Psoriatic arthritis (PsA) is a chronic immune-mediated disease that affects approximately 30% of plaque-type psoriasis (PsO) patients. There are different steps in the transition process from PsO to clinically manifest PsA, including genetic disposition, dysbiosis and mechanical triggers for PsA development (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. In their recent work, Singla et al 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...
免疫细胞，特别是T细胞，对疾病的刺激促进了细胞的增殖和激活，对银屑病的发病机制起着至关重要的作用。T细胞、特别是Th17细胞，例如IL-23抑制剂，如古塞库马和瑞坦库马，可以预防IL-23与免疫细胞的相互作用，从而降低炎症细胞因子的产生。

数据表明，IL-23抑制剂，如古塞库马和瑞坦库马，可以预防IL-23与免疫细胞的相互作用，从而降低炎症细胞因子的产生。然而，这些发现仅在合理假设下才能被合理地解释：(1) 所有PsO患者在出院日期的观察期后是否会发生只有皮肤表现的现象，即是，关节炎已经是由其他原因引起的；(2) 任何新出现的PsA在观察期后已被可靠地检测和编码。

图1：从PsO到PsA的过渡过程（修改自Scher等人和Köhnm等人）：(A) 提出的"机会窗口"的时间框架；(B) 预防PsA的生物标志物研究。

根据多变量回归分析，PsO患者中有501人符合纳入标准，占6.3%，1551人符合纳入标准，占2.6%。PsO患者中有2.6%的人在100名患者中是皮炎性关节炎。数据表明，IL-12/23或IL-23抑制剂与TNF抑制剂-治疗的患者相比。没有显著差异。对于IL-17抑制剂与TNF抑制剂相比。结果表明，对IL-17抑制剂的敏感性分析显示与IL-12/23或IL-23抑制剂相比，具有显著较低的风险。IL-17抑制剂，如古塞库马和瑞坦库马，具有较高的敏感性，但有较低的特异性。在PsO患者中，PsA的累积发病率是2.6/100人-年。虽然PsA是一种疾病，其风险人口PsO患者已经定义，但PsO患者有高概率发展PsA的生物标志物尚未确定。当PsA发展时，但可能也是骨骼肌肉炎症。例如，附着炎，如肌腱炎或附着炎等，是骨骼肌肉炎症的一种。然而，临床症状（如关节炎或疲劳）和解剖学迹象不特定于骨骼肌肉炎症。对于PsA的迹象在PsO患者中很难检测到，因为没有明确的指导。亚临床形式的PsA患者可能被错误地归类为PsO患者，其后不会发展为PsA。这些数据表明，虽然PsO患者有出现PsA的可能性，但PsA的发展可能受生物标志物的影响。
a large population-based study based on coding from healthcare records, similar to the approach of Singla et al. The population-based study included large data sets (193,709 patients); 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. 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 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, 1.37, and 1.51. Meer et al. reported a lower incidence of 0.975, whereas Singla et al. reported a much higher overall rate of 2.6. 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, 1.20, and 0.87. However in the fourth study by Meer et al., 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., the Meer et al. 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 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. 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.

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. The possible efficacy of other classes of biological treatments on disease interception has also been suggested in studies by Acosta Felquer et al., Gisondi et al. and Rosenthal et al. 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.
REFERENCES