

Successful Treatment of Pediatric Generalized Pustular Psoriasis (GPP) with Spesolimab: 5 Case Reports and Evaluations of Circulating IL-36 Levels

Yunliu Chen^{1,2,*}, Zhaoyang Wang^{1,2,*}, Yuan Liang^{1,2}, Chunping Shen^{1,2}, Lei Jiao^{1,2}, Xin Xiang^{1,2}, Chaoyang Miao^{1,2}, Zigang Xu^{1,2}

¹Department of Dermatology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, People's Republic of China; ²Key Laboratory of Major Diseases in Children, Ministry of Education, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zigang Xu, Email zigangxu@163.com

Background: Generalized pustular psoriasis (GPP) is a rare, severe, and potentially life-threatening inflammatory cutaneous disease. IL-36 is a key treatment target in GPP. Spesolimab, a humanized monoclonal antibody of the IL-36 receptor, has demonstrated a good efficacy and a favorable safety profile in adults with GPP. However, data on its use in children are scarce.

Methods: We treated patients aged 4–12 years with GPP with a single dose of spesolimab. The Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score, GPPGA pustulation sub-score, Generalized Pustular Psoriasis Area and Severity Index (GPPASI), and the Japanese Dermatological Association severity index for GPP were evaluated. The levels of IL-36 α , IL-36 β , and IL-36 γ were detected by the magnetic bead-based immunoassays, and the levels of IL-17A, IL-17C, IFN- γ , TNF, IL-6, and IL-8 were measured by the Olink proximity extension assay technology.

Results: We included five patients (four boys and one girl) with a median age was 6.9 years old (range: 4.8 to 10.6 years), and a median age of onset of 1.7 years (range: 3 months–10 years and 5 months). After 1 week of spesolimab administration, all patients had a total GPPGA score of 0/1 and pustulation subscore of 0, all patients had a GPPASI of 50, and four patients had a GPPASI of 75. Meanwhile, plasma levels of IL-36 α , IL-36 β , IL-36 γ , IL-17A, IL-17C, IFN- γ , TNF, IL-6, IL-8 all decreased, and those of IL-36 α , IL-36 β , IL-17A, IL-17C, and IL-6 were statistically significant. There was no recurrence after 2 to 8 months of treatment. No other adverse event was recorded apart from one patient who experienced an upper respiratory infection in the first week.

Conclusion: Spesolimab might be a prospective option for children aged 4 to 12 years.

Keywords: generalized pustular psoriasis, pediatrics, spesolimab, IL-36R

Introduction

Generalized pustular psoriasis (GPP) is a rare chronic, relapsing, and severe inflammatory cutaneous disease characterized by generalized pustular edematous erythema, and usually associated with fever, headaches, asthenia, myalgia, and raised C-reactive protein (CRP) level and white blood cell count (WBC).¹ Most GPP patients who present with an earlier onset of disease and no history of psoriasis vulgaris have a homozygous or compound heterozygous mutation of the *IL36RN* gene.^{2,3} Moreover, patients with alternative genetic mutation of IL-36 associated inflammatory cascade, such as *CARD14*, *APIS3*, and *MPO*, could have similar phenotypes.⁴

The IL-36 pathway plays a central role in the pathogenesis of GPP.⁵ IL-36 is a pro-inflammatory cytokine, with subunits IL-36 α , IL-36 β , and IL-36 γ , belonging to the IL-1 cytokines family. Upon binding to its receptor, IL-36

activates nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinase (MAPK) signal pathways resulting in the secretion of extensive pro-inflammatory cytokines and chemokines, such as IL-36 precursors, IL-1 β , TNF- α , IL-6, IL-23, CXCL8, CXCL1, and CXCL2.⁶ Those chemokines and cytokines recruit and activate immune cells, hence forming an inflammatory loop.⁶ Dysfunction in the IL-36 receptor (IL-36R) results in an overactivity of the inflammatory cascade.

GPP always requires systemic drugs, as topical drugs alone are insufficient.⁷ Biologic agents targeting TNF- α , IL-23, IL-17, and IL-36, or their receptors might be good candidates.⁸ Considering the key role of IL-36 in GPP,⁵ inhibitors of IL-36 or IL-36R could be effective. Spesolimab is a humanized monoclonal antibody of the IL-36R, which could inhibit the over-activation of the IL-36/IL-36R signal. Moreover, spesolimab has been approved by the US Food and Drug Administration, European Medicines Agency, and China Food and Drug Administration to treat GPP in adults. In china, all treatments for GPP are off-label except spesolimab, which was approved in 2022. However, data on its use in children under 12 years with GPP is scarce. We present five children with GPP treated with a single dose of spesolimab and followed up for its efficacy on disease symptoms and its impact on circulating IL36 levels.

Methods

Participants

Five patients aged 4–12 with GPP were enrolled at the Beijing Children's Hospital from November 2023 to March 2024. We included patients who met the GPP criteria of the Japanese Dermatological Association (JDA);⁷ with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score ≥ 3 , GPPGA pustulation subscore ≥ 2 , body surface area (BSA) $\geq 10\%$, and Generalized Pustular Psoriasis Area and Severity Index (GPPASI) score ≥ 10 ; and with progressing disease severity. The five patients included did not achieve long-term remission on previous treatment, including adalimumab, secukinumab, acitretin and topical drugs.

Intervention

A single intravenous dose of spesolimab was given on day 0. This dose depended on the patient's body weight (450mg for 20–50kg and 900mg for ≥ 50 kg). Although spesolimab is off-label in children with GPP, previous data showed its efficacy and safety. Before starting spesolimab, we excluded current or latent infections of viral B and C hepatitis, tuberculosis, and HIV.

Outcome Measure

GPP severity was assessed by BSA, GPPGA total score, GPPGA pustulation sub-score, GPPASI, and JDA severity index for GPP.⁷ Drug-related adverse events were assessed from day 0. Cytokines and chemokines were measured in EDTA plasma before treatment and 1 week after spesolimab administration. The concentrations of IL-36 α , IL-36 β , and IL-36 γ were assessed by magnetic bead-based immunoassays (magEasyQplex). The levels of IL-17A, IL-17C, IFN- γ , TNF, IL-6, and IL-8 in the plasma were quantified by the Olink inflammation panel based on the proximity extension assay technology in the plasma, and the amount of protein was evaluated by Normalized Protein Expression (NPX).

Statistical Analysis

Data analysis was performed via the statistical SPSS26.0 software. Median and range were used for descriptive statistics. A paired-samples *t*-test was carried out for normally distributed data. Otherwise, the Wilcoxon-signed ranks test was used. A *P* < 0.05 was considered statistically significant.

Result

We included four boys and one girl with GPP (Table 1). The median age was 6.9 years (range: 4.8–10.6 years), and the median age of onset was 1.7 years old (range: 3 months–10 years and 5 months). The median disease course was 48 months (range: 2–64 months). No participant had psoriasis vulgaris in the course of the disease. One patient had a family history of psoriasis, whose grandfather suffered from psoriasis plaque. Three patients presented with a map tongue. One patient was obese, and the BMI of other patients was within normal range.

Table I Clinical Characteristics and Spesolimab Treatment Protocols in Five Juveniles with GPP

Patients	Sex	Age/Onset Age, y	Disease Course, m	IL-36RN Mutation	Previous Therapies	Fever Peak, °C	SPE Dose/Weight
1	Male	5.6/0.3	64	c.115+6T>C hom	Sec & Ada	39.5	450mg/23.5kg
2	Male	4.8/0.9	46	c.115+6T>C hom	Topical drugs ^a	40.5	450mg/24kg
3	Male	6.9/1.7	63	c.115+6T>C hom	Acitretin	39	450mg/25kg
4	Male	10.6/10.4	2	c.115+6T>C het	Topical drugs ^a	39.2	900mg/82kg
5	Female	8.0/4.0	48	Negative	Ada	39.4	450mg/24kg

Notes: ^aTopical drugs including topical glucocorticoids and topical Chinese herbs.

Abbreviations: y, years old; m, months; hom, homozygous mutation; het, heterozygous mutation; sec, secukinumab; Ada, adalimumab.

Four patients had the *IL-36RN* c.115+6T>C variants, including three homozygous mutations and one heterozygous. No patient carried the *CARD14*, *AP1S3*, or *MPO* variant. Three patients had received systemic treatment for previous eruptions (adalimumab and secukinumab in patient 1, acitretin in patient 3, and adalimumab in patient 5).

Before treatment, all patients presented with high fever and an increased number of pustules. At baseline, the median BSA was 65% (range: 61–97%), median GPPASI was 38.5 (range: 29.6–63.5), and median JDA scores were 13 points (range: 10–17 points). The GPPGA total score was 3 (moderate) in four patients, and 4 (severe) in one patient. The GPPGA pustulation subscore was 3 in three patients, and 4 in two patients.

No new skin lesion developed at the median of 3 days (range: 1–5) after treatment. Overall, the body temperature decreased to $\leq 38^{\circ}\text{C}$ after a median of 2 days (range: 0–4) and returned to normal after a median of 4 days (range: 0–6). Moreover, one patient had no fever within 2 hours. At the end of 1 week with spesolimab-treatment, BSA, GPPGA, GPPGA pustulation subscores, and JDA scores decreased significantly ($P = 0.008$, $P = 0.003$, $P = 0.034$, $P = 0.038$, and $P = 0.001$ respectively), and all patients had a GPPGA total score of 0/1, with a median of 3 days (range: 2–6), all patients had a GPPGA pustulation subscore of 0, with a median of 4 days (range: 1–6), all patients had a GPPASI of 50, with a median of 3 days (range: 2–4), and four patients had a GPPASI of 75. The median time achieving GPPASI of 75 in five patients was 6 days (range: 5–8). After spesolimab treatment, the median JDA scores decreased to 7 points (range: 5–9) on day 3, and 3 points (range: 2–4) on day 7 (Figure 1).

The WBC and CRP levels significantly decreased ($P = 0.029$, and $P = 0.001$) and the albumin level significantly increased ($P = 0.018$) 7 days after spesolimab administration.

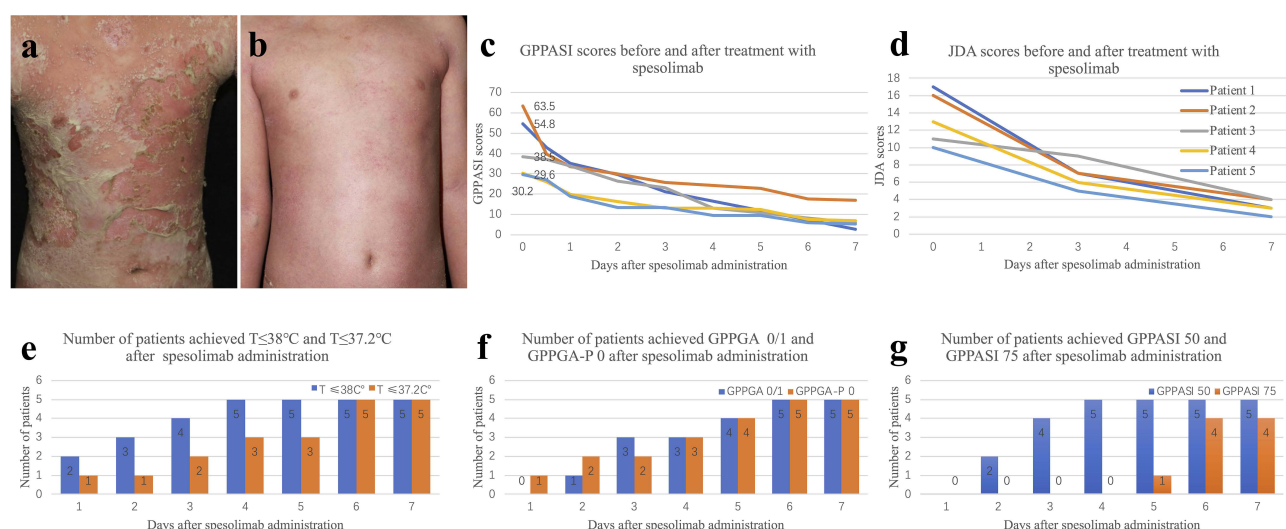


Figure 1 Cutaneous presentation before treatment (a) and after one-week treatment with spesolimab (b); (c and d) showed GPPASI scores and JDA scores at baseline and after treatment with spesolimab; e-g showed number of patients whose body temperature decreased to $\leq 38^{\circ}\text{C}$ or $\leq 37.2^{\circ}\text{C}$ (e), GPPGA 0/1 or GPPGA pustulation subscore of 0 (g), and number of patients achieved GPPASI of 50 or GPPASI of 75 (f) after treatment with spesolimab.

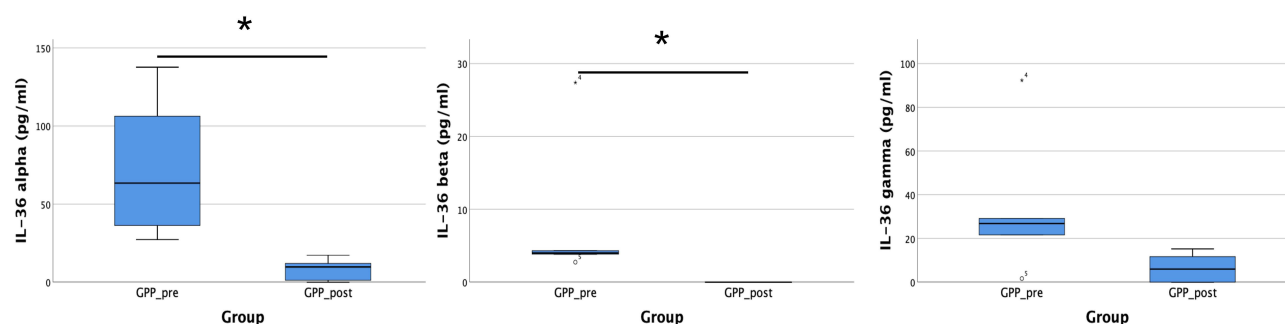


Figure 2 The concentrations of IL-36 α , IL-36 β , and IL-36 γ before treatment and after one-week treatment with spesolimab. GPP_pre, means before treatment; GPP_post, means after one week with a single dose of spesolimab administration; * means $P \leq 0.05$.

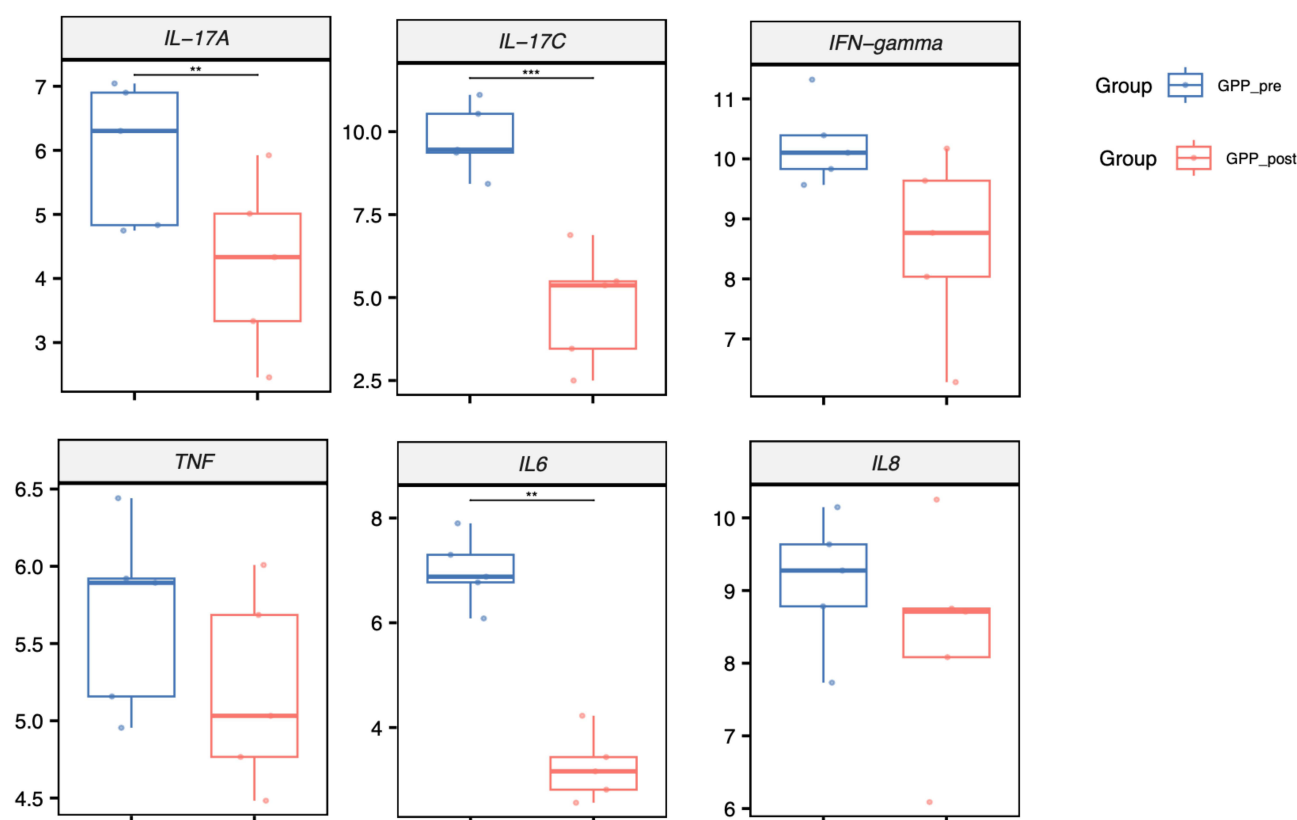


Figure 3 The levels of IL-17A, IL-17C, IFN-gamma, TNF, IL-6, and IL-8 before treatment and after one-week treatment with spesolimab. GPP_pre, means before treatment; GPP_post, means after one week with a single dose of spesolimab administration; * means $P \leq 0.01$; *** means $P \leq 0.001$.

The median level of IL-36 α was 63.44 pg/mL (range: 27.25–137.66) and 9.73 pg/mL (range: 0–17.25) before treatment and 1 week after treatment ($P = 0.023$), respectively. The median level of IL-36 β was 4.00 pg/mL (range: 2.74–27.38) and 0 pg/mL before treatment and 1 week after treatment ($P = 0.043$), respectively. The median level of IL-36 γ was 26.82 pg/mL (range: 1.63–92.32) and 5.98 pg/mL (range: 0–15.20) before treatment 1 week after treatment ($P = 0.097$), respectively (Figure 2). Meanwhile, IL-17A, IL-17C, IFN- γ , TNF, IL-6, and IL-8 levels decreased 1 week after treatment. Among them, IL-17A, IL-17C, and IL-6 levels decreased significantly ($P = 0.004$, $P = 0.001$, and $P = 0.001$, respectively) (Figure 3).

No relapse occurred 2 to 8 months after treatment. One patient experienced an upper respiratory infection in the first week following spesolimab administration and improved rapidly on regular antibiotics. No other adverse event was recorded.

Discussion

GPP treatment is a challenge, especially in children. Concerning the efficacy and safety, biologics are a favorable option compared with conventional oral treatment in adults.^{9–11} However, data on the use of biologics in children is scarce, especially those under 12 years.

Spesolimab could ameliorate GPP lesions rapidly. A multicenter, double-blinded, placebo-controlled trial (Effisayil 1) showed that 54% and 43% spesolimab-treated adults with GPP achieved GPPGA pustulation subscore 0 and GPPGA0/1, respectively, at week 1.¹² After subgroup analysis considering Chinese patients in Effisayil 1, the percentages rose to 60% and 60% for GPPGA pustulation subscore 0 and GPPGA0/1, respectively.¹³ The finding of real-world studies were consistent with those of randomized controlled trials (RCTs) (Table 2).^{14–20} Our study is the first spesolimab-treatment report involving GPP patients under 12 years. All our five participants had a GPPGA pustulation subscore of 0 and GPPGA0/1 at week 1. In contrast to findings from the RCTs and real-world studies, spesolimab might result in better clearance of lesions in children. Few studies evaluated its effect on body temperature. Ran et al¹⁷ found that the body temperature normalized 2 and 5 days after spesolimab administration in two patients presenting with fever. In our five participants, the body temperature reduced to $\leq 38^{\circ}\text{C}$ after the median of 2 days, and normalized after the median of 4 days, while one patient experienced rapid relief. After 1 week, WBC and CRP levels significantly reduced in all patients. Those proposed systemic inflammation may rapidly improve in patients with GPP after spesolimab administration. As shown by other reports, spesolimab was effective in our five patients irrespective of the presence of *IL-36RN* mutations.^{12,21}

A single dose of spesolimab could control the flare of GPP in our five children. However, this regimen could not be generalized to all participants. In the Effisayil 1 clinical trials, 12 of 32 patients who had persistent symptoms and 4 of 32 patients who had a recurrence of a flare received a second dose of spesolimab on day 8, and 4 of 32 patients received a standard-of-care escape treatment.¹² In a real-world study including 11 patients, 1 patient received two doses of spesolimab.¹⁶ Mostly, GPP has a relapse-remission course or its persistent. Thus, long-term treatment might be required to control or prevent flares. Effisayil 2 clinical trials assessed different models of spesolimab administration to prevent GPP flare after 48 weeks of observation and found that high-dose spesolimab (600 mg loading dose followed by 300 mg every 4 weeks) might be a promising option to prevent GPP flares.²¹

Our study showed that IL-36 α , IL-36 β , and IL-36 γ levels were all decreased after spesolimab administration, with a significant decrease in IL-36 α and IL-36 β . Moreover, downstream cytokines and chemokines levels, including IL-17A, IL-17C, and IL-6 also decreased. IL-36 cytokines, including IL-36 α , IL-36 β , and IL-36 γ , could cause a positive feedback loop in an autocrine or paracrine manner.²² Spesolimab is an IL-36R inhibitor that decreases IL-36 cytokines levels by suppressing IL-36 signaling pathway. Those elucidated IL-36 and related inflammatory storm could decrease through inhibiting IL-36Rs.

Spesolimab was well tolerated by our five participants. Patients presented mild adverse effects without death or hypersensitivity events. The tolerance of spesolimab was also shown in other trials in adult or children above 12 years old. According to a Phase 2 RCT, the rates of adverse events were similar in spesolimab and placebo groups during the one-week and 48-week observation periods.^{12,21} However, the incidence of infections was indeed higher in the spesolimab group (17% vs 6%) during the one-week trial,¹² and the proportion of serious adverse events was greater during the 48-week trial (10% vs 3%).²¹ The adverse events in real-life studies were mainly mild infection, anemia, asthenia, and raised uric acid levels and liver enzymes.^{16,23} However, data on real-life experiences and long-term research assessing its safety profile are limited.²⁴ Thus, further studies in diverse populations, using different research methods, and with long-term spesolimab administration are required.

Above all, our five pediatric GPP patients showed a good response to a single dose of spesolimab. However, due to the small sample size, absence of control groups, and short follow-up period, high evidence-level trials are required to confirm our findings.

Table 2 Real-World Studies of the Effectiveness and Safety of Spesolimab in Patients with GPP Flare

Literature	Patients, n	Age, y	Gender	PV	Disease Severity	Doses ^c	Combined Treatment	Efficacy	Adverse Events	Follow-up Periods, m	GPP Relapse
Jiang et al 2023 ¹⁴	1	34	Female	Yes	GPPGA 2, GPPGAp 2	One 900mg IV	Acitretin	Week 1: GPPGAp 0, GPPGA 0	None	5	None
Matsuo et al 2023 ¹⁵	1	82	Male	None	JDA 11, GPPASI 32.6	One 900mg IV	Oral steroid	Week 1: GPPGAp 0; week 3: JDA 5, GPPASI75	NM	NM	NM
Bellinato et al 2023 ¹⁶	11	58.9 ± 13.5 ^a	4/11 Male	7/11 patients	GPPGA 3, 6 ± 0.5, GPPASI 20.0 ± 6.5	One 900mg in 10 patients, two in 1 patient	None	Week 1: GPPGAp 0 in 6/11 patients, GPPASI75 in 6/11 patients	2/11 patients ^e	NM	NM
Ran et al 2023 ¹⁷	5	26 (25–65) ^b	1/5 Male	2/5 patients	GPPGA 3, GPPASI 35.6 (25.2–56.4) ^b	One 900mg IV	None ^d	Week 1: GPPGAp 0 in 5/5 patients, GPPGA 1 in 2/5 patients, GPPASI 75 in 2/5 patients; Week 4: GPPGA 1 in 4/5 patients, GPPASI 75 in 5/5 patients	4/5 patients ^f	NM	NM
Brigenti et al 2024 ¹⁸	1	48	Female	Yes	GPPGA 3, GPPASI 32.6	Two 900mg IV	None	Week 2: GPPGA 1, GPPGAp 0, GPPASI90	None	13	None ^h
Cardenas-de la Garza et al 2024 ¹⁹	1	63	Male	Yes	NM	Two 900mg IV	NM	Week 1: notable improvement; Week 2: complete remission	None	12	None
Dattola et al 2024 ²⁰	1	82	Male	None	NM	Two 900mg IV	Oral steroid	Week 1: GPPGAp 0; Week 2: complete remission	NM	NM	NM
Our cases	5	6.9 (4.8–10.6) ^b	4/5 Male	None	GPPGA 3 (3–4), GPPGAp 3 (3–4), GPPASI 38.5 (29.6–63.5), JDA 13 (10–17) ^b	One dose IV	None	Week 1: GPPGAp 0 in 5/5 patients, GPPGA 1 in 5/5 patients, GPPASI 75 in 4/5 patients, JDA 3 (2–4)	1/5 patient ^e	2 to 8	None

Notes: ^aMean ± 2SD was used for descriptive statistics; ^bMedium and range was used for descriptive statistics; ^ctwo doses are applied one week apart; ^dacitretin and methotrexate was applied in the two patients with PV separately after 4 weeks with spesolimab; ^e1/11 patient reported a mild asthenia, 1/11 patient reported moderate worsening of itch; ^f4/5 patients experienced various mild adverse events, including infection, mild anaemia, increase in uric acid levels, elevated liver enzymes, and so on; ^g1/5 patient reported an upper respiratory infection; ^hsecukinumab was started at last 8 months for plaque psoriasis.

Abbreviations: n, number; y, years old; m, months; PV, psoriasis vulgaris; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment total score; GPPGAp, GPPGA pustulation sub-score; GPPASI, Severity Index for Generalized Pustular Psoriasis; JDA, Japanese Dermatological Association severity index for GPP; NM, not mentioned; IV, intravenous injection; GPPASI75, improvement ≥75% in GPPASI score.

Abbreviation

GPP, Generalized pustular psoriasis; CRP, C-reactive protein; NF- κ B, nuclear factor- κ B; MAPK, mitogen-activated protein kinase; FDA, US food and drug administration; EMA, European medicines agency; CFDA, China food and drug administration (CFDA); BSA, Body surface area; GPPGA, Generalized pustular psoriasis physician global assessment; GPPASI, Severity Index for Generalized pustular psoriasis; JDA, Japanese dermatological association severity index for GPP; PEA, proximity extension assay; NPX, Normalized protein expression; WBC, White blood count; SAEs, Serious Adverse Events.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Statement

Informed consent was obtained from all participants' parents. The study complies with the Declaration of Helsinki.

Ethical Approval

Reviewed and approved by Beijing Children's Hospital, Capital Medical University, National Center for Children's Health ([2024]-E-102-R).

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Disclosure

The authors report no conflicts of interest in this work.

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