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Title

Intercepting Psoriatic Arthritis in Patients with Psoriasis- Buy one get one free?

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Psoriatic arthritis (PsA) mostly develops in patients with an established diagnosis of psoriasis (PsO) (1). Following the onset of PsA, structural articular damage and loss of function often occur, leading to impairment in quality of life above and beyond that seen in PsO alone (2). Psoriasis registry studies show a progression to PsA in around 1.5-3% per year in PsO subjects, although figures may be even higher when PsO associates with other factors (e.g. arthralgia) (3). Reducing this rate of PsA development and identifying PsO subjects at higher risk for PsA progression is of paramount importance, especially given that many PsO therapies have been independently verified as being efficacious for established PsA. Therefore, by extension, these therapies might also be expected to work at the earliest stages of PsO-associated inflammatory arthritis, where better therapeutic effectiveness is generally expected (4).

The ability to characterise the pre-clinical phases of autoimmune diseases, as initially in type 1 diabetes (T1DM) (5), was followed by other diseases, including rheumatoid arthritis (RA) (6) or autoimmune connective tissue diseases (CTD) (7). They provide the unique window of opportunity for therapeutic interventions in the pre-clinical stage of disease. Interventions applied at this point, as the hypothesis goes, would minimise disease burden and subsequent irreversible joint damage leading to functional impairment, and long-term disability, eventually to reducing the complications and socioeconomic impact of disease. Historically, the prevention of diseases such as T1DM, e.g. with cyclosporine, were marred by incomplete responses and drug toxicity (8). Nonetheless, proof of concept for disease prevention was established. In this editorial, we discuss emerging and conflicting evidence about early stage therapy for PsA. Specifically, we will explore the concept of prescription of disease-modifying anti-rheumatic drugs (DMARDs), including biological DMARDs (b-DMARDs), in subjects with moderate-to-severe PsO, at no extra cost to the health payers and no additional risk for patients, and the related impact on the interception of the evolution of PsO to PsA (Figure 1A-B). We dubbed this approach “buy one, get one for free”, as beneficial effects on one manifestation of psoriatic disease would result from interventions prescribed to treat other, different signs or symptoms.

Predictive markers for inflammatory disease development usually focus on laboratory biomarkers, like anti-citrullinated protein antibodies (ACPA) used in RA (positive in 70% of cases). However, rather than laboratory tests in PsA the most relevant biomarker seems to be the clinical presentation of PsO itself, as present in 70% of subjects who will subsequently develop PsA (2,9). This aspect of PsA disease interception is unique compared to other immune-mediated disorders prevention, where

interventions would be prescribed to otherwise healthy (at risk) subjects (Figure 1). Different, interventions for preventing PsA in the presence of clinically active PsO would, if effective, mitigate the risks/benefits ratio considerably. Increasingly recognised shared immune-pathological mechanisms between the skin and the enthesis - an early musculoskeletal key target lesion (Figure 2) in PsA - are likely to provide a rationale for efficacy of PsO interventions beyond the skin level.

Therefore, several unique aspects around the potential for PsA prevention are distinguished from diseases like RA. Firstly, several licensed systemic therapies for the treatment of PsO were independently verified as effective in established PsA (10). Whilst the therapy of PsO included conventional DMARDs (c-DMARDs) initially, this evolved into the anti-TNF agents about 15 years ago with these agents showing improved skin efficacy (11). In recent years the IL-23/IL-17 axis cytokine blockade has been introduced to PsO where complete skin clearance has been reported in up to 50% of cases (10). Such efficacy, an acceptable safety profile and the lack of clinically relevant neutralizing antibodies, more often encountered with the use of the anti-TNF blockers, positions the IL-23/IL-17 blockers as therapies that are both liked, tolerated and show even better long-term retention. All factors that auger well for continuous use of therapies that could prevent manifestation of PsA in PsO patients. Some small preliminary studies have hinted that the use of both c-DMARDs and b-DMARDs may be associated with a lower incidence of PsA development compared to topical or phototherapy (12).

In this issue of ARD, the impact of systemic treatment on the development of PsA in PsO patients was evaluated in a retrospective cohort of PsO patients (13–15). *Gisondi et al.* and *Acosta Felquer et al.* showed that PsO patients, without clinical evidence of PsA, treated with b-DMARDs had a lower risk of PsA development compared with those treated with narrow-band ultraviolet light B (nb-UVB) phototherapy or those treated with topicals or without treatment (13,14). Both studies found similar results in terms of incidence rates of PsA, (i.e. 1.2 and 1.6 cases per 100 patients/year, respectively) and nail involvement as predictor of later PsA development. The role of biologics as possible interceptor of PsA development in PsO was also described in a recent study, published in another journal (16) . In contrast, Meer et al., the third study on the topic published in this ARD issue, used an electronic health record database and found a higher incidence of PsA among PsO patients treated with bDMARDs than patients on oral or phototherapy(15). These results appear inconsistent with clinical practice, in fact the authors stated these findings should not be interpreted causally, i.e. it is common experience that bDMARDs do not cause PsA. The key message of Meer et al. is to use caution in interpreting results from retrospective studies. Several confounders and sources of bias

should be taken in consideration, such as confounding by indication and the protopathic bias. Furthermore, results could be different depending on the cohort analysed (e.g. dermatology clinic-based population or population based) and the way the data were analysed.

Hence, in the topic of transition from PsO to PsA, retrospective studies should be considered as hypotheses generating, but findings need to be validated in prospective studies and randomised controlled trials with an adequate follow-up depending on the selected PsO population.

Factors including the severity of PsO, nail involvement and family history of PsA are long-term predictors of PsA development, while the presence of arthralgia is a short-term predictor (3,17). These factors for the transition from PsO to PsA may assist researchers in definition of target populations at risk and adequate timing of follow-up periods for prospective transition studies.

In the "PsO to PsA march" there is good evidence that the earliest stage of PsA in experimental models and latterly in humans is linked to early enthesitis with subsequent inflammation spreading to the synovium (18). In humans, PsO subjects without musculoskeletal complaints have a much greater burden of subclinical articular inflammation compared to healthy controls (19,20). The evolution towards PsA is associated with the development of synovitis and tenosynovitis, which is again linked to the synovio-entheseal complex (21). Ultrasound determined subclinical enthesopathy regresses under biological therapy in PsO subjects (22) and likewise subclinical MRI determined synovitis also regresses under biological therapy (23), with both these studies providing mechanistic corroborative evidence that underpins the findings from the *Gisondi et al.* and *Acosta Felquer et al* et al. studies (13,14).

Potential therapy for PsA interception

Noting the aforementioned arguments around the centrality of enthesitis it is noteworthy that methotrexate was thought not to work for enthesitis but is now endorsed in some quarters for that purpose (24). This raises the possibility that c-DMARDs that are less effective for established enthesitis may nevertheless have a role in preventing it. The anti-TNF agents work less efficiently for skin disease compared to the emergent IL-23/IL-17 inhibitors and it will be interesting to see whether there are any emergent differences between biological classes for possible PsA interception (25,26). Furthermore axial PsA evolution may overlap with ankylosing spondylitis (AS) - a disease where Il-23 pathway blockade failed (27). However, in experimental models the pre-emptive use of IL-23 blockers was associated with the non-evolution of axial disease even though it could not treat established disease (28). Overall, this supports the idea that there may be broad protection with different conventional and biological DMARD classes for the interception of PsA.

Biological Rationale for PsA Prevention and Interception

It is increasingly clear that there is a close connection between the immunopathogenesis of skin and joint disease in PsO and PsA with both the normal skin and enthesis sharing IL-23/IL-17 axis immunogenetics and innate as well as adaptive IL-23/17 lineage immune cells in healthy tissue (25,26). The emergent IL23/IL-17 axis blockers are associated with skin clearance in up to 50% of cases, however responses in signs and symptoms of PsA (e.g. American College of Rheumatology 20/50/70% response rates) are modest, which has been interpreted as a relative lack in depth of response in PsA. However, the clearance of dactylitis, the pathognomonic lesion of PsA, is reported up to 80-90% of cases at 6 and 12 months (29). This illustrates a closer therapeutic connection between skin and joint than hitherto appreciated as does the similar responses of PsA to IL-17A, IL23 and TNF inhibitor class drugs.

Implications

Many questions remain. Might the prevention of PsA, which is one systemic feature of PsO, also have implications for prevention of other complications of PsO as for example ischemic heart disease that appears to be more frequent in PsA subjects ? What is the impact of different modes of action of bDMARDs on the metabolic syndrome and its clinical consequences? The majority of PsA patients present with mild skin involvement and usually do not need a systemic treatment or a dedicated dermatological follow up. The crux for this group is how to prevent/intercept PsA in PsO patients if biological therapies for skin disease with lower PASI scores would be based on a higher PsA risk (Figure 1). These milder PsO cases lead to the new hypothesis of “Treat the skin To Intercept PsA” (T2I) (Figure 1B) - a fascinating challenge in the next years. Moreover, the consideration of reduction of PsA development as new clinical outcome/endpoint in PsO clinical trials may be of specific importance, particularly in the subset of PsO patients at high risk for transition.

To summarise, our Dermatological colleagues may have already ushered in the era of PsA prevention without additional toxicity or cost implications. Validating and refining and understanding this across the full spectrum of PsO including mild disease represents a new challenge.

Figure 1

Panel A. Comparing autoimmune disease evolution to PsA evolution.

Unlike humoral immune mediated autoimmune diseases where the autoantibodies that predate disease are a risk factor for disease that cannot be therapeutically manipulated at present, the psoriasis (PsO) biomarker is both a predictor of PsA and a target for therapy itself. This is a unique feature and means that the initiation of therapy does not increase risk of toxicity or costs providing the psoriasis is extensive enough to merit therapy that could intercept arthritis evolution.

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Panel B. The concept of Treat to Intercept (T2I) algorithm for interception of PsA in PsO patients. *Moderate to severe PsO is defined as either extensive (body surface area involvement >10%), or as important to the patient: more limited psoriasis leading to significant impact on quality of life (eg, face/hand/feet/genital involvement). When patients have mild PsO but risk factors for PsA then systemic therapy for PsO would not ordinarily be initiated. However, risk factors for imminent PsA could make this group a potential target for therapy or T2I.

Figure 2. Emerging biological basis for the therapeutic prevention of PsA with drug use for PsO.

When considering psoriasis and PsA from the perspective of the enthesis, there is clear evidence for convergent paths from tissue microanatomy to immunological mechanisms. Both sites show microanatomical similarities including an avascular (epidermis and fibrocartilage zone respectively) and both are subject to Koebnerization responses, whereby injury can trigger disease. Convergent immune homeostasis mechanisms between both sites are increasingly recognised including resident myeloid cells capable of IL-23 production and the presence of both innate and adaptive T cells even in health including ILC3 and γδ T –cells at both the skin and enthesis. Conventional T cells

including CD4 and CD8 T-cells including TRM cells are present at both sites. Also some therapies show similar efficacy between skin and joints with respect to pathognomonic dactylitic lesion resolution. Collectively these provide a strong basis for PsA prevention in PsO treated cases.

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