REVIEW

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# The update of treatment strategies in pediatrics with generalized pustular psoriasis in China

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**ABSTRACT**
Generalized pustular psoriasis (GPP) is a severe subtype of psoriasis, commonly combined with systemic inflammation. Gene mutations have been found to be associated with GPP and vary by ethnicity. Systemic treatments are usually required for the severity and potential complications of GPP. However, there is no common consensus in China, especially among pediatric patients, whose data are scarce. Acitretin, methotrexate, and cyclosporine are widely used in pediatrics with GPP, while the adverse effects should be highlighted. The emergence of different biological agents brings us into a new era. This article discusses the genetic background of Chinese patients and demonstrates the evidence of treatment in pediatrics with GPP.

**KEYWORDS**
Generalized pustular psoriasis, Pediatrics, Treatment

## INTRODUCTION

Generalized pustular psoriasis (GPP) is a severe inflammatory cutaneous disease that presents as generalized pustular, edema erythema, and systemic inflammation, including fever, joint pains, headaches, and leukocytosis (Figure 1). Patients might experience a relapse-remission course or a persistent condition lasting for more than 3 months.[1] GPP can be primary or secondary to psoriasis vulgaris (PV), and triggered by infections, drugs, stress, or pregnancy. Primary GPP usually occurs during childhood and is caused by gene variants. Considering the severity of GPP, systemic treatments are required.

In pediatric patients, the treatment of GPP is a definite challenge, as highlighted by the balance in efficacy and safety. In China, all systemic treatments for GPP are off-label. According to the American National Psoriasis Foundation, acitretin, methotrexate, cyclosporine, and etanercept are regarded as first-line therapies for childhood GPP, and adalimumab, infliximab, and ultraviolet B (UVB) phototherapy are regarded as second-line therapy.[2] Miyachi et al.[3] identified 1516 adult patients with GPP in the Japanese national inpatient database and categorized the patients into three medication groups: biologics (tumor necrosis factor [TNF] inhibitors, interleukin [IL]-12/IL-23 p40 inhibitors, or IL-17 inhibitors), oral agents without biologics (cyclosporine, retinoids, or methotrexate), and systemic corticosteroids only. The biologics group had favorable outcomes compared with the other treatments. Takeichi et al.[4] summarized the biologics, including adalimumab, ixekizumab, secukinumab, brodalumab, and guselkumab in adults, and showed that the biologics

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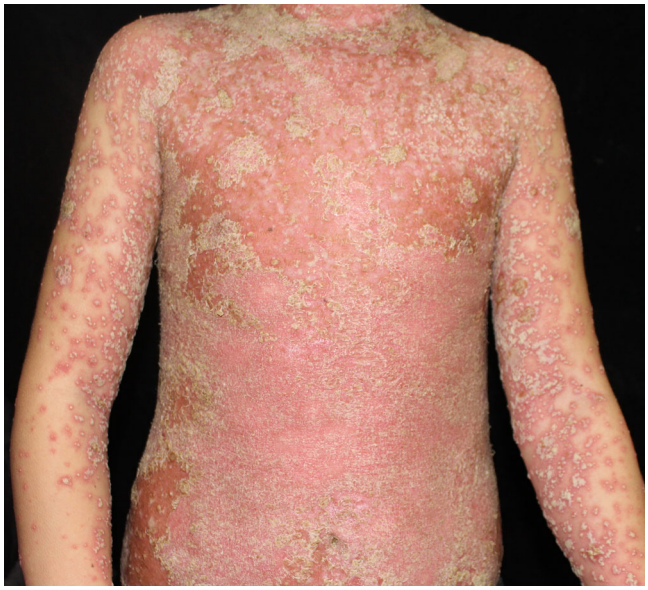

**FIGURE 1** The clinical presentation of generalized pustular psoriasis.

seemed to be effective and relatively well tolerated. With the introduction of biological agents targeting variable cytokines and receptors, the treatment algorithm for GPP enters a new era. However, treatment reviews for children with GPP are scarce. Here we summarize the genetic background of Chinese patients and treatment in pediatrics with GPP through a literature review. The literature search was performed in PubMed with the keywords, "generalized pustular psoriasis", "children", "interleukin-36", and "treatment".

## EPIDEMIOLOGY

Feng et al.[5] investigated the epidemiology of GPP in China based on Urban Basic Medical Insurance. In 2016, the GPP-adjusted national prevalence is 1.108 per 100 000 person-years, and the incidence is 0.509 per 100 000 person-years. The prevalence of GPP in China tends to be higher than in France and Brazil, whose prevalence is 0.176 and 0.7 per 100 000 respectively. Males count a slightly higher ratio than females. The bimodal age distribution is observed, the 0–3-year age and the 30–39-year age. In the children group, the GPP crude prevalence and incidence are 0.927 and 0.742 per 100 000 person-years in the 0–3-year age group, 0.471 and 0.441 per 100 000 person-years in the 4–9-year age group, 0.204 and 0.158 per 100 000 person-years in the 10–19-year age group.[5]

## GENETIC BACKGROUND

In recent years, gene mutation has been associated with GPP, including IL-36 receptor antagonist (*IL36RN)*, caspase recruitment domain-containing protein 14 (*CARD14*), adapter protein complex 1 subunit sigma 3 (*AP1S3*), myeloperoxidase (*MPO*), serine protease inhibitor gene serpin family A member 3 (*SERPINA3*), and TNF alpha-induced protein3 (TNFAIP3)-interacting protein 1 (*TNIP1*).[6–11] The *IL36RN* gene mutation is the most common one, which is known as a deficiency of the interleukin-36 receptor antagonist (DITRA).

Li et al.[6] found an association between *IL36RN* variants and GPP in Chinese Han patients using 62 sporadic GPP, 96 healthy controls, and 174 sporadic PV patients. The patients had an age of onset of 33.10 ± 19.77 years in the GPP patients, and 29.31 ± 21.83 years in the PV patients. The *IL36RN* mutation was detected in 46.77% of the GPP, 6.90% of the PV patients, and 6.25% of the healthy controls. Additionally, Wang et al.[12] found the *IL36RN* mutation in 66.7% of children with only GPP with an average onset age of 4.27 ± 3.66 years. Our group found the *IL36RN* mutation in 76.67% of children with GPP with a median onset age of 2.37 years.[13] The *IL36RN* c.115 + 6T > C variant was the most frequent variant in Chinese patients and was reported in 63.6% of children with only GPP.[12] This differs from the European and African populations, whose dominant variants are p.Ser113Leu and p.Leu27Pro respectively.[12,14,15]

Patients who carried recessive alleles (homozygous or compound heterozygous) had an earlier age of onset than those without the *IL36RN* mutation.[12] Wang et al.[12] reported the average age of onset in pediatric patients with only GPP and carried an *IL36RN* variant was 3.55 ± 3.29 years and 5.72 ± 3.55 years in pediatric patients with only GPP and no *IL36RN* variant. The frequency of *IL36RN* variants was positively correlated with GPP with acrodermatitis continua of Hallopeau (ACH) and negatively correlated with GPP with PV.[13,16] In our group, the *IL36RN* mutation was detected in 100% of children who suffered from GPP with ACH, 78.05% of children who suffered from GPP without PV and ACH, and 44.44% of children who suffered from GPP with PV.[13] Furthermore, more patients with the *IL36RN* mutation converted to ACH.[12]

The *IL36RN* mutation might be associated with a more severe inflammatory reaction in GPP. Wang et al.[12] found that the incidence of confluent lakes of pustular, perianal erosion, flexural erosion, and conchal pustules was higher in patients with the *IL36RN* mutation. Our study discovered that patients who carried the *IL36RN* mutation had a longer length of hospitalization and a longer time to reach normal body temperature after treatment.[13] The *IL36RN* mutation seems to not affect the treatment response, but patients with *IL36RN* variants had a much higher half-year recurrence rate after acitretin withdrawal.

## SYSTEMIC TREATMENTS

### Retinoids

Japanese guidelines recommend retinoids as a C1 degree for GPP in children, in which acitretin, the active metabolite of etretinate, is used most frequently.[17] Acitretin inhibits keratinocyte proliferation and inflammatory cytokines expression by interfering with the JAK-STAT pathway and down-regulating the activities of Th1 and Th17 cells and the level of interferon (IFN)-$\gamma$.[18]

Our group showed the effectiveness of acitretin in 16 Chinese children with GPP, with a mean age of 8.69 $\pm$ 2.12 years.[19] After acitretin was administrated, the average time for pustules to fade was 6 days, the temperature to normalize was 6.14 days, and the C-reactive protein to normalize was 8.73 days. Two weeks later, 25% of the patients had a Japan Dermatology Association (JDA) severity index of 0/1, and 12 weeks later, 87.5% had a JDA severity index of 0/1. Additionally, Chen et al.[20] observed 15 Chinese children with a mean age of 3.4 $\pm$ 2.9 years treated with acitretin, including ten patients with GPP, three with palmoplantar pustulosis (PPP), and two with ACH. New pustulosis formation ceased in three days, and skin lesion remission started in 5–7 days. Fourteen patients (93.3%) achieved a good response, and one patient with ACH achieved a moderate response. Overall, acitretin was effective in about 90% of children with PP as a monotherapy or combination therapy.[20]

Zhu et al.[21] analyzed 61 patients with GPP from China, discovering that *IL36RN* mutations did not affect the efficacy of acitretin and that maintenance therapy with low-dose acitretin might decrease the recurrence rate. Recently, Yang et al.[22] proposed that plasma retinol might be a reliable biomarker to assess the severity of GPP and the effectiveness of acitretin monotherapy in Chinese children.

Attention must be paid to the side effects of acitretin treatment in patients with PP should be noticed. Of our 16 patients, 75% had mucocutaneous dryness, 37.5% had dyslipidemia, and 25% had abnormal liver enzymes.[19] Chen et al.[20] recorded dry skin in 66.7% of patients, itching in 26.7%, cheilitis in 20.0%, and dry mouth in 6.7%. In children, growth disturbance is a major concern, including early closure of the epiphysis and hyperostosis. Our group preliminarily found that acitretin had no significant effect on the growth and development of children.[23] We retrospectively analyzed 106 patients who were treated with oral acitretin for 1–90 months retrospectively, in which 79.2% of the patients suffered from pustular psoriasis. Of the 96 patients under 18 years, 94.8% had a normal stature, and 5.2% had short stature. Of the 83 patients receiving acitretin alone, 97.6% had a normal stature, and 2.4% had short stature. The risk of short stature was mostly associated with acitretin combined with glucocorticoid. Thirteen patients who reached near-adult height had a normal stature. Bone age was calculated by radiology in 45 patients, the bone age minus chronological age had no significant difference after treatment, and premature closure of epiphysis was not detected in all 45 patients.

### Methotrexate

Methotrexate (MTX) plays an anti-inflammatory role in psoriasis. Recently, studies have found that MTX might inhibit the JAK/STAT pathway and restore the immunosuppressive function of Tregs.[24,25] The finding might explain the mechanism to a degree. In children, MTX is widely used for PV, and its efficacy and safety have been shown by our group.[26] However, evidence of the use of pustular psoriasis is scarce. Japanese guidelines recommend MTX as a C1 degree for GPP in children.[17]

Haustein et al.[27] reviewed 157 adult patients with psoriasis, including 24 generalized pustular forms and 12 localized pustular forms, and a good response was found in 80% of the patients with generalized pustular psoriasis and 66% of the patients with localized pustular psoriasis. There are also some cases that shed light on childhood cases.[28–32] A two-year-old boy with GPP achieved remarkable pustules clearance and resolution of toxemic features after the first dose of MTX.[28] Garg et al.[29] reported on two siblings with GPP. The 7-year-old sister responded dramatically to MTX and showed almost 90% clearance of skin lesions after a 4-week treatment. The 3-year-old brother was given combined prednisolone and MTX treatment and significantly improved. Kumar et al.[30] treated childhood psoriasis with MTX in seven patients, including two with GPP, one 14 years old and one 16 years old. Their disease was controlled at weeks 8 and 10, respectively, and they experienced disease-free intervals for 16.8 weeks and 14.6 weeks, respectively. However, in some pediatric patients, the responses were unsatisfactory.[31,32] When the treatment goal is not met, combining MTX with other systemic medications, such as anti-TNF$\alpha$ inhibitors and retinoids, may be a choice.[33,34]

### Cyclosporine

Cyclosporine inhibits T-cell function, cytokine production, and MHC-II expression by acting as an immunosuppressive agent and calcineurin inhibitor, exerting antipsoriatic effects.[35] Cyclosporine was effective in adults with GPP.[36,37] The efficacy is also observed in children, including a three-month-old infant.[38] Kiliç et al.[39] reported on three children with GPP treated with low-dose cyclosporine ($1–2\,mg{\cdot}kg^{-1}{\cdot}d^{-1}$) and observed the clearance of psoriatic lesions after 2–4 weeks of therapy.

Adverse events such as hypertension, nephrotoxicity, and increased risk of infection should be noted. Considering the side effects of cyclosporin are dose and treatment-duration-dependent, short-term therapy might be a prospective option.[40] However, the recurrence of GPP may occur with the reduction or withdrawal of cyclosporine.[41–44] Thus, using cyclosporin for induction and then choosing other treatments for maintenance, such as acitretin and narrow-band UVB (NBUVB) phototherapy, is worth consideration.[45]

### TNF-α blocking agents

TNF-α inhibitors, including infliximab, etanercept, and adalimumab, are used widely for PV. Infliximab is a chimeric anti-TNF-α monoclonal antibody. In data from adults, infliximab is safe and highly effective for GPP and acts as a rescue treatment that induces resolution of pustules within 1–8 days.[46] A similar effect was also observed in Chinese children. Lu et al.[47] treated two Chinese juveniles with GPP successfully, one achieved complete resolution within 2 weeks, and one had their disease controlled within 72 h. No relapse or exacerbation occurred in the two juveniles during 12 months. Pan et al.[48] described a Chinese juvenile with GPP and *IL36RN* c.115+6T > C homozygous mutation who had a good rapid response to short-term infliximab and had no relapse for 21 months. However, for long-term disease resolution, combining MTX or acitretin or switching to other biologic agents was required.[31,46] In contrast, infliximab also could induce GPP as a paradoxical reaction through up-regulating Th17 and IFN-α expression.[49]

Adalimumab is a recombinant human immunoglobulin G1 monoclonal antibody. Du et al.[50] reported on seven Chinese children with GPP treated with adalimumab, and all of them had obvious improvement in skin lesions and systemic inflammatory reaction within the first week, and almost total clearance of skin lesions within one month. Du et al.[50] reviewed six Chinese pediatric patients treated with adalimumab, three with adalimumab monotherapy, two with adalimumab combined with methotrexate, and one with adalimumab combined with methotrexate and cyclosporine. All patients had complete remission within 1–15 months. In those 13 patients, no severe adverse events were recorded, and only one patient experienced flu-like symptoms.

Etanercept is a soluble TNF receptor fusion protein. Several cases have described its efficacy in children with GPP.[51–55] Alvarez et al.[56] reported on a 3-year-old child with GPP, refractory to cyclosporine and acitretin, and experienced a relapse when infliximab was ceased, resulting in slow but sustained improvement with etanercept. Etanercept also did well in children with GPP and the *IL36RN* gene mutation or psoriatic arthritis.[51,52] Etanercept was well tolerated in those patients. Our group also observed a good response to etanercept in six Chinese patients under 4 years old. All patients achieved a JDA severity index of 1 and Generalized Pustular Psoriasis Area and Severity Index (GPPASI)-75 after a 4-week treatment and a JDA severity index of 0 and GPPASI-100 after a 12-week treatment. The treatment effect was maintained for 24 weeks. In three patients, with a median follow-up duration of 12 months (10–12 months) after drug withdrawal, one patient relapsed at four months. No severe adverse events were recorded. This manuscript is currently being submitted.

### IL-17 pathway inhibitors

Secukinumab is a fully human immunoglobulin-Gκ IL-17A monoclonal antibody and decreases IL36R activation by inhibiting IL-17A and disturbing the inflammatory loop of GPP. Several cases and case series have described the efficacy and safety of secukinumab.[19,57–66] Our team reviewed the efficacy and adverse events of secukinumab in 20 Chinese pediatric patients with GPP, with the ages ranging from 6 to 12 years and the age of onset ranging from 2 months to 11 years.[19] All the children had improvement in symptoms in the first week, and all patients achieved a JDA severity index of 0/1 in 3 weeks. Six children developed adverse events; two had abnormal alanine aminotransferase, two had atopic dermatitis-like lesions, two had mild neutropenia, and one had herpes simplex. We compared these data with acitretin in 16 children with GPP and demonstrated that secukinumab had a more favorable response. Ruan et al.[58] demonstrated similar results in 18 Chinese children with GPP treated with secukinumab monotherapy and found the efficacy was maintained for 48 weeks. Wu et al.[57] described four Chinese children with DITRA aged from 5 to 11 years, and one had ACH lesions. Secukinumab monotherapy was used in one patient, co-therapy with acitretin was used in two patients, and secukinumab with an antibiotic was used in one patient. All the children had defervescence and clearance of non-acral pustules within 72 h, and all the participants except for the one with ACH achieved an Investigator's Global Assessment (IGA) 0/1 at week 24. Secukinumab was also effective in a 4-week-old infant with *IL36RN* and *CARD14* gene mutations.[63]

Ixekizumab is a humanized immunoglobulin G4 monoclonal antibody that targets IL-17A and was approved in 2018 in Japan for patients with GPP and erythrodermic psoriasis (EP). Adult patients with GPP treated with ixekizumab had rapid and sustained improvements, and it was well tolerated.[67,68] Brodalumab is a human immunoglobulin G2 monoclonal antibody that blocks IL-17 via inhibiting IL-17R. In phase III, an open-label multicenter

study, 12 adults with GPP demonstrated that brodalumab significantly improved the symptoms throughout the 52 weeks without any new adverse events.[69] However, treatment data in children are lacking.

### IL-23 and IL-23/IL-12 inhibitors

Ustekinumab is a fully human L-12/IL-23 p40 monoclonal antibody. Case and case series have demonstrated that adults with GPP whether with or without the *IL36RN* gene mutation responded to ustekinumab.[70–72] Guselkumab is a human IL-23 p19 subunit monoclonal antibody. A 52-week, phase 3, multicenter, open-label study reported the efficacy and safety in adults with GPP.[73] Risankizumab is another human IL-23 p19 subunit monoclonal antibody. A phase 3, randomized, multicenter study in Japan studied eight adults with GPP treated with risankizumab, improvement was seen in week 4, and the patients continued to improve through week 52.[74] The improvement was maintained through week 160.[74] However, data on children are limited.

### IL-36R inhibitors

The IL-36 pathway is central to the pathogenesis of GPP. Thus, a monoclonal antibody targeting the IL-36 pathway is a prospective drug, theoretically. Spesolimab is a humanized monoclonal antibody that targets IL-36R. In a phase 2 trial, 53 adults with GPP were enrolled in the placebo-controlled trial, 35 received the spesolimab, and 18 received the placebo.[75] At week one, a pustulation subscore of 0 was achieved in 54% of the spesolimab group and 6% of the placebo group, a GPPASI score of 0/1 was achieved in 43% of the spesolimab group and 11% of the placebo group. The improvement was sustained to week 12. The improvement also was observed in the patient-reported outcomes.[76] In the spesolimab group, two of the 35 patients reported drug reactions, one had a drug-induced hepatic injury, and six of the 35 had infections in the first week. In the open-label stage, 24 of the 51 patients had an infection, and 23 of the 50 detected antidrug antibodies at week 12.[75]

## CONCLUSIONS

In China, the adjusted national prevalence of GPP is 1.108 per 100 000 person-years, and the incidence is 0.509 per 100 000 person-years. The prevalence is higher than in France and Brazil. The first prevalence peak appears at the age of 0–3. *IL36RN* variants are associated with GPP in the Chinese population, especially in those with earlier age of onset, with ACH, without PV, severe inflammatory reactions, and likely to recurrence. Biological agents targeting different inflammatory mediators might be a prospective option for Chinese pediatrics with GPP.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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