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
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

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)
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-enthesal inflammation was observed in the present cohort from month 6; PASI 75 was reached in all cases (Fig. 1).

Guselkumab is a human immunoglobulin G1κ 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-enthesal 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 downregulated 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.

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