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VIEWPOINT

Association between biological immunotherapy for psoriasis and time to incident inflammatory arthritis: limitations and opportunities

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ABSTRACT

Psoriatic arthritis (PsA) is a chronic inflammatory immune-mediated disease that affects approximately 30% of psoriasis patients. In most cases, skin disease clearly precedes the musculoskeletal disease. Some studies suggest that targeted treatment may intercept the disease course and prevent psoriasis patients from developing PsA. A recent population-based retrospective analysis in 15 501 psoriasis patients evaluated the association between different biological treatment strategies and time to incident inflammatory arthritis based on data in a US electronic health records database. A cumulative incidence of 2.6 PsA cases per 100 person-years was determined. The multivariable regression analysis revealed a significantly lower risk of developing inflammatory arthritis in patients who had been prescribed interleukin (IL)-12/23 or IL-23 inhibitors compared with tumour necrosis factor (TNF) inhibitor-treated patients, whereas there was no significant difference in risk for patients prescribed inhibitors of IL-17 versus TNF. Although the analysis was based on a large set of clinical data and the findings were rigorously evaluated, there are some limitations in interpretation due to the study design. Prospective clinical trials are missing, and retrospective data analyses from clinical trials or population-based studies show conflicting results. Overall, the recent data on prevention of PsA in patients with psoriasis support the high need to characterise biomarkers of increased risk and perform prospective clinical trials to give a clear guidance on possibilities for disease interception in psoriatic disease.

Psoriatic arthritis (PsA) is a chronic immune-mediated disease that affects approximately 30% of plaque-type psoriasis (PsO) patients.[1] There are different steps in the transition process from PsO to clinically manifest PsA,[2] including genetic disposition, dysbiosis and mechanical triggers for PsA development[3] (figure 1). However, it is still unknown which PsO patients will later develop PsA. Many studies have shown that the severity of PsO may be associated with the risk of developing PsA. Therefore, it might be assumed that efficient disease control or even remission of the skin condition reduces the risk of PsA. This hypothesis leads to several-related questions: To interrupt PsA development, does it really matter how the skin condition is controlled? And if the type of skin treatment does matter, is there a need for systemic therapy, or is it equivalent to use ultraviolet and/or topical treatment? If there is the need for systemic treatment, would reduced PsA development also be expected in 'super-responders' to methotrexate or ciclosporin A, or does the therapy have to be a biological or targeted synthetic therapy? If so, does the systemic therapy need to have a specific mechanism of action?

Targeted biological immune-modulating therapies, such as inhibitors of tumour necrosis factor (TNF), interleukin (IL)-12/23, IL-23 or IL-17, are licensed and effective in both PsO and PsA. These treatments show high levels of efficacy for treating skin PsO, but response rates for musculoskeletal outcomes in PsA are lower.[4]

In their recent work, Singla *et al*[5] performed a post hoc analysis of data from PsO patients who were treated with different types of biological immunotherapy, with a focus on the time to onset of inflammatory arthritis. Data were derived from the US-based TriNetX electronic health records database between January 2014 and June 2022. Patients were included if they had PsO (based on International Classification of Diseases (ICD) codes at ≥2 time points >30 days apart) and a newly prescribed biological treatment (inhibitors of TNF, IL-17, IL-23 and IL-12/23) on or after the date of a first PsO diagnosis code. The time to incident inflammatory arthritis, defined by the first occurrence of a diagnostic code for PsA or other inflammatory arthritis after initiation of biological therapy, was analysed to

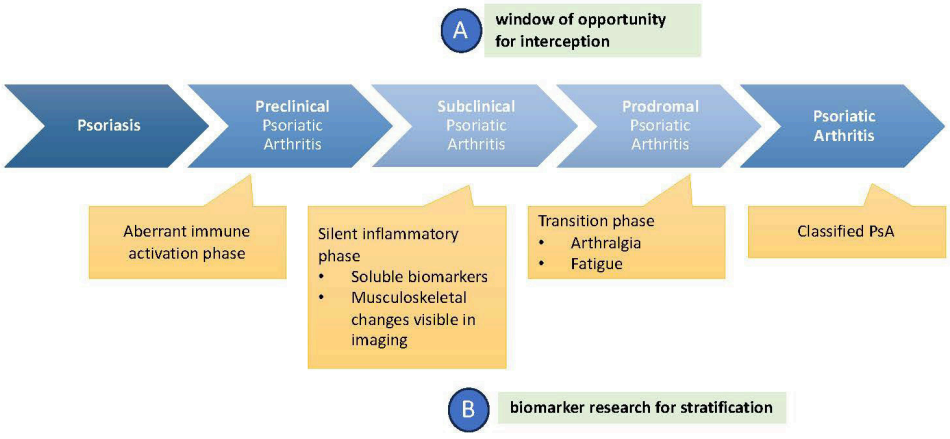

Figure 1 Transition process from PsO to PsA (modified from Scher *et al*[2] and Köhm *et al*[23]); (A) time frame for the proposed 'window of opportunity' for disease interception[21]; (B) time frame for biomarker research for stratification of at-risk patients for PsA development. PsA, psoriatic arthritis; PsO, plaque-type psoriasis.

calculate the time-dependent risk for the development of arthritis. A total of 15 501 patients fulfilled the inclusion criteria and 976 (6.3%) developed inflammatory arthritis; the cumulative incidence was 2.6 cases per 100 person-years. Multivariable regression analysis revealed a significantly lower risk of developing inflammatory arthritis in patients who had been prescribed IL-12/23 or IL-23 inhibitors compared with TNF inhibitor-treated patients. There was no significant difference for IL-17 inhibitors compared with TNF inhibitors. The results were stable for numerous sensitivity analyses including an increased threshold for diagnosis of inflammatory arthritis, indicating sound findings. However, these findings are only meaningful if the following can be assumed with reasonable certainty: (1) all patients with a code for PsO but no code for PsA on the cut-off date of the observation period are certain to have only a skin manifestation, that is, arthritis has been competently excluded; and (2) any new PsA during the observation period has been reliably detected and coded.

The goal to prevent PsA development or delay its occurrence in PsO patients by targeted treatment is one of the hottest topics in rheumatology today. The work of Singla *et al*[5] based on retrospective data from health records reveals promising results in favour of IL-12/23 or IL-23 inhibitor treatments, but it also illustrates the limitations of data analysis and interpretation of the results.

Of the different biological and targeted synthetic systemic treatment options available for PsO and PsA, the IL-17/23 pathway is believed to be a vital driver of the inflammatory processes observed in PsO and PsA and seems to have a particularly high potential for PsA disease interception.[6] IL-23 is a proinflammatory cytokine that plays a crucial role in the pathogenesis of psoriatic disease by stimulating the proliferation and activation of immune cells, particularly T-helper 17 (Th17) cells, which produce other inflammatory cytokines such as IL-17.[7 8] A potentially important function of IL-23 inhibition in the prevention of PsA is its effect on tissue-resident memory T cells.[8] IL-12/23 inhibitors, such as ustekinumab, and IL-23 inhibitors, such as guselkumab and risankizumab, prevent the interaction of IL-23 with immune cells, thereby reducing the production of inflammatory cytokines and potentially improving memory T-cell function.

Although PsA is a disease for which a risk population (PsO patients) is already defined, biomarkers to identify PsO patients with a high probability of developing PsA are still under investigation. Clinical risk factors have been reported from different meta-analyses but are limited by low sensitivity and specificity.[2 9] Initiatives to characterise PsO patients at high risk for the development of PsA by imaging did not reveal clear guidance. Subclinical forms of PsA are not easy to detect in PsO patients because clinical symptoms (eg, arthralgia or fatigue) and anatomical signs of inflammation are not specific for musculoskeletal inflammation. For example, enthesitis, which is described as prodromal musculoskeletal inflammation in PsA patients,[10] can be triggered in healthy patients by extensive mechanical stress[11] and is detectable in PsO patients without later development of PsA.[12 13] These data suggest that there is not only a one-way street to PsA development, but may also be musculoskeletal inflammatory disease states that resolve on their own.

Data from prospective controlled clinical studies on the potential of biologics to prevent or delay PsA development are missing. A prospective randomised controlled trial on prevention of PsA using guselkumab recently started recruitment.[14] A few retrospective data analyses are available, in addition to the work of Singla *et al*,[7] but interpretation of these studies is complicated by the heterogeneity of populations and settings, thereby limiting the studies' ability to address the underlying question. Aronovich *et al*[15] analysed the potential of lowering the risk of PsA development by biological treatment from the existing literature data in a systemic review. Only four publications were sufficiently reliable to be included in this review, and all were based on retrospective data analysis with B-level evidence. Two of the studies included preselected patients attending dermatology or dermatology–rheumatology collaboration centres, and one was

a large population-based study based on coding from healthcare records, similar to the approach of Singla *et al*.[5] The population-based study included large data sets (193 709 patients[16]); the range of data from the three other studies varied from >400 to 1000 patients and the overall observation period ranged between 2.5 and 18 years.[17] PsA was determined by a rheumatologist in the dermatological–rheumatological collaborative studies, but not in the others. Two studies were performed in Europe, one in North America, and one in South America. The use of biologics to treat PsO ranged from 5.9% to 50% of patients. TNF inhibitor treatment was the most frequently used biological treatment (at least 50% in each study), followed by IL-23 and IL-17 inhibitors (both approximately 10%). PsO treatments in the control group ranged from no therapy to phototherapy to conventional synthetic systemic treatments with or without combination to phototherapy.

The incidence rate of PsA (per 100 patient-years) in the overall population of patients with PsO showed similar values for three of the four studies: 1.55,[18] 1.37[17] and 1.51.[19] Meer *et al*[16] reported a lower incidence of 0.975, whereas Singla *et al* reported a much higher overall rate of 2.6.[5] Taking biological treatment into account, the incidence of PsA was consistently lower in patients receiving biological systemic treatments than in the control group in three studies: 0.55,[18] 1.20[17] and 0.87.[19] However in the fourth study by Meer *et al*,[16] which included the largest number of patients (>150 000), the PsA incidence was higher in patients treated with biologics than in the control group (7.72 vs 6.20). So, the existing data show conflicting results with respect to the ability of biologics to prevent PsA development.

As in the study by Singla *et al*,[5] the Meer *et al*[16] study was able to include a large number of patients due to its population-based design. Unfortunately, diagnosis was determined by ICD coding only, without confirmation by a dermatologist or rheumatologist. This is a limitation of the design, as diagnosis is not verified and documentation via healthcare records might be biased due to local circumstances. Especially for PsO/PsA cohorts, in which some medications may be limited in different regions based on the exact diagnosis, there is a risk of a fast diagnosis without precise classification, making the results less reliable.

Due to the limitations of currently available studies on prevention of PsA, prospective clinical trials are clearly needed to give consistent guidance on the potential of biological treatments for disease interception. There are specific activities of a dedicated European Alliance of Associations for Rheumatology task force to define clinical and imaging landmarks in the transition from PsO to PsA to harmonise patient groups for specific clinical trials on prevention and disease interception. Zabotti *et al*[20] recently published 'points to consider for the definition of clinical and imaging features suspicious for progression from psoriasis to psoriatic arthritis' as a helpful guidance for clinical research projects in this field. But controlled trials are not the only elements needed for future research on this topic. In addition, the stratification of at-risk profiles must be expanded, including molecular-level biomarker research to characterise PsO patients at high risk for PsA development, which may help to increase the acceptance of early treatment with targeted biological therapies for those patients. This is not currently reflected in treatment recommendations and needs to be added. Otherwise, the chance to identify those patients early, during the 'window of opportunity' to intercept PsA development, is low independent of treatment options. The correct timing seems to be as important as the choice of treatment and the stratification of PsO patients (figure 1). Zabotti *et al*[21] discussed the potential of guselkumab treatment in a 'window of opportunity' for arthritis interception observed in their outpatient clinic in four patients with PsO at risk for the development of PsA as defined by clinical data and inflammatory signs in ultrasound imaging. Despite the high-risk profiles of these patients, disease activity assessments revealed an improvement at month 6 after guselkumab initiation in Psoriasis Area and Severity Index, tender joint count and pain, and at 52 weeks, none of the patients had a diagnosis of PsA. Here, the timing of biological treatment to prevent PsA or delay the onset is also associated with clinical findings. Both treatment optimisation and biomarker research on the transition process from PsO to PsA will be the key components of the research agenda for the next decade to optimise the treatment and care of psoriatic disease and lower costs for treatments and diagnostics. Promising initiatives have already started, for example, the European consortium HIPPOCRATES (Health initiatives in Psoriasis and PsOriatic arthritis ConsoRTium European States) which has published the first results on OMICs (e.g. proteomics, metabolomics, lipidomics) analysis as an additional tool for the stratification of patients at-risk.[22]

In conclusion, IL-23 inhibition seems to be a promising treatment option to delay or prevent the onset of PsA in PsO patients, given its pathophysiological characteristics, its safety profile and the findings from Singla *et al*.[5] The possible efficacy of other classes of biological treatments on disease interception has also been suggested in studies by Acosta Felquer *et al*,[18] Gisondi *et al*[17] and Rosenthal *et al*[19] but the data are not fully consistent and should be interpreted with caution given the limitations of these studies. To fully understand how best to achieve the promising goal of preventing or reducing PsA development in patients with PsO, more information on biomarkers for at-risk patients and prospective clinical trials of different therapies will be required.

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