intervention, supporting an integrated treatment paradigm in PsA that addresses both immune and potential metabolic drivers of disease.

7.0 Conclusion and future directions

It is clear that the understanding and treatment of PsA has evolved substantially over recent years. The expansion of biologic and targeted synthetic therapies has transformed outcomes for many patients, particularly in relation to peripheral arthritis and skin disease. However, despite these advances, a number of important unmet needs remain. Many patients continue to experience persistent symptoms across specific domains, incomplete or short-lived treatment responses, or difficulty maintaining long-term disease control. In parallel, challenges around treatment selection, sequencing, safety, and patient preference continue to complicate routine clinical decision-making.

A recurring theme throughout this review is that many of the limitations of current therapies reflect the underlying biological complexity and heterogeneity of PsA. The disease is driven by overlapping immune pathways, tissue-specific inflammatory processes, and interactions between metabolic, innate, and adaptive immune mechanisms. As such, expansion within existing therapeutic classes has not been sufficient to fully address domain discordance, treatment resistance, or progressive structural damage in a proportion of patients. There is therefore a strong rationale for exploring therapeutic strategies that move beyond single-pathway inhibition. A visual overview of the discussed therapeutic strategies in this review is provided in Figure 1.

The emerging approaches discussed in this review highlight a broadening of therapeutic potential in PsA. These include targeting metabolic inflammation, selectively modulating pathogenic immune cell populations, inhibiting upstream inflammatory amplifiers, and developing structurally novel biologics and next-generation oral agents. While many of these strategies remain at an early stage of development, they reflect a shift towards addressing the drivers of disease persistence and heterogeneity, rather than focusing solely on downstream cytokine blockade.

There is a clear need for evolution in how new therapies are evaluated. Future clinical trials will need to better capture the multidomain nature of PsA, incorporating outcomes relevant to enthesitis, axial disease, structural progression, and patient-reported measures alongside traditional joint and skin endpoints. In addition, greater emphasis on biomarker development and validation will be essential if more personalised, domain-sensitive treatment strategies are to be realised.

Without improved tools to predict treatment response and guide therapeutic selection, the growing number of available options risks adding complexity without necessarily improving outcomes. It is likely that the management of PsA will continue to move towards a more integrated and individualised approach. This may involve earlier intervention, more rational sequencing or combination of therapies, and closer alignment between biological mechanism, clinical phenotype, and patient preference. In parallel, there is increasing interest in whether selected high-risk individuals, analogous to the preventative strategy explored in the APIPPRA trial in RA, might benefit from early intervention aimed at delaying or preventing progression to PsA[70]. However, translating these concepts into routine practice will require careful evaluation of long-term safety, tolerability, and cost, as well as realistic expectations about what can be achieved.

Ultimately, even in the absence of dramatic step-changes in short-term efficacy, meaningful progress in PsA may come from better matching treatments to patients, improving durability of response, and adopting a more holistic approach to disease management. Continued collaboration between clinicians, researchers, and patients will be essential to ensure that emerging innovations lead to genuine improvements in long-term outcomes and quality of life for people living with PsA.

Declarations

During the preparation of this work the author(s) used ChatGPT in order to improve readability of the manuscript. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Practice points:

• Psoriatic arthritis (PsA) is a multidomain inflammatory disease requiring treatment strategies that consider peripheral arthritis, enthesitis, axial involvement, dactylitis, and skin disease simultaneously.

• Targeted therapies including TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors and JAK inhibitors have significantly improved outcomes, but incomplete responses and domain-specific refractory disease remain common.

• Treatment selection should consider comorbidities such as obesity, inflammatory bowel disease and cardiovascular risk, as well as patient preferences regarding route of administration.

• Emerging evidence suggests that metabolic factors, particularly obesity, influence treatment response and disease activity, highlighting the importance of addressing metabolic comorbidity as part of PsA management.

• Next-generation biologics and targeted oral agents may expand therapeutic options, but careful evaluation of efficacy across all PsA domains and long-term safety will remain essential.

Research Agenda:

• Identification and validation of biomarkers capable of predicting treatment response and guiding personalised therapy selection in PsA.

• Development of clinical trials designed to capture multidomain outcomes, including enthesitis, axial disease, structural progression and patient-reported outcomes.

• Prospective evaluation of combination or sequential targeted therapies to determine whether multi-pathway inhibition improves outcomes in refractory PsA.

• Investigation of therapies targeting upstream immune pathways and pathogenic immune cell populations, including TL1A inhibition and selective immune cell depletion strategies.

• Further exploration of immunometabolic pathways and the role of metabolic interventions, including incretin-based therapies, as potential disease-modifying approaches in PsA.

Tables and Figures

Drug (Brand)	US Approval	UK Approval	EU Approval	Mechanism of Action (MOA)	Drug Class
Abatacept (Orencia)	2017	2017	2017	T-cell costimulation inhibitor (binds CD80/86 to inhibit T-cell activation)	bDMARD
Adalimumab (Humira)	2005	2005	2005	Anti-TNF monoclonal antibody	bDMARD
Apremilast (Otezla)	2014	2015	2015	Phosphodiesterase-4 (PDE4) inhibitor	tsDMARD
Certolizumab pegol (Cimzia)	2013	2014	2013	PEGylated anti-TNF antibody fragment	bDMARD
Etanercept (Enbrel)	2002	2002	2002	TNF receptor-Fc fusion protein	bDMARD
Golimumab (Simponi)	2009	2009	2009	Anti-TNF monoclonal antibody	bDMARD
Guselkumab (Tremfya)	2020	2020	2020	Anti-IL-23p19 monoclonal antibody	bDMARD
Infliximab (Remicade)	2005	2005	2004	Chimeric anti-TNF monoclonal antibody	bDMARD
Ixekizumab (Taltz)	2017	2018	2018	Anti-IL-17A monoclonal antibody	bDMARD
Leflunomide (Arava)	*N/A*	1999	1999	Dihydroorotate dehydrogenase inhibitor (pyrimidine synthesis inhibition)	csDMARD
Risankizumab (Skyrizi)	2022	2021	2021	Anti-IL-23p19 monoclonal antibody	bDMARD
Secukinumab (Cosentyx)	2016	2015	2015	Anti-IL-17A monoclonal antibody	bDMARD
Tofacitinib (Xeljanz)	2017	2018	2018	JAK1/3 inhibitor (modulates multiple cytokine signaling pathways)	tsDMARD
Upadacitini	2021	2021	2021	Selective JAK1	tsDMARD

b (Rinvoq)				inhibitor	
Ustekinumab (Stelara)	2013	2013	2013	Anti-IL-12/23p40 monoclonal antibody	bDMARD

Table 1: Approved treatments for PsA in the United States (FDA), United Kingdom (MHRA), and European Union (EMA), including year of regulatory approval, mechanism of action (MoA), and drug class. csDMARD: conventional synthetic disease-modifying antirheumatic drug; bDMARD: biologic DMARD; tsDMARD: targeted synthetic DMARD.

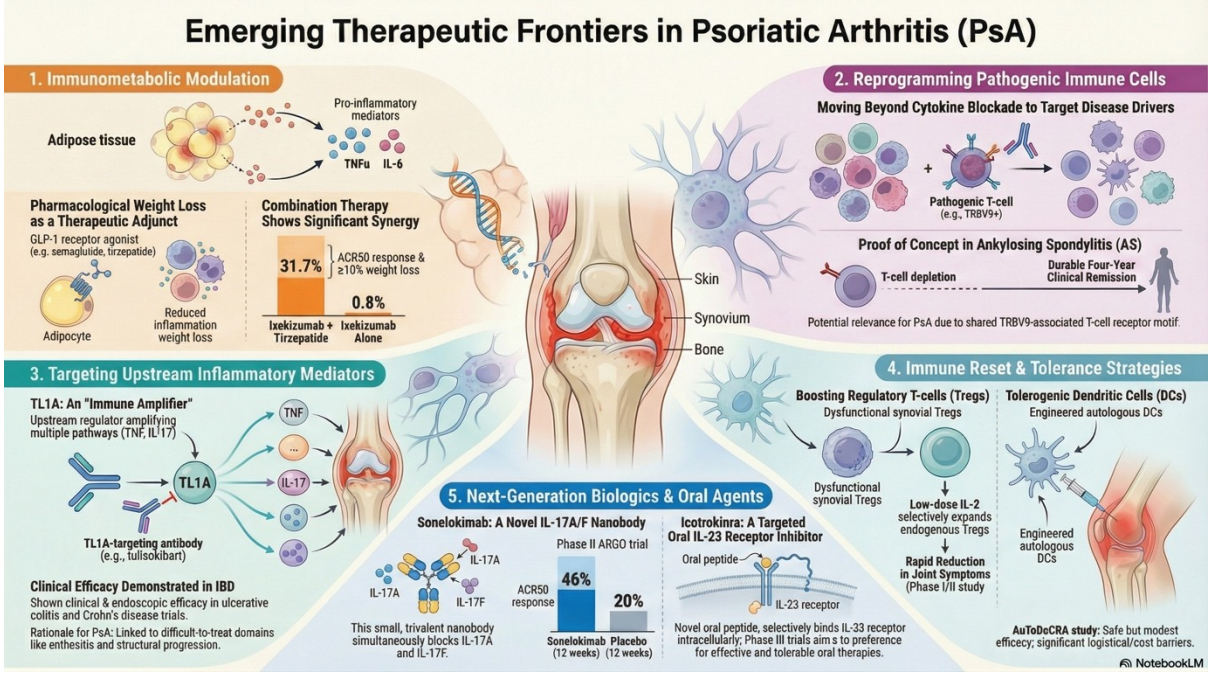

Figure 1: Overview of evolving treatment strategies in PsA, including immunometabollic modulation, reprogramming of pathogenic immune cells, targeting upstream inflammatory pathways, immune tolerance approaches, next-generation biologics and oral agents, and emerging combination and precision therapeutic strategies for multidomain disease

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