Clinical Letter

Acute generalized pustular psoriasis successfully treated with the IL-23p19 antibody risankizumab

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Dear Editors,

a previously healthy 70-year-old Caucasian woman was admitted to our hospital suffering from fever and an acute, severe flare of generalized pustular psoriasis (GPP). A history of psoriasis, infection or new medication use in the past was denied.

Erythematous scaly plaques with non-follicular bound pustules were present on the entire integument with emphasis on the trunk, arms, and thighs (Figure 1a). There was generalized erythema involving around 80 % body surface area (BSA) and her GPP area and severity index (GPPASI) was 48/72. The Physician Global Assessment (PGA) score was 4/5, the Japanese Dermatological Association severity index of GPP (JDA-SI) was 10/17, and the Dermatology Life Quality Index (DLQI) on admission was 12/30.

Laboratory findings revealed neutrophil leukocytosis with a white blood cell count (WBC) of 13.96 × 10^9/l (reference range [ref.] 4.0–9.0 × 10^9/l), neutrophils 11.93 × 10^9/l (ref. 1.8–8.0 × 10^9/l), a significantly increased Serum Amyloid A (SAA) of 993.0 mg/l (ref. < 6.4 mg/l) and an elevated C-reactive protein (CRP) level of 18.6 mg/dl (ref. < 0.5 mg/dl). Histologically irregular acanthosis with a focally thinned stratum granulosum was found. Additionally, parakeratosis with intracorneal pustules of neutrophils and a superficial perivascular lymphocytic infiltrate with budding neutrophils were observed.

To characterize predominant cytokine-producing cell populations in GPP, we performed fluorescence-activated cell sorting (FACS) analysis of lesional skin of our patient and of two patients suffering from chronic plaque psoriasis (PsO) for comparison (Figure 2). Comparing our GPP patient to the PsO patients, we observed a lower percentage of $CD3^+IL17A^+$ cells for GPP, whereas the percentage of $CD11c^+IL23p19^+$ cells was similar. Taking our findings and published literature into account [1–5], a therapy with the anti-IL-23 (p19)-antibody risankizumab was started (150 mg subcutaneously at weeks 0 and 4, thereafter every 12 weeks). Additionally, topical steroids were applied and PUVA therapy was provided for three weeks with no observed side effects.

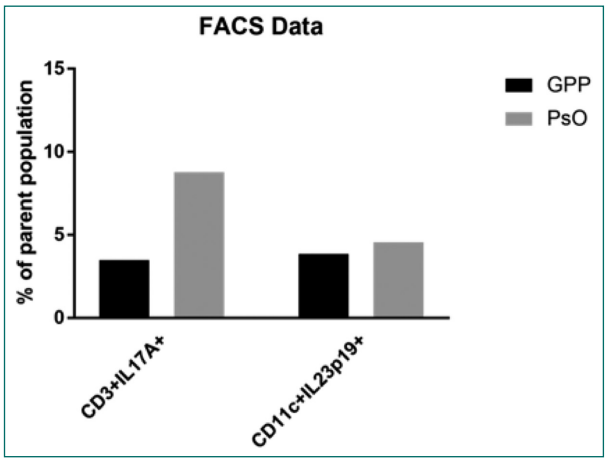

Figure 2 Fluorescence-activated cell sorting (FACS) data of our patient were compared to two reference psoriasis patients. $CD3^+IL17A^+$ cells were, on average, more abundant in psoriasis patients (PsO; n = 2) than in our GPP patient (GPP; n = 1) whereas the percentage of $CD11c^+IL23p19^+$ cells was comparable.

Clinical symptoms, skin lesions and laboratory parameters improved within days after the first administration of risankizumab (Figure 1b). Seven weeks after the first injection, the skin lesions had resolved almost completely (BSA: 4 %, GPPASI: 4/72, PGA: 1/5, JDA-SI: 1/17, DLQI: 0/30) (Figure 3). To date, after six months of risankizumab therapy, the patient remains symptom-free.

In the pre-biologic era, therapy options of GPP have been limited and outcomes were often unsatisfactory. As targeted

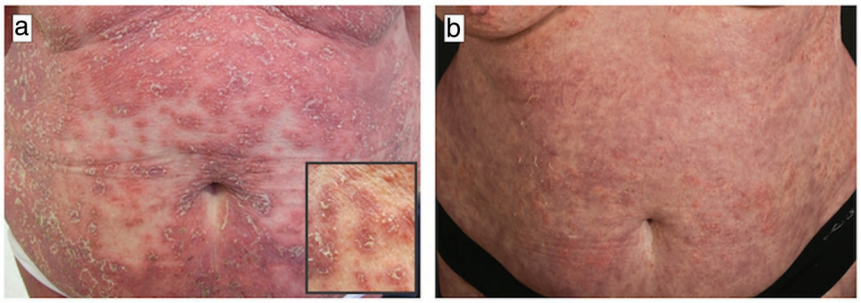

Figure 1 Clinical images of the abdomen including close-up image of pustulosis before (a) and one week after therapy initiation (b)

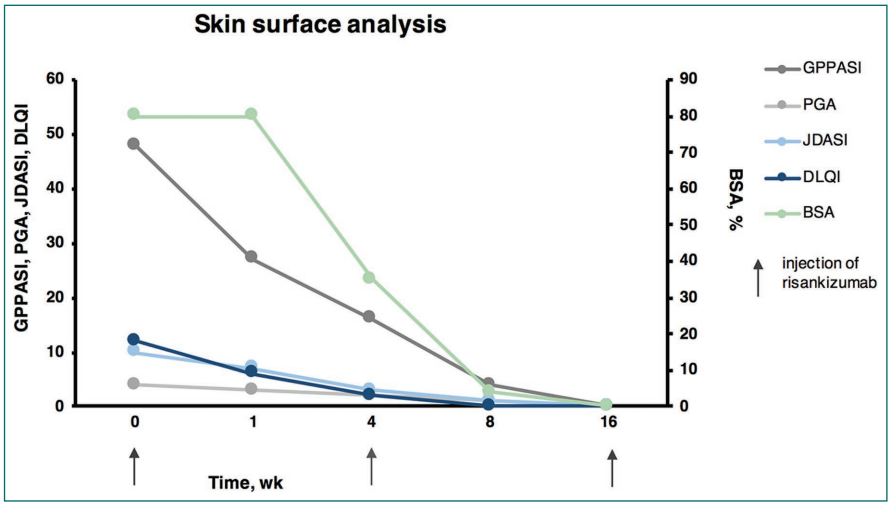

Figure 3 Clinical response to risankizumab.
Abbr.: BSA, body surface area; DLQI, dermatology life quality index; CRP, C-reactive protein; GPPASI, generalized pustular psoriasis area and severity index; JDASI, Japanese dermatological association severity index of GPP; PGA, physician global assessment; SAA, serum amyloid A.

biologic therapies for PsO have emerged, a new and promising therapeutic door for GPP patients has opened.

Although considered two distinct entities, PsO and GPP share several key features in etiology and pathogenesis [2]. Whereas GPP lesions show higher interleukin (IL)-1 and IL-36 expression compared to PsO, there are several cytokines, including IL-17A, IL-23, tumor necrosis factor alpha (TNFα), and interferons, that are overexpressed in both GPP and PsO [2]. Our FACS analysis supports these mRNA expression data [6]. Nevertheless, in our patient the proportion of IL-17A-expressing lymphocytes was lower than in PsO patients, whereas the percentage of IL-23-producing cells were comparable for GPP and PsO (Figure 2). These findings suggested inhibition of IL-23 as a therapeutic goal rather than direct inhibition of IL-17A as previously reported [6].

Th17 cells, which produce high levels of IL-17, generate a self-amplifying, inflammatory response in keratinocytes under the control of IL-23 [7, 8]. Risankizumab is a humanized IgG monoclonal antibody that binds to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor. It was recently approved as first-line therapy for PsO after demonstrating remarkable results during phase III trials [9, 10]. A phase 3 study to investigate the effectiveness of risankizumab in GPP patients was recently completed [11]. Whereas initial data on the exposure-response relationship, safety, and pharmacokinetics have already been made available, efficacy data have not yet been published [12, 13].

Our therapy showed remarkable efficacy in terms of clinical symptoms and laboratory findings within a few days after the first injection of risankizumab. After the third injection, the patient remained asymptomatic, emphasizing the high therapeutic potential of targeting the IL-23/Th17/IL-17-axis in GPP. In the past, GPP patients had to rely on retinoids or broad immunosuppressants like cyclosporine, methotrexate or azathioprine, which are accompanied by low efficacy, slow onset of action and common side effects.

As illustrated by the exceptional and long-lasting response to risankizumab in our patient, a new era of targeted GPP therapy with novel IL-23p19 inhibitors has begun. Nevertheless, prospective randomized controlled trials are needed to evaluate the efficacy and safety of biologics for the treatment of GPP and to answer the question of whether continuous therapy is required for disease control.

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Conflict of interest

Dr. Boehner and Prof. Biedermann have been supported by Abbvie in the past. The other authors declare that there is no conflict of interest.

Sarah Heyer[1]*, Peter Seiringer[1,2,3]*, Stefanie Eyerich[2], Anna Caroline Pilz[1,2], Susanne Annette Steimle-Grauer[1], Kilian Eyerich[1,2,3,4], Tilo Biedermann[1], Alexander Böhner[1]

(1) Department of Dermatology and Allergy Biederstein, Technical University Munich, Germany
(2) Center of Allergy and Environment (ZAUM), Helmholtz Center and Technical University of Munich, Germany
(3) Division of Dermatology and Venereology, Department of Medicine Solna, and Center for molecular medicine, Karolinska Institutet, Stockholm, Sweden

(4) Department of Dermatology and Venereology, University of Freiburg, Germany

* Both authors contributed equally to this article.

Correspondence to

Sarah Heyer, MD
Department of Dermatology and Allergy Biederstein
Technical University Munich

Boedersteiner Strasse 29
80802 Munich, Germany

E-mail: sarah.heyer@mri.tum.de

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