Preventing psoriatic arthritis in patients with psoriasis

Authors
Arani Vivekanantham*[1], Mariano Alves*[2], Alexis Ogdie[3], Enrique Soriano[2], Laura Coates[1]
***Authors contributed equally.**
Affiliations
Botnar Research Centre, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford, UK; 2. Rheumatology Section, Internal Medicine Service, Hospital Italiano de Buenos Aires, and University Hospital Italiano de Buenos Aires; 3. Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States1.
Corresponding author
Arani Vivekanantham, arani.vivekanantham@ndorms.ox.ac.uk

Abstract

Where is the evidence?

Can effective treatment of psoriasis (PsO) prevent the development of psoriatic arthritis (PsA)? In a Hot Topic Debate at the 7th World Psoriasis & Psoriatic Arthritis Conference, Dr Soriano and Dr Ogdie, both experts in the field, presented contrasting views based on existing research and clinical studies.[1] Dr Soriano argued that biologic treatments for PsO may reduce PsA risk, citing several retrospective studies. On the other hand, Dr Ogdie argued that current observational data are plagued by biases, making it difficult to conclude whether biologics play a protective role. The session outlined the complexity of this issue, with both speakers agreeing on the need for prospective randomised controlled trials, such as the ongoing PAMPA study, to provide definitive answers. Prof. Laura Coates added that identifying at-risk patients and intervening early to potentially prevent PsA may point to a strategic research approach to address these unanswered questions.

Can effective treatment of psoriasis prevent the development of psoriatic arthritis?

By Dr Soriano

To answer this question, Dr Soriano began his presentation by spotlighting two recent studies about this matter. One study by Acosta Felquer et al, a single centre retrospective cohort study with 461 patients years with psoriasis taking biologics, showed a lower risk of developing Psoriatic Arthritis (incidence rate ratio (IRR)=0.26; 95% CI 0.03-0.94; P=0.0111) compared with topics.[2] On the other hand, another study by Meer et al, a multi-centre retrospective cohort study that included data on 32,460 patients-years, reported an increased incidence of PsA among PsO patients using biologics (Hazard Ratio (HR)= 4.8; 95% CI 4.23 to 4.75) compared with oral or phototherapy users.[3] For an association found in these studies to be considered likely causal, the following Bradford Hill criteria must be met: consistency of findings, temporal sequence of association, and biological plausibility.[3] With respect to the consistency of findings, to date 7 retrospective studies have explored this association.[2,3,5-9] Six of them found a lower incidence of PsA in psoriatic patients treated with biologics compared with those treated with topi-cals or phototherapy.[2,59] The remaining manuscript concluded the opposite: patients with PsO treated with biologics have an increased incidence of PsA.[3] Two additional studies investigated the incidence of PsA in patients with severe psoriasis, using biologic therapy usage as a surrogate marker for severity and assessed the association with PsA risk.[10,11.] These results may differ because observational studies are susceptible to bias. Here, several types are particularly relevant: selection bias, confounding by indication, protopathic bias, survival bias, and assessment bias.[12] It should be emphasised that the possible direction of bias must always be considered. Most biases present in these observational studies tend to overestimate the incidence of PsA in patients treated with biologics, which might explain the results of Meer et al, Merola et al, and Lindberg et al. but not those of other studies. Moreover, these three studies showing increased risk were in large databases whereas the others are in clinical populations which could lead to some of these differences.

The reliance on electronic health records (EHR) and coded diagnoses for patient identification in Meer et al, a large retrospective study, raises concerns about potential confounding by indication and protopathic bias They found that there was a considerable number of diagnoses of PsA within the first year of biologic treatment. Although sensitivity analysis demonstrated a persisting increased risk of PsA development during the first 5 years, protopathic bias might be playing a role.[3]

In terms of biological plausibility, studies have shown that subclinical (asymptomatic) enthesitis is present in patients with PsO.[13] This enthesitis is pathogenic and a risk factor for PsA. Additionally, it can be effectively treated with biologics.[14] Similarly, biologic treatment can effectively abort subclinical synovitis.[15] Since skin inflammation triggers and activates inflammatory cells in joints and entheses,

it's reasonable to believe that a signifi-cant reduction in skin inflammation with effective treatment can decrease the incidence of PsA.[16] Therefore, Dr Soriano contended that resolving subclinical enthesitis, subclinical synovitis and skin inflammation might prevent PsA development. As a final point, Dr Soriano cited Meer et al study: "We do not suggest that these results should be interpreted causally; in other words, biologics likely do not cause PsA. On the contrary, there are several biases that may play a role in this finding, suggesting that caution should be used in interpreting observational studies that study the impact of biologic therapy on the development of PsA."[3]

Summing up, Dr Soriano alleged that, despite the lack of consistent findings across studies, the available data suggest a potential benefit of PsO treatment in PsA preven-tion. To conclude, Dr Soriano declared that while actual evidence suggests the potential benefits of biologics in preventing PsA development for PsO patients, definitive proof requires randomised trials. When finished, the PAMPA (Preventing Arthritis in a Multicentre Psoriasis At-Risk cohort) trial by Haberman et al. may be able to shed light on this issue.[17] Until then, although biologics aren't currently indicated for PsA prevention, they might offer an additional benefit for PsO patients already prescribed them.

Argument: Treatment of Psoriasis does not prevent PsA by Dr Ogdie.

Dr Ogdie described the complex story of progression to PsA among patients with psoriasis. She explained that multiple environmental factors (such as obesity, biomechanical stress, and infections) and genetic factors (such as having a first-degree relative with PsA or carrying the HLA-B27 allele) are known to contribute to inflammation or disease activity in psori-atic patients. This may be called preclin-ical PsA. Then, an unknown factor, such as trauma, comorbidities, biomechanical stress, or a microbiome-related event, may trigger a "second hit" response, leading to the development of evident PsA.[18]

When subclinical enthesitis, synovitis, or nonspecific symptoms are detected, this may be known as subclinical PsA.

Dr Ogdie then focused on the question "What is the effect of biologic therapies on the development of PsA in psoriasis?" Based on current evidence (observational studies), it is uncertain whether treating psoriasis with biologics reduces the risk of developing PsA. Data from retrospective observational studies have inherent design biases that make it difficult to draw firm conclusions.[19]

Dr Ogdie presented data from the Meer et al. study[3] suggesting a higher incidence of PsA in PsO patients treated with biologics (77/1000 person/years [PY]) compared with patients who had not received therapy (6/1000 PY), those who received oral therapy (62/1000 PY), or those who received phototherapy (26/1000 PY). These differences persisted despite adjustment for confounders, use of a time-varying analysis, use of propensity score matching, and after several sensitivity analyses. However, she raised concerns about several biases that may contribute to the results.

First of all, in the best-case scenario, treatment decisions for psoriasis involve a collaborative approach between dermatologists and patients, taking into account several factors:

- Severity of PsO
- Affected locations (e.g., face or genital regions)
- Emotional impact of skin lesions on the patient
- Severity of fatigue or other symptoms attributable to PsO
- Success and tolerance of previous treatments
- Comorbidities
- Risk tolerance of both the doctor and the patient
- Accessibility to treatments
- Presence of joint pain (e.g., if the dermatologist suspects the patient has or is about to develop PsA)
- Accessibility to a rheumatologist (surrogate for PsA diagnosis)

This approach is known as confounding by indication. None of these factors are directly measured and potential unmeasured confounders may alter the results. Second, dermatologists might prescribe biologics due to suspected PsA and not necessarily PsO severity alone. In this study, using EHR data, the highest incidence of PsA was within 6 to 12 months after prescription of the biologic therapy or oral therapy (protopathic bias).[3] Therefore, questions about whether the observed association reflects a direct effect of biologics on PsA risk or not, remain unanswered.

Then, Dr Ogdie mentioned potential biases of these retrospective studies which are important to consider when interpreting data to infer causality: confounding by indication, confounding by prognosis, unmeasured confounding, survival bias, protopathic bias, and collider stratifica-tion bias. She highlighted confounding by indication bias: patients are prescribed medication for "reasons" beyond a simple set of rules and often these reasons are not measured, and protopathic bias: a therapy is prescribed because of a symptom or an undiagnosed disease that is also the outcome of interest.

Singla et al. investigated the effects of different biologics prescribed to psoriatic patients on the incidence of PsA. They found that patients prescribed anti-TNF as their first biologic had the highest prob-ability of developing PsA vs other biologics, and that the risk was significantly lower with IL-12/23 (adjusted HR 0.58; 95% CI 0.430.76) and IL-23 (adjusted HR 0.41;95% CI 0.17-0.95) than with TNF inhibitors.[20] This highlights changeling bias but generates hypotheses.

A retrospective study based on electronic data presented at EULAR 2024 by Joven-Ibañez analysed the effect of different biologic therapies on the development of PsA in 1.101.000 psoriatic patients. They found a risk reduction in psoriatic patients receiving IL-12/23 and IL-23 in both first- and second-line treatment versus TNF inhibitors. These differences persist after propensity score matching and adjusted for different known risk factors for PsA.[21] However, the possibility of confounding by indication bias should be considered when interpreting these results.

Dr Ogdie remarked on the numerous limitations of retrospective analyses, such as reliance on codes, associations, not causations, observation bias, missed diagnoses, and missing data. For example, she noted that dermatologists in the US rarely code for symptoms like arthralgia/itis the six years prior PsA diagnosis.[22] Then Dr Ogdie presented a lighthearted interpretation of what an epidemiologist does, explaining they spend time doing precise "guesswork" based on "unreliable" data provided by those of "questionable data entry skills".

Finally, Dr Ogdie went to discuss the ongoing PAMPA study, a randomised, double-blind, placebo-controlled trial in the US investigating whether Guselkumab can prevent PsA in psoriatic patients with power doppler ultrasound evidence of inflammation.[17]

In conclusion, the available evidence is insufficient to answer whether biologic therapy can prevent the onset of PsA. Prospective studies and randomised controlled trials are needed to answer this question.

Can we prevent psorriatic arthritis?

Prof. Laura Coates gave an inspiring keynote talk on the topical area of 'Can we prevent psoriatic arthritis (PsA)?'[23] She began by explaining that we do not know if PsA can be prevented but that she will focus on how we should answer the question through the 'PICO' (Population, Intervention, Comparison, Outcome) framework.

In terms of identifying the population that we need to recruit and study; this will need to include patients with psoriasis who are at high risk of developing PsA. From the current evidence, we know that the following features increase your risk of developing PsA: positive family history, higher psoriasis severity (PASI), longer psoriasis duration, arthralgia, stiffness, fatigue, being overweight (BMI >35), uveitis history, thyroid disease history, site of psoriasis (nail, scalp, gluteal), hyperlipidaemia, depression, smoking and trauma. In contrast, protective features include very long psoriasis duration and smoking (which can also be a risk of developing PsA)[24]. Lindbergh et al's study showed that the more severe the psoriasis is (using treatment as a proxy), the higher the risk of developing PsA is.[25] However, this may be due to confounding; Merola et al found that patients' risk of developing PsA is much higher after being started on a conventional synthetic or biologic DMARD.[26] This may be due to the Dermatologists choosing a systemic treatment as the patient may have reported having joint symptoms.

Eder et al. have recently published a study on a clinical risk prediction model for PsA, called 'PRESTO' (prediction of PsA tool), which aims to predict your risk of developing PsA in 1- and 5-years' time. The predictors in the 1-year model included age, male sex, positive family history of psoriasis, back stiffness, nail pitting, stiffness level (VAS 0-100), use of bDMARD for psoriasis, PtGA (very good/good versus fair/poor), patient pain severity (any level versus none). The predictors in the 5-year model included morning stiffness, PASI score, psoriatic nail lesion, FACIT-fatigue score, use of non-bDMARD systemic therapy or phototherapy and patient pain severity (any level versus none).[27]

Another important consideration when identifying the population to study is when to intervene. There is an evolution of psoriasis to PsA with people developing sub-clinical symptoms/imaging changes/basic immunological changes before they are diagnosed with PsA. Currently, we only treat once someone has developed a diagnosis of PsA, but Prof. Coates questioned whether if we treat people in the phases (pre-clinical, sub-clinical, prodromal) before they develop PsA, we can change the outcome of them then developing PsA.

Prof. Coates then went on to highlight the important work of Perez-Chada et al in defining classification terminology for patients who are in this 'middle' phase where they have not yet got a diagnosis of PsA but have some features to show they are progressing towards that diagnosis.[28]

Moving onto the 'intervention' part of the PICO question- this can be done either via pharmacological or non-pharmacological (i.e., lifestyle) modifications. The key questions around this are how long we treat people and how long we keep monitoring them for off-treatment/inter-vention afterwards. The iPROLEPSIS consortium running across Europe in PsA is looking at digital non-pharmacological interventions through a series of games which aim to manage stress, for example, to improve people's outcomes.[29]

In terms of the 'comparator' part of the PICO question, the control could be no treatment and we ideally should be randomising patients but the ethical implications of this need to be considered. It would not be ethical to withhold treatment from people with moderate to severe psoriasis. If we do not randomise, we need to consider if we can control for confounders, and this may be easier for lifestyle interventions as opposed to medications. For the 'outcome' part of the PICO question, Prof. Coates reiterated the importance of having agreed definitions of the pre-PsA phases to ensure we recruit suitable patients for our studies.

Prof. Coates then went on to discuss several ongoing studies in this area. The PAMPA study in the US is looking at giving psoriasis patients who have had the disease >2 years, with a BSA <3% and USS inflammation but no symp-toms, guselkumab versus placebo over 24 weeks and following them up over 2 years to see if this impacts on their outcomes.[30] The HIPPOCRATES consortium, which is also running across Europe in PsA, is running a study called the HIPPOCRATES Prospective Observational Study (HPOS). This study is currently recruiting patients for a web-based study to follow people with psoriasis to see who gets PsA and embed interventional studies into this. Over 3000 participants have been recruited to date. The Psorcast study developed an app which helps patients monitor themselves for the development of PsA.[31] Moreover, the iPROLEPSIS study is also developing an app to identify and monitor changes in psoriasis patients before they develop PsA or a flare of their PsA.

In conclusion, Prof. Coates concluded that there is a huge potential to answer this question with an easily identifiable psori-asis population that we can study. She explained that we need to evaluate the risk of developing PsA more accurately and we need to know what treatment is best; it might not be the same treatment that treats disease that also prevents disease. She reiterated that all the way through it is important to consider patient acceptability and whether they would be happy to take part in such studies.

Take home messages

The debate at the 7th World Psoriasis & Psoriatic Arthritis Conference covered the complex relationship between psoriasis treatment and the prevention of psoriatic arthritis. While Dr Soriano highlighted studies suggesting that biologics may lower the risk of developing PsA, Dr Ogdie countered with the limitations of current observational studies, which are prone to biases such as confounding by indication and protopathic bias. Both experts acknowledged the need for prospective randomised trials, such as the ongoing PAMPA study, to determine whether biologic therapies can effectively prevent PsA. Moreover, Prof. Laura Coates stressed the importance of identifying at-risk patients early and exploring both pharmacological and non-pharmacological interventions. Ultimately, more robust data is required before definitive conclusions can be drawn about whether biologic treatment of psoriasis can prevent PsA.

Conflict of interest

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Mental health in psoriatic disease

Authors
Wiebke Sondermann[1], Frederik Krefting[1], Stefanie Hölsken[2]
Affiliations
1. Department of Dermatology, Venereology and Allergology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany; 2. Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany.
Corresponding author
Wiebke Sondermann, wiebke.sondermann@uk-essen.de

Abstract
Psoriatic disease is strongly associated with psychological comorbidities such as depression and anxiety disorders. One possible explanation for the close association between psychological burden and psoriatic disease is the common stigmatising attitude of society due to easily visible skin manifestations in affected patients. However, this relatively straightforward explanation may not be sufficient to account for all the observed effects. Current understanding views psoriatic disease as a systemic inflammatory condition with documented proinflammatory reactions that go beyond the skin. The observation of peripheral inflammation both in psoriatic disease and in depression suggests that this may be one of the shared mechanisms of both diseases, underlying the high rates of psychological comorbidity and especially depression. Several studies that assessed the efficacy of systemic treatments for psoriatic disease could show an improvement in psychological symptoms over the course of the treatment. A question that is still difficult to answer in the overall context is in how far improved depression is a direct effect of the anti-inflammatory treatment or rather an indirect effect of the improved skin condition that leads to a better psychological status. Screening for comorbid mental health diseases should be standardised and implemented on a regular basis in the dermatological practice in order to alleviate the associated psychological burden.

Introduction
Psoriatic disease is a chronic inflammatory condition that leads to typical erythema-tous, scaly skin plaques and affects 2-3% of adults in Western countries.[1,2]

Current understanding views psoriatic disease as a chronic, systemic, immune-mediated inflammatory disorder com prising three major domains: the skin, the bones/ joints, and the blood vessels, all characterised by a similar pattern of inflammation.[3] Apart from these major domains, psoriatic disease is associated with a number of concomitant conditions referred to as comorbidity.[4] Among these, cardiovascular and metabolic disorders need to be mentioned in particular. Meanwhile, different psychiatric diseases such as depression have also been recognised as comorbidity of psoriatic disease, which was insufficiently taken into account in the past.[5]

A growing body of data shows that the presence of psychiatric comorbidity is of high importance in the management of psoriatic disease for several reasons.

Prevalence of psychiatric comorbity

Depression
Depression is a serious psychiatric illness that often presents with a combination of