## Title

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# Successful secukinumab treatment of generalized pustular psoriasis

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## Abstract

Generalized pustular psoriasis is a rare variant of psoriasis. Evidence recommending generalized pustular psoriasis treatment with secukinumab is limited. This report aims to evaluate the use of secukinumab in two patients with generalized pustular psoriasis. The standard treatment regimen for secukinumab was as follows: 300mg subcutaneously once weekly in weeks 0–4, followed by 300mg every four weeks. The efficacy was evaluated by analyzing the psoriasis area and severity index (PASI) and dermatology life quality index (DLQI). One patient had generalized pustular psoriasis, which had developed from palmoplantar pustulosis over 12 years. The second patient was an adolescent with recurrent generalized pustular psoriasis. The first patient achieved PASI-75 response by week 3 and both PASI-90 and a DLQI score of 0 were observed by week 8. The second patient achieved PASI-75 response by week 4 and complete clinical resolution, except for nail changes, and a DLQI of 0 by week 8, without any adverse events.

*Keywords: generalized, pustular psoriasis, secukinumab*

## Introduction

Pustular psoriasis is an unusual form of psoriasis clinically characterized by sterile pustule formation superimposed over inflamed, erythematous skin. It has two distinct subtypes: localized disease on the palms and soles, called palmoplantar pustulosis (PPP), and generalized pustular psoriasis (GPP), [1]. A recent study used different geographical GPP prevalence results to estimate a global prevalence range of 1.76-124 patients with GPP per million people (0.0001% of the global population), [2]. Secukinumab, a fully-human anti-interleukin (IL)-17A monoclonal antibody, is the recently approved drug for moderate-to-severe plaque-type psoriasis and psoriatic arthritis in China. Nonetheless, evidence regarding GPP treatment with secukinumab is limited. In this study we evaluated secukinumab in two patients diagnosed with GPP. The efficacy was evaluated by analyzing the psoriasis area and severity index (PASI) and dermatology life quality index (DLQI).

## Case Synopsis

### Case 1

A 30-year-old man presented with a 12-year history of PPP. He had recurrent palmar keratosis and pustules (**Figure 1A**), accompanied by finger swelling and nail damage (**Figure 1B**); the same was the case with soles. Intermittent treatment with cyclosporine, acitretin, and low doses of glucocorticoids provided unsatisfactory results. About a month prior to admission, the patient experienced a sudden exacerbation for unknown reasons with generalized pustular eruptions (**Figure 2A**), associated with fever (38.5°C), pain, and itching. On admission, laboratory tests revealed increased white blood cells, neutrophil counts, and elevated

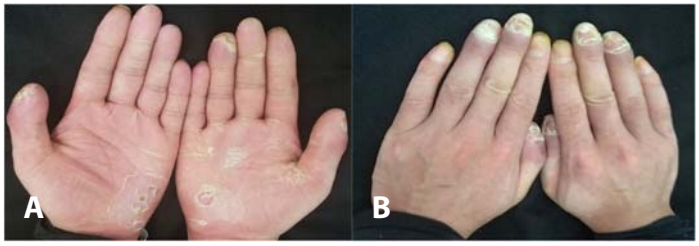

**Figure 1**. ***A)*** *Keratosis and small pustules were seen locally on the palms.* ***B)*** *Fingers were red and swollen with clubbing, and the nails were damaged.*

erythrocyte sedimentation rate. His PASI was 35.2 and DLQI was 15. He was diagnosed with GPP. After obtaining informed consent for off-label treatment, the patient received the standard regimen of secukinumab: 300mg subcutaneously once weekly in weeks 0-4, followed by 300mg every four weeks. Within 8h after the first dose, defervescence occurred (body temperature down to 36.6°C). After the first week of secukinumab treatment, itching and pustular psoriasis had rapidly improved. PASI-75 response was achieved by week 3 and PASI-90 and a DLQI score of 0 were observed by week 8. Also, erythema and pustules disappeared (**Figure 2B**) and palmar keratosis was reduced (**Figure 3A**). In addition, redness and swelling of the fingers were decreased and some new nails started to grow (**Figure 3B**). The standard treatment was maintained for 24 weeks, followed by 3-to-6-month maintenance intervals. The patient has been followed up for three years without experiencing any recurrence or adverse reactions.

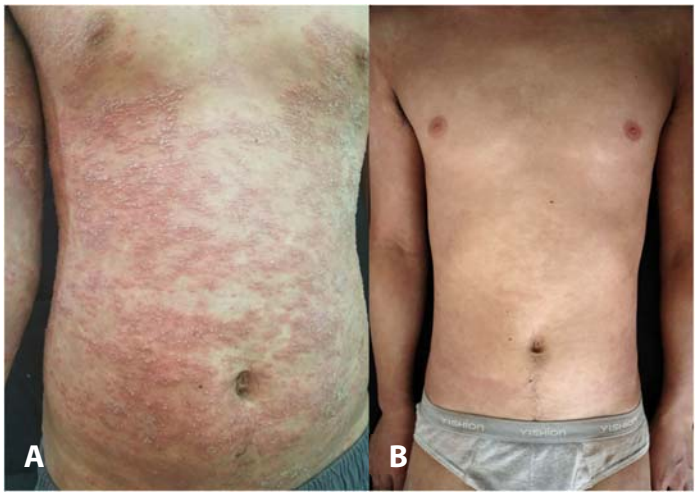

**Figure 2**. ***A)*** *Chest and abdomen exhibited numerous milia-sized pustules, coelescing into lakes of pus.* ***B)*** *Erythema and pustules were resolved.*

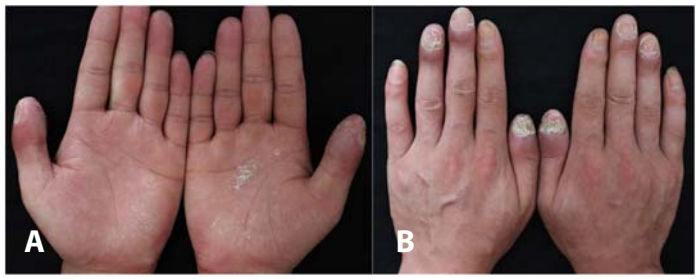

**Figure 3**. ***A)*** *Decreased keratosis of the palms is observed.* ***B)*** *Redness and swelling of the fingers decreased and new nail growth can be seen.*

## Case 2

A 14-year-old boy had been experiencing recurrent GPP since the age of 11 years. He was treated with intermittent low-dose corticosteroids and Chinese herbal medicine. Approximately two weeks prior to presentation, he experienced a sudden recurrence of large erythematous pustules (**Figure 4A**) with no obvious cause (PASI-37 and a DLQI score of 20). He developed a high fever (body temperature up to 41°C) with a white blood cell count of $35.81\times10^9$/L (reference range, $4\text{-}10\times10^9$/L) and neutrophil count of $33.41\times10^9$/L (reference range, $1.8\text{-}6.4\times10^9$/L). Treatment with methylprednisolone 40mg/day for a week was ineffective, and then secukinumab was started. Four days after the first dose of secukinumab, an additional 300mg was administered subcutaneously due to the persistence of new pustules and fever. Fever and pustules improved rapidly after two doses. Subsequently, 300mg secukinumab was injected subcutaneously weekly for three weeks, followed by 300mg every four weeks. PASI-75 response and a normal blood cell count were achieved after four treatment courses. Complete clinical resolution was observed (**Figure 4B**), along with a DLQI score of 0 by week 8. After 12 weeks of treatment, the treatment interval

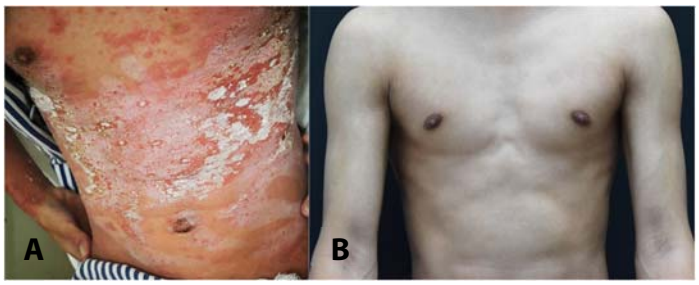

**Figure 4**. ***A)*** *Large areas of erythema and small pustules on the chest and abdomen were partially covered with calamine drug crusts.* ***B)*** *Erythematous pustules resolved completely.*

was extended to 3-6 months. Now two years have passed since the initiation of treatment and no recurrence or adverse reactions have been observed.

## Case Discussion

IL23 production by myeloid dendritic cells is considered to be critical in activating Th17 T cells and activating keratinocytes in patients with psoriasis [3]. IL23 regulates the synthesis of IL17, which in turn, stimulates the synthesis of pro-inflammatory IL36R agonists, further up-regulating the IL36 pathway [4]. Neutrophils and keratinocytes play an essential role in the pathogenesis of GP. IL36 cytokines synergizes with IL17A, amplifying the vicious cycle between keratinocytes and neutrophils in GPP [5].

Treatment guidelines for GPP are not well established. The available options for patients with GPP are limited and based on the existing therapies for plaque psoriasis [6]. Biologic agents have been used to treat refractory cases. Spesolimab, a humanized anti-IL36 receptor monoclonal antibody, was recently approved by the U.S. Food and Drug Administration for treating GPP [7]. In a pivotal trial [7], 54% of patients (19/35) given a single dose of intravenous spesolimab had pustular regression on day 7. Additional anti- IL36 pathway therapies for GPP, such as imsidolimab, are currently under development, demonstrating good tolerability and acceptable safety [8]. IL23 inhibitors, including guselkumab and risankizumab, as well as IL17A and IL17RA inhibitors, including secukinumab, ixekizumab, and brodalumab, are approved for use in Japan [9]. The biologic agents specific to GPP are not approved in China.

Secukinumab was first reported for use in GPP in 2016 [10]. It has been demonstrated to have a high response rate with rapid improvement in erythematous areas and pustules in adult patients with GPP and those with pustular psoriasis of pregnancy [11-15]. The neutrophil-keratinocyte axis in GPP as the early target of secukinumab may explain its efficacy [16].

## Conclusion

We observed a progression from PPP to GPP in a patient over 12 years in one patient and the recurrence of GPP in an adolescent patient. We evaluated the use of secukinumab in two patients with GPP. Our observations validly support the rapid and safe clinical use of secukinumab in treating GPP, suggesting that secukinumab may serve as a viable therapy for severe refractory cases of GPP. However, additional studies are needed for further confirmation. Although treatments of GPP are limited, the anti- IL36 pathway therapies, spesolimab and imsidolimab, may be ideal options. However, the long- term efficacy of spesolimab in preventing GPP has yet to be elucidated and it is not yet readily available in some countries.

## Potential conflicts of interest

The authors declare no conflicts of interest.

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