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COMMENTARY

Arthritis Interception in Patients with Psoriasis Treated with Guselkumab

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Psoriatic arthritis (PsA) is one of the main extracutaneous manifestations of psoriasis (PsO), with 20–30% of patients with PsO developing this condition over time [1–3]. Joint involvement typically follows PsO onset, although PsA may less commonly occur before or concomitantly with skin lesions [1–3]. Interestingly, growing evidence supports that patients with PsO go through three clinically silent and progressive stages before developing clinically evident PsA ("pre-PsA"), in a "multi-step PsO to PsA march" [1]. These preclinical stages are (I) immunological phase (typified by an aberrant immune system activation starting from skin, intestinal mucosa, or entheses), (II) subclinical phase (featuring soluble and/or imaging findings of joint inflammation with no clinical symptoms), and (III) prodromal phase (patients having arthralgia and fatigue without clinical evidence of arthritis, enthesitis, or spondylitis) [1]. Such a model of disease progression opens the way for an early intervention aiming to treat patients with PsO carrying a high risk of transition towards clinically full-blown synovio-entheseal inflammation ("PsA interception"), with consequent benefit on PsA-related morbidity [1–3]. Notably, two categories of predictors for PsA development have been identified in patients with PsO, including medium/long-term (PsA development greater than 2 years) and short-term (PsA development within 2 years) predictors [2]. The latter include arthralgia (defined as musculoskeletal symptoms not explained by other diagnosis without clinical evidence of PsA) and imaging evidence of synovio-entheseal inflammation, with PsA development risk ratio being 2.15 (95% CI 1.16–3.99) and 3.72 (95% CI 2.12–6.51), respectively [2, 3].

Herein, we report our experience of four patients with PsO carrying a short-term risk of PsA development treated with guselkumab for

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Table 1 Demographic and musculoskeletal features of the guselkumab-treated patients

	Patient 1	Patient 2	Patient 3	Patient 4
Demographic and PsO data				
Sex (M/F)	M	M	F	F
Age (years)	54	56	38	65
BMI	24.1	26.3	23.4	24.2
Smoke (yes/no)	No	Yes	Yes	No
Familiarity for PsA (yes/no)	Yes	No	No	No
PsO (yes/no)	Yes	Yes	Yes	Yes
PsO duration (years)	25	10	8	10
PsO previous treatment	MTX	CYS	CYS	MTX
PASI score	28.2	24.1	14.2	8*
NAPSI score	52	0	17	0
Preclinical PsA MSK features				
Arthralgia (yes/no)	Yes	Yes	Yes	Yes
Arthralgia duration (months)	24	12	12	36
VAS pain (0–10)	3	4	4.5	7
Fatigue (yes/no)	Yes	No	No	No
Tender joints count (0–68)	4	7	2	6
Swollen joints count (0–66)	0	0	0	0
Leeds Enthesitis Index (0–6)	0	1	1	2
HAQ	0.25	0.125	0.125	0.5
US-detected inflammatory signs (yes/no)	No	Yes	Yes	Yes

CYS cyclosporine, *MSK* musculoskeletal, *MTX* methotrexate, *PsA* psoriatic arthritis, *PsO* psoriasis, *US* ultrasonography
*Patient had the involvement of sensitive areas (face and hands)

skin disease. It included two women and two men, with a mean age of 53.3 years (38–65 years) and a mean PsO duration of 13.3 years (8–25 years). Baseline (guselkumab beginning) mean Psoriasis Area and Severity Index (PASI) score was 18.6 (SD 9.2), with figures ranging from 8 to 28.2, whereas nail involvement was present only in two cases (case 1 and 3, with NAPSI score of 52 and 17, respectively). All the patients reported arthralgia at baseline (mean duration of 21 months, range 12–36 months), with a mean tender joint count (TJC) of 4.74 (SD 2.2), without swollen joints and a mean VAS pain of 4.6 (SD 1.7). Sonographic evidence of subclinical active enthesitis/synovitis was present in one and three patients, respectively. More details are reported in Table 1. Guselkumab was the first-line biologic in all cases after the failure (primary/secondary) of at least one conventional treatment (i.e., methotrexate or cyclosporine). During a 1-year follow-up, no patient developed clinical arthritis and fulfilled ClASsification criteria for Psoriatic ARthritis (CASPAR). All

patients reported a significant reduction in VAS pain after 6 months of therapy, with three patients showing a complete regression of arthralgia (no tender joint and VAS pain of 0) and one patient (case 4) reporting a major regression of musculoskeletal pain and TJC (Fig. 1). No sonographic sign of active synovio-entheseal inflammation was observed in the present cohort from month 6; PASI 75 was reached in all cases (Fig. 1).

Guselkumab is a human immunoglobulin G1λ monoclonal antibody blocking the interleukin-23 (IL-23)-mediated signaling pathway [4]. It is approved for moderate to severe plaque-type PsO and administered subcutaneously at the dose of 100 mg at week 0, week 4, and every 8 weeks thereafter [4]. Our data support the possible usefulness of this biologic therapy to revert preclinical manifestations of PsA (i.e., arthralgia/sonographic enthesitis/synovitis) carrying a high risk of short-term development of clinically full-blown synovio-entheseal inflammation, thereby potentially modifying the natural course of PsA. Interestingly, in all our patients, conventional treatments failed to control such PsA preclinical stages, thus backing a higher efficacy of anti-IL-23 agents for this purpose. In this regard, IL-23R blockade has been shown to completely prevent spondylitis and arthritis development in HLA-B27tg rats [5]. The same study showed that IL-23 would be more involved in the initiation rather than persistence of SpA as downstream effector cytokines (IL-17A/IL-22) were down-regulated only after prophylactic and not therapeutic IL-23R blockade [5].

In conclusion, guselkumab might intercept PsA during a potential "window of opportunity" in individuals with moderate-severe PsO having short-term predictors of PsA development. Randomized controlled trials are needed to confirm our preliminary findings.

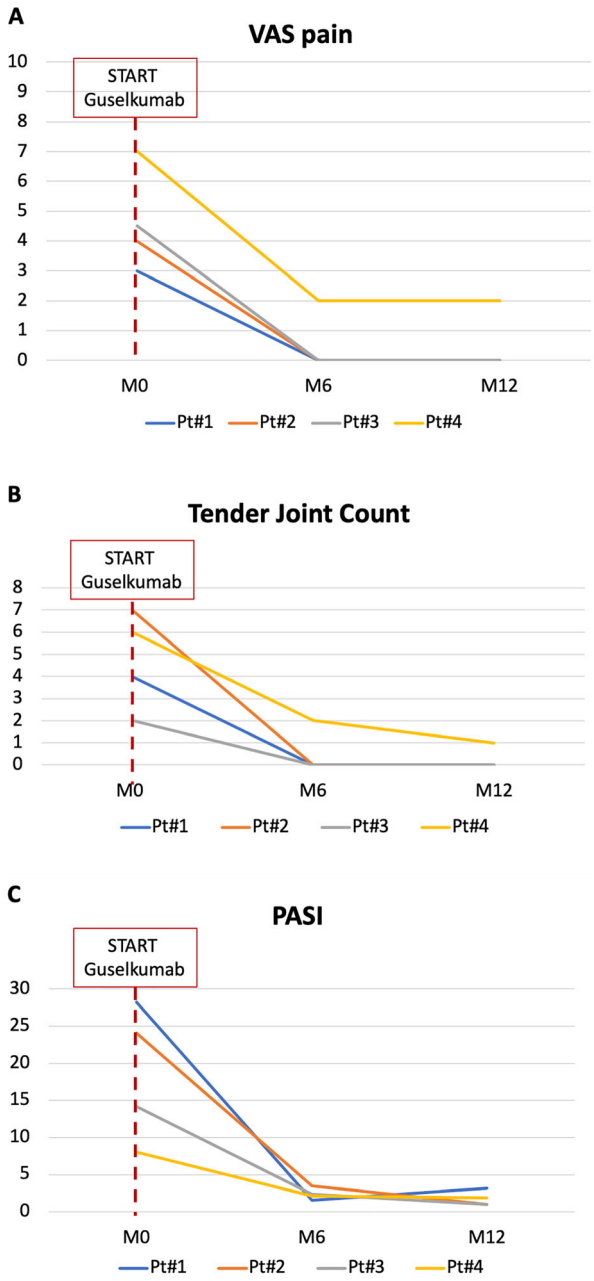

Fig. 1 Variation of VAS pain (**a**), tender joint count (TJC) (**b**), and PASI score (**c**) over 1 year

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