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Can We Prevent Psoriatic Arthritis?

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Abstract

Psoriatic arthritis (PsA) is a chronic, inflammatory musculoskeletal disease that often develops in individuals with psoriasis (PsO), typically following an average latency period of 7 years. Without treatment, PsA can lead to irreversible joint damage, functional impairment, and a range of comorbidities. Despite therapeutic advances, only a minority of patients achieve sustained remission, highlighting the need for new approaches, including disease prevention and early interception. This review explores the emerging concept of PsA prevention in individuals with psoriasis, by addressing modifiable risk factors—such as severe skin disease, nail involvement, and obesity—and predictors such as arthralgias and asymptomatic abnormalities on musculoskeletal ultrasound. Notably, PsO patients represent a unique preventive opportunity in rheumatology, as many treatments address both PsO and PsA, potentially minimizing additional therapeutic risks.

A recently proposed framework by the European Alliance of Associations for Rheumatology (EULAR) outlines three stages of progression from PsO to PsA, ranging from individuals 'at higher risk', to those with 'subclinical PsA', and finally to those with 'clinical PsA'. Findings from observational studies suggest that treatment of modifiable risk factors may reduce PsA incidence, though prospective data remain limited. Subclinical inflammation detected on imaging and the presence of arthralgia may identify individuals at imminent risk who could benefit from escalation of therapy. Nonetheless, further refinement of this population is necessary to avoid overtreatment. Ongoing clinical trials are expected to help clarify whether early intervention can truly intercept PsA and alter its natural history. Ultimately, success in PsA prevention will require multidisciplinary collaboration, refinement of risk stratification, and thoughtful integration of these screening strategies into clinical practice.

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease that shares both genetic and clinical features with other forms of spondyloarthritis. While it is commonly characterized by psoriasis (PsO) and arthritis, PsA encompasses other disease domains, such as enthesitis, axial disease, uveitis, inflammatory bowel disease, dactylitis and nail disease. PsA is also associated with numerous comorbidities, including cardiovascular disease, obesity, type

2 diabetes, hypertension, metabolic syndrome, fatty liver disease, osteoporosis, fibromyalgia, depression, and anxiety.[1] Left untreated, PsA can result in irreversible structural damage, functional impairment, and reduced quantity and quality of life—highlighting the need for timely and effective therapy.[2]

Despite available treatments, only approximately 30% of patients with PsA achieve remission with any given biologic therapy, making disease prevention an increasingly appealing concept.[2] This idea of disease prevention is not new to rheumatology, with several research groups across various rheumatologic diseases working to identify at-risk populations that may benefit from intervention prior to the onset of irreversible disease.[3] However, any early intervention must balance the potential benefits against both the risks and costs of treating individuals who may never develop the disease.

PsA presents a unique opportunity for interception, as approximately 70% of cases are preceded by PsO, with PsA developing on average 7 years after the onset of PsO.[4] This latency period offers a window for risk stratification—as only 30% of patients with PsO will develop PsA—and early intervention. Furthermore, PsO and PsA share common immunopathological pathways and many of the same therapies, potentially reducing incremental risks from early treatment. Therefore, carefully selected interventions could not only treat PsO but also prevent PsA and its associated complications in patients at high-risk for PsA development.[2] This review outlines current progress toward this goal.

Developing a Framework for Pre-Clinical Psoriatic Arthritis

Identifying patients at high-risk of developing PsA begins with understanding its risk factors. Established risk factors include obesity, severe psoriasis, nail involvement, and a family history of PsA in a first-degree relative.[4-6] Other potential risk factors include infections, mechanical stress, and depression, though data are mixed.[7]

Imaging of the synovio-entheseal complex may offer more sensitivity than clinical examination for detecting early musculoskeletal inflammation. Studies have shown that asymptomatic synovitis and enthesopathy occur more frequently in PsO patients compared to controls.[8,9] At the same time, the presence of such abnormalities in over 50% of PsO patients—and even in some healthy controls—on musculoskeletal ultrasound raises concerns about the lack of specificity with isolated imaging changes.[9]

Arthralgias, regardless of inflammatory pattern, also appear to be a predictor of imminent PsA. One study found that PsO patients with arthralgias had markedly higher PsA progression at 12 and 36 months (9.4% and 22.7%, respectively), compared to the annual incidence of 0.3 3.7% reported in the literature for all-comers with psoriasis.[10]

To support coordinated research efforts, three working groups have proposed frameworks to define the progression from PsO to PsA, integrating these risk factors and predictive markers.[4-6] Most recently, in 2023, the European Alliance of Associations for Rheumatology (EULAR) task force proposed a three-stage model describing the PsO-PsA continuum.[6]

- **Stage 1: At Higher Risk:** PsO patients with risk factors such as severe skin disease, nail involvement or high body mass index (BMI)
- **Stage 2: Subclinical PsA:** PsO patients with arthralgia and/or imaging evidence of synovio-entheseal inflammation without clinical synovitis
- **Stage 3: Clinical PsA:** Patients with PsO and clinical synovitis

While some task force members argue that patients with arthralgia and imaging evidence of synovio-entheseal inflammation could already be considered to have clinical PsA, EULAR consensus favours reserving the 'clinical PsA' label for those with definitive physical examination findings of synovitis, given the limited specificity of imaging as discussed previously. By designating patients with arthralgia and imaging findings as 'subclinical PsA', the framework encourages targeted research on this high-risk group.[6]

The EULAR model also outlines a typical timeline for disease progression: Stage 1 on average spans 7–12 years, Stage 2 usually precedes clinical PsA by 1–3 years, and Stage 3 marks disease onset. Risk factors are temporally stratified, with obesity, severe psoriasis, and nail disease being long-term risk factors (Stage 1), while arthralgia and musculoskeletal imaging abnormalities are short term risk factors (Stage 2). EULAR recommends that "prevention" applies to interventions targeting Stage 1, and "interception" refers to strategies aimed at Stage 2.[6]

The framework also shows the timeline required for prospective studies aiming to use PsA incidence as the outcome. For patients in Stage 2, the authors suggest that changes in arthralgias or

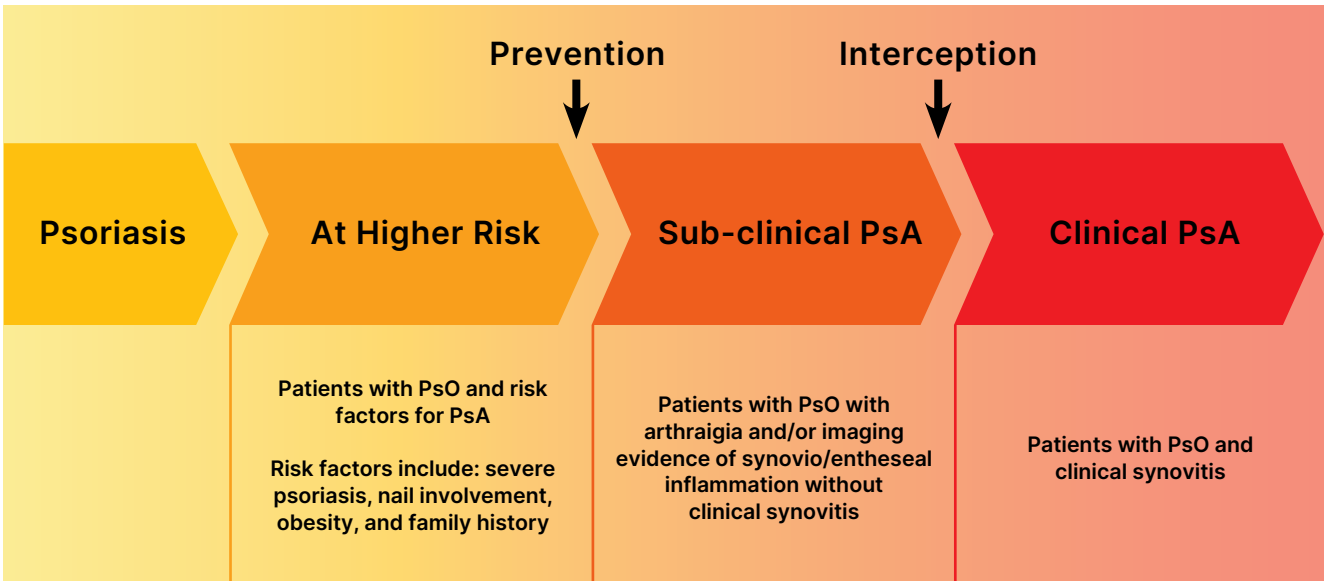

Figure 1. EULAR proposed phases of transition from PsO to PsA, adapted from Zabotti et al.[6]

Abbreviations: PsO: psoriasis; **PsA:** psoriatic arthritis

resolution of imaging abnormalities could serve as surrogate outcomes in trials evaluating PsA interception.[6] The EULAR framework is presented in **Figure 1**.

Shared Immunopathology of Psoriasis and Psoriatic Arthritis

A key rationale for focusing on PsA interception in PsO patients is the shared immunopathology between skin and joint disease as illustrated in **Figure 2**. Many therapies are effective in treating both PsO and PsA, suggesting that preventive treatment may pose minimal additional risks beyond treating PsO itself.[1] This is in contrast with strategies in other autoimmune diseases, where prevention often involves treating otherwise healthy individuals.

Both the skin and enthesis share similar microanatomical features, with the epidermis and fibrocartilage zones being relatively avascular and susceptible to Koebnerisation—a phenomenon whereby mechanical injury can trigger disease onset. Both sites are populated by similar innate immune cells—including resident macrophages, neutrophils, and plasmacytoid dendritic cells—as well as intermediate lymphocytes, such as group 3 innate lymphoid cells, γδ T cells, and mucosal-associated invariant T (MAIT) cells. Interleukin (IL)-23 released by innate myeloid cells can activate the intermediate lymphocytes, leading to the release of IL-17A, tumour necrosis factor (TNF), and other pro-inflammatory cytokines that drive skin and joint inflammation, bone erosion, and pathological bone formation. In addition, conventional T cells, including CD4+ and CD8+ T cells—particularly tissue-resident memory CD8+ T cells—are found at both sites.[12] These shared immune pathways support the feasibility of targeting this pathway to intercept disease before clinical joint symptoms arise.

Evidence to Date

Several studies to date have explored the prospect of PsA prevention and interception. Beginning with the risk factor of obesity, a prospective study of 90,189 individuals with incident psoriasis by Green et al found that linear reductions in BMI over a 10-year period were associated with a decreased risk of developing PsA, compared to those who maintained a constant BMI from the same baseline. This finding suggests that weight management may help prevent the onset of PsA.[13] Bariatric surgery has also been associated with lower PsA incidence: a Danish cohort study found gastric bypass (but not gastric banding) reduced PsA risk (hazard ratio [HR] 0.29, 95% confidence interval [CI] 0.12–0.71). The reason for these discrepant results between gastric bypass and banding remains unclear particularly as weight change data were not available in the study.[14] To date no studies have evaluated the effect of weight loss medications,

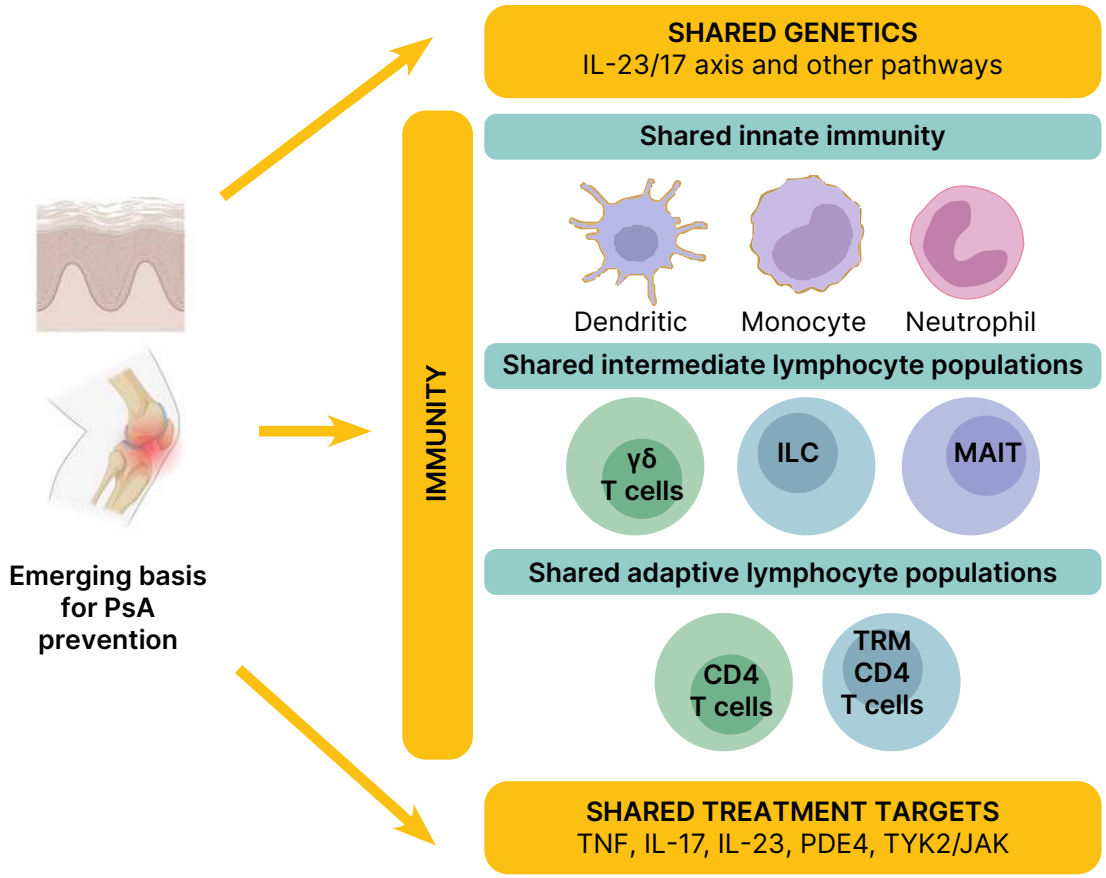

Figure 2. Emerging basis for PsA prevention based on therapeutic management of psoriasis; reproduced from López-Medina et al., Rheumatology (Oxford), 2024,[11] under the terms of the Creative Commons Attribution Licence (CC BY 4.0). https://creativecommons.org/licenses/by/4.0/

Abbreviations: ILC: innate lymphoid cells; **JAK:** Janus kinase; **MAIT:** mucosal-associated invariant T cell; **PDE4:** phosphodiesterase-4; **PsA:** psoriatic arthritis; **TRM:** tissue-resident memory T cell; **TYK2:** tyrosine kinase 2.

such as glucagon-like peptide-1 (GLP-1) receptor agonists for PsA prevention.

Several retrospective studies have assessed the impact of PsO therapies on PsA incidence. Gisondi et al. looked at 464 patients with moderate-to-severe PsO and found lower PsA in patients treated with biologic disease-modifying antirheumatic drugs (DMARDs) versus phototherapy (HR 0.53, 95% CI 0.30–0.94).[15] Conversely, Meer et al. reported higher PsA risk with biologics versus conventional DMARDs or phototherapy in a larger cohort of 193,709 individuals. However, the authors cautioned that these results may be due to confounding by indication and protopathic bias (i.e., treating early PsA symptoms before a formal diagnosis has been made).[16] In another study of nearly 20,000 patients, apremilast has shown lower PsA risk than methotrexate (HR 0.85, 95% CI 0.79–0.91).[17] Additionally, IL-23 and IL-12/23 inhibitors have been associated with lower PsA incidence compared to TNF inhibitors in two studies, while IL-17 inhibitors showed no significant difference in risk compared to TNF inhibitors.[18-19]

While many of these results are biologically plausible, they should be interpreted with caution. Observational studies are prone to confounding by indication, which occurs when treatments are prescribed based on disease severity or early symptoms—resulting in systematic differences between treatment groups that may influence outcomes independent of the treatment itself. These studies are also subject to selection bias (e.g., patients with more severe PsO being more likely to receive biologics), making the results not generalizable for all patients with psoriasis. Additionally, protopathic bias, as described

above, may occur when treatment is initiated for early, undiagnosed manifestations of PsA.[20] Nevertheless, these studies generate hypotheses for prospective trials.

Notably, most studies focus on managing patients with moderate-to-severe PsO, which itself is a major risk factor for PsA (Stage 1 of the EULAR framework). However, more research is needed for patients with subclinical PsA (Stage 2). One such study by Savage et al. evaluated 23 patients with PsO and ultrasound-confirmed subclinical enthesitis who were treated with ustekinumab for 52 weeks. The study reported reductions in ultrasound inflammation scores of 42.2% at week 24 and 47.5% at week 42, suggesting a potential benefit.[21] Additionally, a randomized placebo-controlled trial is currently underway to assess the effects of guselkumab in PsO patients with musculoskeletal ultrasound abnormalities with outcomes focused on changes in imaging and PsA incidence.[22]

Remaining Gaps

These interesting and encouraging results have raised new questions. Is it possible that some interventions could be effective in decreasing PsA incidence for those 'at higher risk of PsA' (stage 1) while others may be more suitable to implement for those with 'subclinical PsA' (stage 2). To achieve this level of precision, additional prospective studies are required to determine which therapies or strategies are the most effective at each stage. Given that not all patients with arthralgias and/or musculoskeletal imaging abnormalities progress to PsA, more precise tools are needed to define the group of patients most suitable for interception. Furthermore, the impact of PsA prevention on associated metabolic and psychological comorbidities remains unclear, as do the risk-benefit profile and cost-effectiveness of such strategies.

The feasibility and efficacy of screening all PsO patients with musculoskeletal ultrasound also requires further evaluation. Furthermore, since 30% of PsA patients do not have preceding PsO, the challenge remains as to how to prevent or intercept disease in this group. Ultimately, achieving success in PsA prevention and interception will require a substantial expansion of dedicated research and coordinated efforts among rheumatologists, dermatologists, and primary care physicians.

Conclusion

Preventing and intercepting PsA is becoming an increasingly feasible and compelling goal, particularly among individuals with psoriasis who exhibit well-established risk factors. The shared immunopathology between psoriasis and PsA, coupled with a defined pre-clinical window, provides strong justification for early, targeted intervention before the onset of clinical synovitis. Currently, there is good clinical rationale and evidence to treat risk factors—obesity, severe psoriasis, nail disease—based on existing guidelines, as they also have the potential to prevent the development of PsA.

However, despite growing momentum around PsA prevention and interception, caution is still warranted when considering escalation of therapy in psoriasis patients presenting with arthralgias and/or subclinical musculoskeletal abnormalities on imaging. Further stratification of this population is necessary to better identify those at highest risk of PsA development and to avoid potential overtreatment. The recently proposed EULAR framework offers a useful structure for studying this group and designing future trials. Observational insights can now be tested in prospective, controlled settings to evaluate whether PsA—and its associated comorbidities—can be effectively intercepted. As evidence continues to evolve, the thoughtful integration of preventive strategies into clinical practice holds significant promise for reducing the long-term burden of PsA before irreversible joint damage and comorbidities arise.

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