Clinical, Cosmetic and Investigational Dermatology

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CASE SERIES

Spesolimab Treatment in GPP: Impact of IL-36RN Mutations and Concomitant Plaque Psoriasis

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Abstract: We present a case series involving five patients with generalized pustular psoriasis (GPP) who received a single intravenous dose of 900 mg spesolimab in our department from September 2023 to January 2024. Spesolimab was effective in three patients, regardless of their IL-36RN gene mutation status. Two patients with concomitant plaque psoriasis, despite initially poor responses to spesolimab, achieved resolution of pustules after switching their therapy to ixekizumab or secukinumab. This study highlights the potential of spesolimab in managing GPP, especially in genetically distinct groups, and emphasizes the importance of tailored therapeutic approaches. These findings suggest that spesolimab can effectively treat GPP, regardless of IL-36RN gene mutation status. However, its therapeutic efficacy may be suboptimal in patients with concomitant plaque psoriasis, indicating the need for further investigation to optimize treatment outcomes in this subgroup.

Keywords: spesolimab, generalized pustular psoriasis, IL-36RN mutations

Introduction

Generalized pustular psoriasis (GPP) is a rare and chronic disease that can be life-threatening. It is marked by repeated episodes of painful redness, sterile pustules, and "lakes of pus". These episodes may occur with or without systemic inflammation or plaque psoriasis.[1] The clinical course of GPP is highly variable, occurring either de novo or triggered by various factors. Current guidelines for the treatment of GPP are lacking. Traditional systemic treatments, including corticosteroids, acitretin, cyclosporine, and methotrexate, are often used as first-line therapies for GPP. However, there is limited evidence supporting their effectiveness. Several biologics, including TNF inhibitors, IL-17/IL-17R inhibitors and IL-23 inhibitors, have been used for the treatment of GPP. However the utilization of various non-specific treatments for GPP usually results in only partial control of the disease. Recently, biologic agents that inhibit the IL-36 pathway have demonstrated efficacy and safety in patients with GPP.[2] Spesolimab, an IL-36R antagonist, is currently the only approved treatment for generalized pustular psoriasis in China.[1,2] Previous studies on these treatments have been limited, and their therapeutic effects across different genotypes of pustular psoriasis have not been adequately assessed. In these cases. In this case series, we evaluate the therapeutic efficacy of spesolimab in five GPP patients, focusing on the influence of IL-36RN gene mutations and the presence of concomitant plaque psoriasis.

Case Report

Patient 1 is a 28-year-old Chinese man who has had GPP since he was 3 years old. Genetic analysis confirmed a homozygous IL36RN mutation (c.115 + 6T > C). He experienced recurrent severe flares with fever, leading to multiple hospitalizations, despite receiving intermittent low-dose prednisolone and traditional Chinese medicine. For the past decade, he used only topical traditional Chinese medicine and steroid ointments, yet he still had episodes of pustular

Received: 17 April 2025
Accepted: 17 July 2025
Published: 9 August 2025

eruptions. One month before his hospital admission, a severe flare prompted him to seek treatment. Physical examination revealed extensive erythema, severe scaling, yellow pustular crusts on the scalp, trunk, and limbs, and dystrophic nails covered with pustules (Figure 1A1–3 and Table 1). Laboratory tests showed leukocytosis, elevated platelets (587 × 10□/L), ESR, CRP (40.03 mg/L), and IL-6 (56.24 pg/mL). GPPASI, GPPGA, and JDA-GPPSI scores3 were 51.6, 3, and 12, respectively. After administering a single intravenous dose of 900 mg spesolimab, the patient experienced a 51% reduction in GPPASI scores and a 33.3% reduction in GPPGA scores within one week. Yellow crusts shed within 12 hours, and nails improved significantly by 4 weeks. Only vitamin E ointment was used for moisturizing after

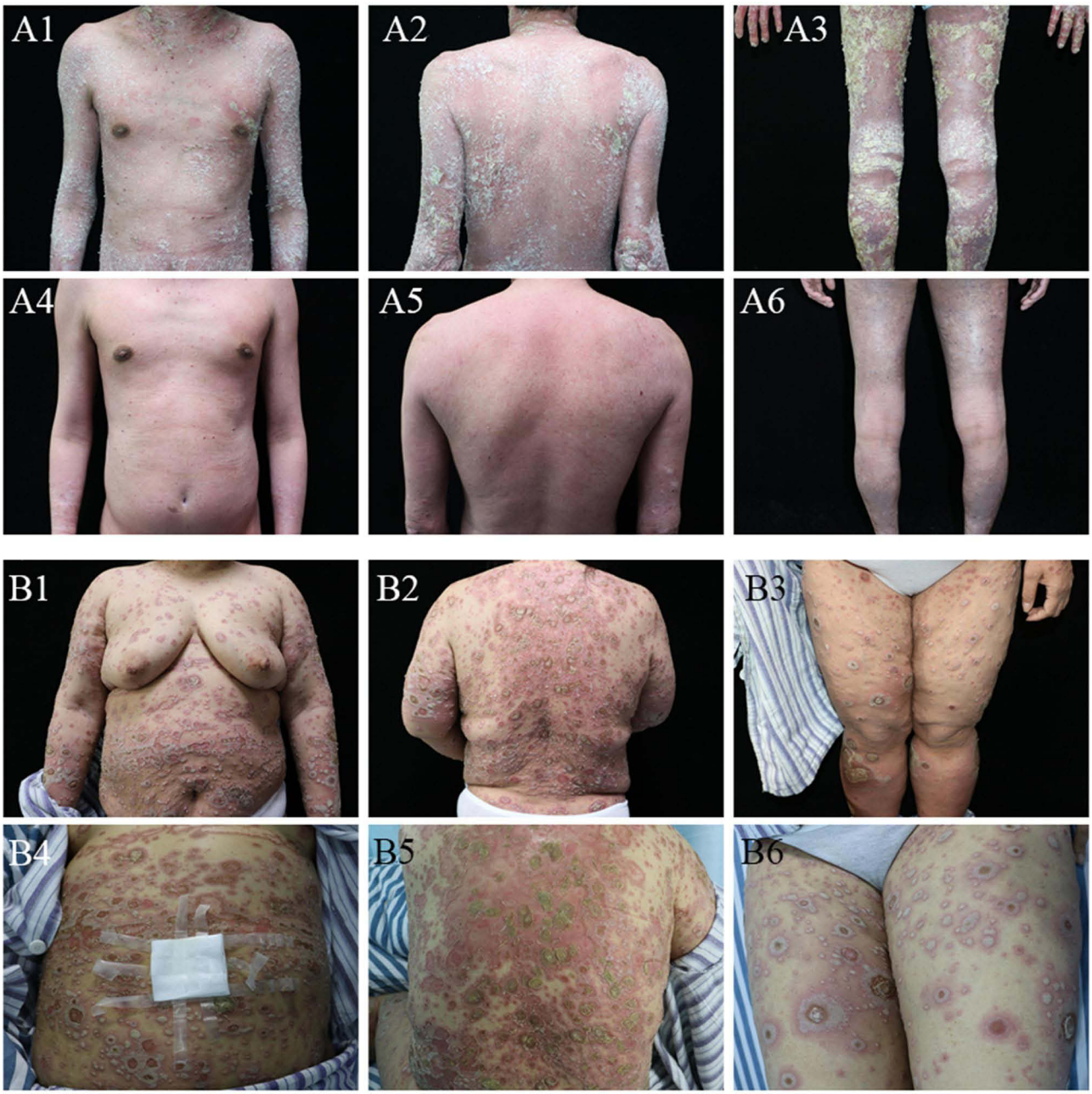

Figure 1 Efficacy of Spesolimab in Treating GPP patients with or without Concomitant Plaque Psoriasis. The skin lesions of GPP patient 1, who did not have coexisting plaque psoriasis prior to treatment (**A1–3**), exhibited notable improvement four months after receiving spesolimab therapy (**A4–6**). In contrast, the skin lesions of GPP patient 5, who presented with coexisting plaque psoriasis before treatment (**B1–3**), displayed worsening of symptoms within one week of spesolimab administration (**B4–6**). Table 1 has been revised regarding the genetic mutations of Case 2 and Case 3. Case 1 (IL36RN homozygous mutation) and Case 2 (IL36RN/CARD14 compound mutations), Cases 3, 4, and 5 did not show IL-36RN gene mutations.

Table 1 The Demographic and Clinical Characteristics of GPP Patients with or Without IL-36RN Gene Mutations and Coexisting Plaque Psoriasis

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (year)	28	35	62	25	44
Sex	Male	Female	Male	Female	Female
Age at onset of GPP	3	5	22	25	44
Previous treatments	Traditional Chinese herb	Acitretin, cyclosporine, and traditional Chinese herb	Chinese herb, acitretin, and Secukinumab	Prednisone, diphenhydramine, and cyclosporine	Adalimumab, cyclosporine, MTX
Plaque psoriasis history	No	No	No	Yes	Yes
Geographic tongues	Yes	No	Yes	No	No
Family history	No	No	No	No	No
IL-36RN gene mutations	Yes	Yes	No	No	No
Accompanying symptom	No	No	Fever (39.1°C)	Fever (39°C)	Fever (40°C)
Treatment	900mg spesolimab	900mg spesolimab	900mg spesolimab	900mg spesolimab	900mg spesolimab
Resolution of pustules	12h	10h	18h	No significant improvement in one week	No significant improvement in one week
Adverse effects	No	No	No	No	No
No Recurrence	12 months	6 months	6 months	❄4 months (switched to ixekizumab)	▲10 months (switched to secukinumab)
	Before after✱	Before after	Before after	Before after	Before after
CRP (mg/L) (0.0–5.0)	40.03, 10.70	150.43, 3.11	65.43, 29.65	85.56, 90.74	105.23, 116.55
IL-6 (pg/mL) (≤ 20.0)	56.24, 16.34	596.73, 209.62	144.64, 32.22	35.46, 37.88	78.33, 135.71
IL-8 (pg/mL) (≤ 21.4)	22.27, 12.34	333.28, 5.61	210.69, 42.42	151.13, 155.67	134.61, 209.83
IL-10 (pg/mL) (≤ 5.9)	8.52, 4.86	80.89, 3.77	14.85, 5.07	20.15, 23.53	11.26, 21.86
IL-17 (pg/mL) (≤ 20.6)	6.65, 1.72	35.28, 0.96	49.77, 2.63	50.26, 63.75	73.16, 130.76

Notes: ❄4 months: No recurrence after 4 months of switching to ixekizumab. ▲10 months: No recurrence after 4 months of switching to ixekizumab. ✱Before: before spesolimab injection; after: one week after spesolimab injection. Except for Case 1, where IL-17 did not show an increase, IL-6, IL-8, and IL-10 were elevated. Moreover, these four cytokines (IL-6, IL-8, IL-10, and IL-17) were elevated in the other cases as well. Additionally, one week after spesolimab injection, the elevated cytokines showed a significant decrease in Cases 1, 2, and 3.

discharge. Platelet levels returned to normal (269.5×10^9/L), with no new pustules observed at 4 months (Figure 1A4–6), and the patient has remained in complete remission for 12 months.

Patient 2 is a 35-year-old Chinese woman with a 30-year history of intermittent erythema and pustules, recently experiencing a one-month uncontrolled flare of GPP. Previous treatments, including acitretin, cyclosporine, corticosteroids, and traditional Chinese medicine, provided only temporary relief. One month ago, extensive erythema and pustules reappeared on her trunk and limbs, accompanied by itching, pain, and bilateral knee joint pain, with poor response to cyclosporine. Physical examination revealed diffuse erythema and dense pustules on the face, trunk, and extremities (Table 1). Laboratory tests showed elevated cytokine levels (eg, IL-6596.73 pg/mL, IL-10 80.89 pg/mL, IL-8333.28 pg/mL) and CRP (150.43 mg/L). Genetic analysis identified IL36RN (c.227C>T, p.P76L) and multiple CARD14 mutations (eg, p.R547S, p.R820W, p.R883H). A single 900 mg intravenous dose of spesolimab was administered, leading to significant improvement within 10 hours as pustules subsided. One week post-treatment, the GPPASI and GPPGA scores were reduced by 83.2% and 66.7%, respectively. The patient has remained in complete remission for 4 months.

Patient 3 is a 62-year-old Chinese man with a 40-year history of GPP unresponsive to various treatments. Symptoms improved with secukinumab since December 2022 but worsened after titanium dental implants, causing a high fever, widespread erythema, pustules, and swelling. Genetic testing revealed no mutations (Table 1), and laboratory tests showed elevated CRP (65.43 mg/L) and hypoalbuminemia (23 g/L). After immunoglobulin therapy, he received a single 900 mg dose of spesolimab, leading to significant improvement within 18 hours. One week later, GPPASI and GPPGA scores were reduced by 60% and 33.3%. The patient has remained in complete remission for 6 months.

Patient 4, a 25-year-old female with a 3-year history of erythematous plaques and scales, developed recurrent pustules one month prior. She experienced recurrent fever. Treatment with prednisone, diphenhydramine, and cyclosporine was

ineffective. The patient has a history of type I diabetes. Examination revealed widespread pustules, and pathology confirmed pustular psoriasis. Genetic testing showed no mutations, and cytokine levels were elevated (IL-17: 50.26 pg/mL, IL-8: 151.13 pg/mL) (Table 1). A single 900 mg dose of spesolimab showed slight improvement after one week but was unsatisfactory. Switched to ixekizumab in the second week, pustules resolved within one week, and no recurrence was observed during four months of follow-up.

Patient 5 is a 44-year-old Chinese woman with a 10-year history of plaque psoriasis and psoriatic arthritis, effectively managed with secukinumab since January 2023 after unsuccessful treatments with adalimumab, cyclosporine, MTX, and topical therapies. Two months prior, she discontinued secukinumab for pregnancy preparation and developed uncontrolled GPP, with widespread pustules, erythema, severe edema, and a high fever of 40°C (Figure 1B1–3 and Table 1). Genetic testing showed no mutations, and cytokine levels were elevated (IL-17: 73.16 pg/mL, IL-8: 134.61 pg/mL, IL-6: 78.33 pg/mL (Table 1). A single 900 mg dose of spesolimab was administered, but one week later, symptoms persisted, including high fever and new pustules (Figure 1B4–6). Slight improvement was noted in pustules on the abdomen and upper limbs, but the patient refused a second injection. She was given 1 mL of betamethasone, resulting in rapid improvement within three days, with resolution of pustules and erythema. Fever subsided, and she was discharged after resuming secukinumab and topical treatments.

Discussion

The case reports presented herein highlight the significant challenges and successes in managing GPP, particularly in the context of varying IL36RN gene mutations. The importance of these cases lies not only in the individual patient experiences but also in their contributions to the broader understanding of GPP management, treatment efficacy, and the implications of genetic factors on clinical outcomes. Current literature emphasizes the pivotal role of IL-36 signaling in the pathogenesis of GPP, where dysregulated immune responses lead to severe inflammatory episodes characterized by pustulation and systemic symptoms.[3]

Genetic analysis in our patients has revealed various mutations, particularly in the IL36RN gene, which are associated with the clinical severity and treatment response. The rapid pustular resolution in Case 1 and Case 2 (detectable IL36RN gene mutations) supports canonical IL-36–dependent inflammation. The IL36RN defects likely drive uncontrolled NF-κB/MAPK signaling cascades, consistent with prior reports linking IL36RN mutations to amplified IL-36 ligand activity.[4,5] The data from these cases, including cytokine normalization post-treatment, underscore spesolimab's efficacy in interrupting the autocrine loop. Case 3 (no detectable mutations) achieving complete remission within 18 hours highlights non-genetic IL-36 pathway activation. Despite the absence of IL36RN mutations, spesolimab effectively suppressed IL-36 signaling, evidenced by post-treatment declines in CRP and IL-6/IL-8 levels. Spesolimab direct targeting of IL-36 receptor (downstream effector molecules) to block IL-36 α / β / γ signaling, regardless of the presence of IL36RN mutations upstream.[6,7] Conversely, Patient 4's limited response to spesolimab suggests that not all GPP cases are responsive to this treatment, highlighting the complexity of the disease. Rising IL-17 levels (50.26→63.75 pg/mL) post-spesolimab, whereas switching to ixekizumab (anti-IL-17A) resolved pustules within one week. IL-17 enhances keratinocyte production of IL-36 ligands, creating a feedforward loop that likely diminishes spesolimab's efficacy in Th17-driven disease.[8] Besides, the treatment failure in Case 5 (plaque psoriasis with PsA) suggests IL-23/Th17 axis dominance may override IL-36-targeted therapy. Prior secukinumab efficacy and rapid relapse after spesolimab indicate IL-36 acts merely as a downstream effector in mixed phenotypes, where single-pathway blockade is insufficient.[9] IL-17 levels remained elevated post-spesolimab, further supporting Th17 pathway resilience. May be anti-spesolimab antibodies could explain poor response.

In conclusion, spesolimab has proven effective in treating generalized pustular psoriasis (GPP), but its efficacy is not universal. IL36RN genotyping does not influence its therapeutic effect, and IL-36 inhibition alone may not be sufficient for all GPP phenotypes. However, the presence of concomitant plaque psoriasis does impact treatment outcomes. This variability highlights the need for multi-pathway stratification in GPP treatment, rather than relying solely on IL36RN mutations. Furthermore, cytokine measurements—such as IL-6, IL-8, and IL-17—appeared to correlate with treatment responses in our study, highlighting the potential of cytokine profiling as a predictive tool for monitoring treatment efficacy.

Consent for Publication

We have confirmed with the patients that the details of any images, videos, recordings, etc can be published, and patients informed consent for publication of their case details and images was obtained in written form. Institutional approval was not required to publish the case details.

Acknowledgments

The authors express profound appreciation to all study investigators and patients for their invaluable contributions to this research.

Funding

This study was supported by Guangzhou Basic Research Plan Jointly Funded by the City, School (Hospital), and/or Enterprise (2024A03J0478); The Bethune Charitable Foundation Immunoinflammatory Disease Research Support Project (J202301E036).

Disclosure

The authors report no conflicts of interest in this work.

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