Prevention of Psoriatic Arthritis

The Need for Prospective Studies

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KEYWORDS

• Psoriasis • Psoriatic arthritis • Biologics

KEY POINTS

- Psoriatic arthritis (PsA) is a chronic inflammatory disease that develops in up to 30% of patients with psoriasis.
- Psoriasis represents a unique "pre-disease" state in which to identify at-risk individuals for PsA and investigate the opportunities for potential disease modification and prevention of PsA.
- Data obtained from retrospective studies have demonstrated a wide range of factors in patients with psoriasis associated with later development of psoriatic arthritis, including comorbidities, genetic, and therapy choice.
- However, given the limitations and potential biases of retrospective data, such as channeling bias, protopathic bias, coding errors/omissions, limited length of time contributed to claims data, and incomplete measurement of confounding variables, it may not be possible to interpret the potential impact of therapy on PsA delay/prevention.
- Thus, prospective observational studies and randomized clinical trials are crucial to understanding our ability to modify the transition from psoriasis to psoriatic arthritis.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, immune-mediated arthritis that presents heterogeneously with a wide range of symptoms, including joint and enthesis inflammation.[1] Around 1 in 3 patients with psoriasis will eventually develop PsA, with a conversion rate of 3% per year.[2,3] Because most patients with PsA will present several years earlier with cutaneous and/or nail psoriasis, identifying patients that are likely to develop PsA within this cohort is key to the early identification and treatment of the disease.[4,5] Identifying risk factors, signs, and symptoms of PsA in patients with psoriasis facilitates early intervention and perhaps even those who might benefit from preventive measures. In this review, the authors review factors influencing psoriatic arthritis development, evaluate evidence from the current literature regarding our ability to potentially impact disease transition from skin to join disease, and suggest

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the importance of future prospective studies in preventing PsA among psoriasis patients.

Epidemiology and Terminology

PsA affects anywhere from 0.1% to 1% of the world's population, and PsA prevalence has increased over the past several years, likely due to an increase in awareness and screening for the disease.[6–8] Studies suggest that PsA often goes underdiagnosed, suggesting a higher prevalence and disease burden than has been previously reported in the literature.[9,10]

PsA may present with a wide range of clinical signs, characterized into 6 domains: peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, nail disease; and associated with comorbidities such as inflammatory bowel disease (IBD), and uveitis.[11–14] The pathophysiology underlying these clinical features is complex, with a variety of factors—genetic, environmental, and immune-related—all contributing to disease progression.[1,6,15] Additionally, the transition from seemingly skin-limited inflammation in psoriasis, to musculoskeletal inflammation in PsA is still not well understood.[15] PsA is often difficult to treat, as only 40% or more of patients with PsA partially respond or fail to respond to therapy.[12,16–18] In this context, the idea of disease prevention and/or early intervention is a compelling strategy. To help support research in this area, a consensus statement from the Psoriasis and Psoriatic Arthritis Clinics Multicenter Advancement Network consortium presented specific terminology to help define individuals in the preclinical and early clinical phases of PsA: "increased risk for PsA," "psoriasis with asymptomatic synovio-entheseal imaging abnormalities," and "psoriasis with musculoskeletal symptoms not explained by other diagnoses" were a few of the categories presented.[13]

Genetic and Environmental Risk Factors for Psoriatic Arthritis

Genetic factors are thought to contribute to a significant risk of developing PsA in patients with psoriasis, with mutations in similar loci implicated in both the development of psoriasis and PsA.[19–21] Several loci have been identified as unique to PsA (IL-23R, TNF-induced protein), giving insight into the gene-related contribution to the development of PsA, with a machine-learning-based algorithm based on genetics accurately predicting PsA development.[22–24] Certain genes, such as HLA-B*44, HLA-C*06, and HLA-DRB1, have also been associated with milder diseases and lower incidences of PsA, with decreased frequencies of enthesitis and other PsA findings.[25,26]

Besides genetics, environmental factors are also thought to play a key role in PsA development. Trauma has been a commonly studied factor demonstrating key associations with an increased risk of PsA, especially fractures.[27–29] The microbiome has also been implicated in the pathogenesis of PsA, with psoriasis and PsA patients demonstrating different microbiota composition, with the precise mechanism still unknown.[30–32] Infection is another common factor thought to be associated with PsA, with several prospective cohort, cross-sectional, and case-control studies have demonstrated a statistically significant relationship between infections and PsA.[3,33] Infection, trauma, and other inflammatory or stressful events fall under the idea of "deep-koebnerization," in which injury or trauma may cause development of arthritis in the affected joints/areas.[27,34]

Comorbidities and Lifestyle Factors Associated with Increased Psoriatic Arthritis Risk

Obesity has been singled out as one of the most important modifiable risk factors for the development of PsA, and multiple studies have demonstrated an increasing risk of PsA with an increasing body mass index (BMI).[3,35–37] The leading pathophysiological explanation for this close relationship is that obesity leads to a chronic low-inflammatory state, with increased levels of inflammatory cytokines accelerating disease pathogenesis and hindering responses to therapy.[36,38–40] Other comorbidities such as alcohol use have been shown to have increased prevalence in PsA cohorts; however, due to the difficulties in accurate measurement and non-linear relationship, it is difficult to understand whether the increased association is due to biases or an actual predictive relationship.[29,41–43]

Clinical Signs of Early Psoriatic Arthritis Often Exist Prior to Diagnosis

PsA development has been shown to be related to several clinical signs such as the location of skin disease, tenosynovitis on imaging/image-based enthesopathy, and musculoskeletal complaints.[15,44–46] Imaging may be 1 key way to detect subclinical PsA development and may be a key tool to use to screen for patients at high risk, with several imaging findings unique to patients with PsA or at risk of developing PsA that may indicate initiation of disease processes leading to PsA.[44] Sonographic signs of enthesitis were linked to future PsA development, and over half of patients with synovitis detected via MRI developed PsA in the following year.[47,48] Besides imaging, studies have demonstrated increased prevalence

of musculoskeletal symptoms in the period leading up to the diagnosis of PsA, indicating that clinicians should be actively screening for PsA in patients with these specific complaints.[45,49] These clinical features are also embedded in the recently developed Psoriatic Arthritis Risk Estimation Tool and others that were developed as potential predictive tools of future transition to PsA.[50,51] However, many of these clinical factors (joint stiffness, imaging findings) found to be associated with PsA and used in prediction models may suggest the presence of already-present PsA, rather than a pre-disease or preventable state.

Reducing the Risk for Psoriatic Arthritis

Weight loss has been implicated as a possible protective factor against PsA development; a study demonstrated shown losing weight decreases disease activity, which may prevent PsA development.[37,42] Thus, given that BMI is a modifiable factor both through lifestyle and medications, weight loss may be one of the most important factors to address in patients with PsA to improve outcomes. Interestingly, statins have also been associated with a decreased risk of PsA and psoriasis, possibly due to anti-inflammatory effects.[52–54]

Do Targeted Systemic Therapies Prevent Psoriatic Arthritis Development in Patients with Psoriasis?

An important question in the field of psoriatic arthritis research is whether treating patients with psoriasis is associated with reduced risk for PsA, with is conflicting evidence supporting the concept that targeted systemic therapies may reduce the risk of PsA in patients with psoriasis. Three studies (Gisondi and colleagues, Felquer and colleagues, and Shalev and colleagues) from Italy, Argentina, and Israel, respectively, studied comparisons of PsA incidence/risk with biologic compared to phototherapy, topical treatments, or non-biologic treatments.[55–57] While Felquer and colleagues and Shalev and colleagues demonstrated statistically significant lowering of PsA rates among patients treated with biologics compared to respective controls (**Table 1**), Gisondi, and colleagues, demonstrated the opposite result, with their propensity-score-matched cohort demonstrating a higher risk of PsA development with biologic therapy. Confounding by indication and protopathic bias remain the key limitations in these studies, as therapeutic choices could have been impacted by outside factors, such as disease subtype, heightened suspicion for musculoskeletal disease, or goals of treatment. Lack of measurement of important confounders may further exacerbate bias. Additionally, channeling bias remains an issue in both these and other retrospective studies, especially those comparing outcomes amongst different biologics; different therapeutic options may be prescribed to groups with varying prognoses.[58]

Studies done in the United States comparing PsA risk in biologic versus other therapies (Meer and colleagues, Miao and colleagues, and Shahsavari and colleagues) have found conflicting information on the use of biologics—Meer, et al. found that biologic use was associated with an increase in PsA risk (hazard ratio [HR] 4.48 [95% confidence interval (CI) 4.23, 4.75]) compared to oral/phototherapy, while Miao, and colleagues and Shahsavari, and colleagues found decreased risk of PsA with biological systemic therapy compared to phototherapy or non-biologic systemic therapy.[53,59,60] The conflicting information between different studies and wide range of results underscore the challenge of relying on claims data, which is limited by potential for coding errors, coding omissions, limited follow-up times, and a lack of detail/ability to capture disease severity.[61,62]

Interestingly, a few studies such as Singla and colleagues and Strober and colleagues examined comparative ability to prevent PsA among different classes of biologics, asking whether one may be better than another in preventing PsA amongst psoriasis patients.[63,64] Singla and colleagues[63] found that IL-12/23 inhibitors and IL-23 inhibitors were associated with a significantly reduced incidence of PsA compared to TNF inhibitors (IL-12/23: HR 0.58 [95% CI 0.43, 0.76] IL-23: HR 0.41 [95% CI 0.17, 0.95]). Additionally, Strober and colleagues found similar results, with IL-23 inhibitors associated with a significant decrease in PsA incidence compared to TNF inhibitors (TNF: HR 2.03 [95% CI 1.48, 2.79]).[64] While thought-provoking, these datasets are similarly prone to risk of bias including protopathic and channeling bias limitations. IL-23 and IL-12/23 inhibitors for example, may be preferentially given to "skin-biased" patients with more skin disease and with fewer signs/symptoms of PsA; IL-17 and TNF inhibitors more likely prescribed to patients with signs/symptoms of PsA (even if uncoded as such) and therefore more likely to "develop" PsA in the future. It is, however, also intriguing to consider the possibility that there are mechanistic reasons to support of their findings—that is, perhaps IL23 inhibition is more impactful in preventing PsA disease progression based upon deeper impact on inflammatory cell populations in psoriatic skin, as opposed to TNF-inhibition, which may have more of a role in established synovial disease.[65] Still, the conflicting information between different

Table 1
Studies assessing psoriatic arthritis risk in patients on systemic therapy compared to other therapies

Author, Year	Study Type (Total Patient Number)	PsA Risk in Different Therapies	Strengths	Limitations
Gisondi et al,[55] 2022	Retrospective non-randomized cohort study (n = 464)	Biologics vs phototherapy: HR 0.27 (95% CI 0.11, 0.66)	Rheumatologist-diagnosed PsA Patients were studied over the course of 5+ years	Confounding by indication Propensity score showed opposite result (HR 2.07; 95% CI 0.87, 4.93)
Felquer et al,[57] 2022	Retrospective non-randomized propensity score-matched cohort study (n = 1719)	Biologics vs topicals: IRR 0.26 (95% CI 0.03, 0.94)	Used CASPAR criteria for PsA diagnosis Long period of follow up Propensity score matched cohorts	Unequal follow-up time; Higher than expected PsA incidence Single center study
Rosenthal et al,[56] 2022	Retrospective non-randomized propensity score-matched cohort study (n = 2965)	Biologics vs non-biologic systemic therapy: HR 0.72 (95% CI 0.53, 0.97)	Propensity score matching Large population-based, real-life cohort	No measurement of clinical features Possible violation of proportional hazards Possible non-expert PsA diagnosis
Meer et al,[86] 2022	Retrospective non-randomized cohort study (n = 34,890)	Biologics vs oral/phototherapy HR 4.48 (95% CI 4.23, 4.75)	Large sample size Propensity score matching	Confounding by indication; Propensity score 2.14 (95% CI 2.00, 2.28)
Singla et al,[63] 2023	Retrospective non-randomized cohort study (n = 15,501)	IL-12/23 vs TNF: HR 0.58 (95% CI 0.43, 0.76) IL-23 vs TNF: HR 0.41 (95% CI 0.17, 0.95) IL-17 vs TNF: HR 0.86 (95% CI 0.54, 1.38)	Utilized EHR data instead of claims data Results persisted in sensitivity analyses Propensity score matching Stratification amongst biologics	Confounding by indication; Collider bias
Miao et al,[59] 2023	Retrospective non-randomized cohort study (n = 1805)	Biologics vs phototherapy: HR 0.49 (95% CI 0.28, 0.83)	Age/sex/therapy length-matched cohorts Removed incident cases to account for confounding	Potential for residual protopathic bias; Variable (and limited) at-risk time among biologic group
Strober et al,[64] 2023	Retrospective non-randomized cohort study (n = 7345)	IL-17 vs IL-23i: HR 1.35 (95% CI 0.87, 2.12) IL-12/23 vs IL-23i: HR 1.24 (95% CI 0.81, 1.92) TNF vs IL-23i: HR 2.03 (95% CI 1.48, 2.79)	Utilized strict eligibility criteria to minimize baseline PsA risk Stratification amongst biologics	Channelling bias; Protopathic bias; Coding errors/coding omissions in claims

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Table 1
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Author, Year	Study Type (Total Patient Number)	PsA Risk in Different Therapies	Strengths	Limitations
Shahsavari et al,[60] 2023	Retrospective non-randomized cohort study (n = 8576)	TNF vs non-biologics: HR 1.15 Il-23 vs non-biologics: 1.03 IL-12/23 vs non-biologics: 0.78	Age/sex-matched cohorts Stratification amongst biologics Large control group sizes	Protopathic bias; No IL-17i included; Unclear what treatments control groups received

studies and wide range of results underscore the need for prospective and mechanistic studies for conclusive support.[66–68]

Limitations of Current Retrospective Studies

Many limitations in the data utilized for these studies stem from the retrospective nature of the data; that is, patients contribute limited amounts of time to claims data sets as they variably may leave and enter coverage; only a small percentage of patients (3%) with psoriasis develop PsA each year, with a median time to event of 9 years, limiting our ability to capture time-to-event.[3,15,69,70] Lack of incident users allows for multiple possible interferences with the data, such as confounding by indication, where the indication for treatment impacts outcome risks (ie, older patients with more comorbidities with PsA may be preferably prescribed a non-TNF inhibitor therapy, making non-TNF biologics appear safer).[71,72] Data utilized in studies are often sparse with regards to measurement of confounding variables, including body surface area, obesity, depression, disease severity, etc. **Box 1**[73–76] Many of these studies also lack stratification by mechanism of action of different biologics. When using retrospective data for genetic analyses, some genetic factors that are strongly associated with risk of PsA may be increasingly related to other risk factors through selective attrition.[77]

Additionally, protopathic bias, defined as when a drug is prescribed for an early manifestation of the outcome not yet detected, may be another common limitation of retrospective research and presents a major limitation, especially when comparing multiple therapies introduced at different timepoints.[78,79] Another significant challenge when studying PsA risk factors in psoriasis patients is collider bias, where because psoriasis is prevalent in the entire study population, it can affect measurements of risk (ie, smoking in PsA).[80,81] Finally, the key benefits of patient randomization are mostly lost in these retrospective analyses. Thus, while retrospective data can provide key information and insights into what factors are true risk (or protective) features, prospective studies are essential to study progression of psoriasis to psoriatic arthritis.

Prospective Studies

Prospective studies that study the transition from psoriasis to PsA are rare. However, a few epidemiologic efforts have examined this topic, demonstrating that a higher BMI, more severe psoriasis,

Box 1
Key biases and issues with retrospective studies

1. Selection bias
   a. Protopathic: Drug is prescribed for an early manifestation of the outcome not yet detected
   b. Confounding by indication: The indication for treatment impacts the risk of the outcome
2. Collider bias: An exposure and an outcome each influence a common third variable, and that variable, or collider, is controlled for by the study design or in the analysis (eg, smoking paradox in PsA)
3. Allocation/Channeling bias: Drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences.
4. Observation bias: a researcher's expectations or opinions influence what they perceive or record in a study
5. Retrospective data limitations:
   a. Lack of stratification on the mechanism of action of the biologic
   b. Lack of incident users
   c. Incomplete measurement of confounding variables, including body surface area (BSA), obesity, and depression.

nail pitting, and uveitis are associated with the development of PsA.[3,82,83] Still, prospective studies allow mitigation and prevention of many of the biases seen with retrospective studies (protopathic, confounding, channeling, observation, collider) with proper study design. Detailed patient characteristics can also be recorded to allow secondary analysis of other factors that may affect therapy effectiveness. However, it is important to acknowledge that there are still limitations even with randomized control trials , including some that are also present in retrospective studies: the lack of clear endpoints (there is no gold-standard diagnostic test of disease in PsA), and the possible requirement for decades of longitudinal data in order to demonstrate a difference between groups.[84,85] One of the more promising prospective studies in this area is the Preventing Arthritis in a Multicenter Psoriasis At-Risk cohort (PAMPA) Trial.[82]

Preventing Arthritis in a Multicenter Psoriasis At-Risk Trial

The PAMPA Trial is a multicenter, prospective, randomized, double-blind, placebo- controlled trial designed to assess the efficacy of an IL-23 inhibitor (guselkumab) in preventing conversion to PsA and ameliorating the severity of PsA in patients with psoriasis compared to placebo and non-systemic therapy.[82] The study includes high-risk psoriasis patients with psoriasis for over 2 years and with a BSA involvement of 3% or greater. The 2 co-primary endpoints are the change in musculoskeletal ultrasound score (modified PSonAR) at week 24, and the proportion of psoriasis patients who develop PsA according to the Classification criteria for Psoriatic ARthritis (CASPAR) criteria at week 96. Several secondary endpoints measure changes in clinical features and disease severity, including % BSA involvement, PsA severity, etc. Some challenges to this study remain—the 6-month/2-year study timeframe may not represent an adequate time for PsA development in the patient cohort to detect differences between groups. Additionally, only modest enrichment criteria for the transition to PsA are employed. Older age subjects in the study may confound the ability to diagnose disease both clinically and radiologically, as they will have less time to onset between skin and joint disease, but ultrasound results may reveal changes associated with aging rather than PsA. PAMPA does represent a key step in the right direction toward developing prospective randomized trials to further aid in the evaluation of preventative and disease-modifying strategies against PsA.

SUMMARY

PsA is an immune-mediated, inflammatory arthropathy with complex clinical signs and heterogeneous patient presentation that typically progresses from psoriasis. Current retrospective data show certain factors such as genetic factors, obesity, infections, bone or joint trauma, and musculoskeletal complaints may indicate increased PsA risk. Additionally, protective factors for prevention of PsA may include losing weight, certain medications like statins, and use of biologics in PsA treatment. However, given the potential biases and limitations of retrospective data such as collider bias, lack of detailed data, lack of incident users/confounding bias, it may not be possible to understand fully how psoriatic arthritis occurs in patients with psoriasis utilizing retrospective data. Thus, prospective studies and clinical trials are the key to fully understanding factors that may influence the transition from psoriasis to PsA. However, retrospective studies do give a key understanding of what areas may be of interest to further explore utilizing more detailed rigorous prospective studies.

CLINICS CARE POINTS

- PsA risk is increased by genetic factors, obesity, infections, or bone or joint trauma, and thus patients with these factors should be carefully monitored for signs and symptoms of psoriatic arthritis.
- Imaging and increased rates of musculoskeletal complaints are 2 possible methods of detecting early PsA.
- Risk factors and clinical features can assist in identifying psoriasis patients at risk for PsA, but the positive predictive value of these variables is not optimal.
- Retrospective studies provide challenges that limit their effectiveness in determining if individual therapies can delay or prevent PsA onset.
- Prospective studies provide the most appropriate strategy to determine if treatment of psoriasis patients at increased risk of PsA can delay or prevent onset of arthritis.

DISCLOSURES

A. Wu has no financial or commercial conflicting interests to disclose. J.U. Scher is a consultant for Bristol-Myers Squibb, Janssen, UCB, and

Pfizer. He is a co-PI in the PAMPA study in collaboration with Janssen. A. Ogdie is a consultant and/or investigator for Amgen, AbbVie, Bristol Myers Squibb, Celgene, CorEvitas, Eli Lilly, Gilead, GSK, Happify Health, Janssen, Novartis, Pfizer, and UCB. Christopher Ritchlin is a consultant and/or investigator for Amgen, AbbVie, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, and UCB Pharma. J.F. Merola is a consultant and/or investigator for Amgen, Astra-Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Abbvie, Dermavant, Eli Lilly, Incyte, Moonlake, Novartis, Janssen, UCB, Sanofi-Regeneron, Sun Pharma, Biogen, Pfizer, and Leo Pharma.

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