



Commentary on a Clinical Trial of Spesolimab, a Humanized Anti-interleukin-36 Receptor Monoclonal Antibody, in Generalized Pustular Psoriasis

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ABSTRACT

Generalized pustular psoriasis (GPP) is a rare and potentially life-threatening autoinflammatory skin disease, mainly mediated by the interleukin (IL)-36 signaling pathway. The irregular and relapsing pattern of the skin symptoms, the GPP-associated complications, as well as the physical pain caused by the disease add burdens to patients with GPP. Currently, spesolimab, a humanized monoclonal antibody targeting the IL-36 receptor, has been approved as a GPP-specific treatment targeting IL-36 signaling. Effisayil 1, a randomized, controlled clinical trial, investigated the efficacy and safety of spesolimab in patients presenting with a GPP flare. In this commentary, we discuss the study design, endpoints, and clinical outcomes of Effisayil 1, which differed from previous clinical trials that investigated other biologic agents (adalimumab, secukinumab, brodalumab, ixekizumab, and guselkumab) in patients with GPP.

Keywords: Effisayil 1; Spesolimab; Generalized pustular psoriasis; Interleukin-36; Biologic agents

Key Summary Points

Effisayil 1 is the first multinational, randomized, double-blind, placebo-controlled, phase II trial to show promising clinical outcomes of spesolimab, a humanized monoclonal antibody targeting the IL-36 receptor, in patients presenting with a GPP flare.

Effisayil 1 has a study design that evaluates the efficacy and safety of spesolimab more accurately; the study also includes more diverse populations and the largest sample size to date, as well as GPP-specific primary and key secondary endpoints.

The IL-36 family plays a dominant role in the pathogenesis of GPP.

INTRODUCTION

Generalized pustular psoriasis (GPP) is a rare and potentially life-threatening autoinflammatory skin disease, characterized by recurrent flares of neutrophil-filled sterile pustules that

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occur with or without systemic inflammation [1]. The irregular and relapsing pattern of disease flares, GPP-associated systemic complications (such as hypoalbuminemia, neutrophilic cholangitis, uveitis, acute respiratory distress syndrome, cardiovascular aseptic shock, heart failure, prerenal kidney failure, and severe infections) and comorbidities (such as anxiety, depression, and psoriatic arthritis) make it challenging to manage the disease, and pose a major clinical burden to patients and their families [2–5]. A retrospective note review in Malaysia showed that, among 102 adult patients (29% of whom were Chinese) diagnosed with adult-onset GPP between 1989 and 2011, 78 patients had acute GPP, among whom 47 had one episode of pustular flare (> 30% body surface area), 21 had two to five episodes, and 10 had more than five episodes during follow-up of about 8 years [6]. The interleukin (IL)-36 family is found to play a dominant role in the pathogenesis of GPP [7]. IL-36 cytokines (IL-36 α , IL-36 β , and IL-36 γ) and the IL-36 receptor antagonist are expressed in various types of cells, including keratinocytes [4]. Sustained activation of the IL-36 signaling pathway can induce hyperactivation of nuclear factor- κ B and mitogen-activated protein kinase, which facilitates overexpression of numerous cytokines [such as IL-1 β , IL-17A, IL-23, tumor necrosis factor (TNF)- α] and chemokines (such as C-X-C motif chemokine ligand 1, 2, and 8) [1, 4]. The neutrophilic infiltration driven by these cytokines and chemokines induces sterile pustule formation with systemic inflammation [1, 4], which is the core characteristic of GPP.

To date, retinoids, cyclosporine, and methotrexate (MTX) are the most commonly used nonbiologic systemic agents and are recommended by global guidelines as first-line therapy for patients with GPP [3, 8, 9]. However, these agents need to be used with caution; cyclosporine is associated with adverse events such as hypertension and renal toxicity in long-term treatment, MTX needs to be considered cautiously for patients with comorbidities such as diabetes mellitus and renal or hepatic injury; in addition, retinoids and MTX are contraindicated in pregnant women due to their teratogenic effect on the fetus [3, 10]. To date, no

randomized clinical trials of systemic therapies have been performed in patients with GPP. The systemic therapies used for GPP have limited study evidence. This commentary summarizes findings from current clinical studies on the efficacy and safety of biologic agents in patients with GPP.

EFFISAYIL 1 STUDY

Effisayil 1 is a multinational, randomized, double-blind, placebo-controlled, phase II trial that was conducted between 20 February 2019 and 5 January 2021; patients were enrolled at 37 sites in 12 countries. This study investigated the efficacy and safety of spesolimab, a humanized monoclonal antibody targeting the IL-36 receptor, in patients presenting with a GPP flare. A total of 53 patients were enrolled and randomly assigned (2:1) to receive a single dose of spesolimab 900 mg ($n = 35$) or placebo ($n = 18$) on day 1. Patients from both groups could receive open-label spesolimab (single dose, 900 mg) on day 8, and/or as rescue therapy after day 8 if the criteria were met. Criteria for open-label therapy were: no escape treatment; Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) ≥ 2 (a clinician assessment of GPP severity based on a modified Physician Global Assessment, which replaces the induration component with a pustular component; the GPPGA score is based on average scores of an individual for erythema, scaling, and pustulation); and GPPGA pustulation subscore ≥ 2 . Criteria for rescue therapy were: experienced recurrence of a GPP flare after achieving a clinical response (CR) to spesolimab, placebo, or standard of care. Patients were followed until week 12 [11] (Table 2). Patients who achieved clinical improvement and completed the trial without flare symptoms were eligible to enter the 5-year open-label extension study (NCT03886246) in which the long-term safety and efficacy of spesolimab in GPP patients will be assessed.

The trial adopted GPP-specific endpoints and various patient-reported outcomes (PROs) to assess the clinical efficacy of spesolimab in patients with GPP; the primary and key

secondary endpoints were GPPGA pustulation subscore of 0 at week 1, and GPPGA total score of 0 or 1 at week 1, respectively. The GPP-specific endpoint GPPGA is adapted from the Physician Global Assessment score with a minimal modification of replacing the induration component with a pustule component. GPPGA is calculated by averaging individual scores of erythema, scaling, and pustulation on all GPP lesions (Table 1) [12, 13]. In addition, GPP Area and Severity Index (GPPASI), and PROs including Psoriasis Symptom Scale (PSS), Dermatology Life Quality Index (DLQI), Pain Visual Analog Scale (VAS), as well as Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale were also assessed. C-reactive protein levels and neutrophil counts were assessed over 12 weeks after initiation of spesolimab [11].

At baseline, 19% of patients had a GPPGA total score of 4 (severe), and most patients had a GPPGA pustulation subscore of 3 or 4 (high or very high density of pustules) [11]. The trial achieved its primary and key secondary endpoints. At week 1, the proportion of patients who had a GPPGA pustulation subscore of 0 in the spesolimab group was higher than that in the placebo group (54% versus 6%; difference, 49%; 95% CI 21–67; $P < 0.001$). The proportion of patients who had a GPPGA total score of 0 or 1 in the spesolimab group was also higher than that in the placebo group (43% versus 11%; difference, 32%; 95% CI 2–53; $P = 0.02$). Spesolimab has shown an acceptable safety profile; the common AE in patients who received spesolimab at week 1 was pyrexia [11].

Although the Effisayil 1 trial showed that patients who received spesolimab had better clearance of lesions than those in the placebo group at week 1; the disease nature and varied severity of GPP flares made it challenging to design clinical trials for GPP, including small sample sizes. Most patients in the placebo group received open-label spesolimab after week 1, as they met the prespecified threshold of disease severity, which reflected that the comparison between the two trial groups was not the conventional comparison between the treatment and the placebo group [11].

Table 1 GPPGA score

Score	Short descriptor	Detailed descriptor
0	Clear	Normal or post-inflammatory hyperpigmentation (erythema); no visible pustules; no scaling or crusting
1	Almost clear	Faint, diffuse pink or slightly red (erythema); low density and occasional small discrete pustules (non-coalescent); superficial focal scaling or crusting restricted to periphery of lesions
2	Mild	Light red (erythema); moderate-density grouped discrete small pustules (non-coalescent); predominantly fine scaling or crusting
3	Moderate	Bright red (erythema); high-density pustules with some coalescence; moderate scaling or crusting covering most or all lesions
4	Severe	Deep fiery red (erythema); very high-density pustules with pustular lakes; severe scaling or crusting covering most or all lesions

The investigator (or qualified site personnel) evaluates erythema, pustules, and scaling of all psoriatic lesions with scores from 0 to 4. Each component is graded separately, the mean score is calculated, and the final GPPGA score is determined from the composite score. The mean composite score is calculated as (erythema + pustules + scaling)/3; the GPPGA total score is 0 if the mean values of all three components are 0, or 1 if the mean values are 0 to < 1.5, or 2 if the mean values are 1.5 to < 2.5, or 3 if the mean values are 2.5 to < 3.5, or 4 if the mean values are ≥ 3.5

GPPGA, Generalized Pustular Psoriasis Physician Global Assessment

Table 2 Summary of clinical trials of biologic agents in patients with GPP

Biologic agent	Study design	Population	Endpoints	Clinical outcomes
IL-36 receptor inhibitor				
Spesolimab	Multicenter, randomized, double-blind, placebo-controlled, phase II trial Single dose 900 mg, i.v. Patients with a GPP flare received spesolimab or placebo on day 1, followed by an open-label dose/rescue therapy of spesolimab on day 8/after day 8, or both, and were followed to week 12	Patients from Europe, North America, North Africa, and Asia ($N = 53$) Mean \pm SD age (years): 43.2 \pm 12.1 in spesolimab group, 42.6 \pm 8.4 in placebo group	Primary endpoint: GPPGA pustulation subscore of 0 at week 1 Key secondary endpoint: GPPGA total score of 0 or 1 at week 1	54% (19/35) of patients in spesolimab group versus 6% (1/18) in placebo group achieved the primary endpoint 43% (15/35) of patients in spesolimab group versus 11% (2/18) in placebo group achieved the key secondary endpoint Acceptable safety profile Common AEs (week 1): pyrexia (spesolimab group versus placebo group: 6% versus 22%); dizziness (11% in the placebo group)
TNF- α inhibitor				
Adalimumab	Open-label, multicenter, single-arm, phase III, 52-week trial Dose 80 mg, s.c. Treatment at week 0, then 40 mg every 2 weeks until week 50	Japanese patients with GPP ($N = 10$) Mean \pm SD age (years): 49.8 \pm 13.3	Primary endpoint: CR (remission or improvement from baseline) at week 16 Secondary endpoints included improvements in PASI response rates and DLQI through 52 weeks	7/10 patients achieved CR at week 16, and 5 patients achieved CR at week 52 Acceptable safety profile Most common AEs (52 weeks): nasopharyngitis, pruritus, and hypoalbuminemia
IL-17/IL-17 receptor inhibitors				
Secukinumab	Open-label, multicenter, single-arm, phase III, 52-week trial Dose 150 mg, s.c. Once per week at week 0, 1, 2, 3, and 4, and then every 4 weeks until week 52	Japanese patients with GPP ($N = 12$) Mean \pm SD age (years): 56.3 \pm 15.33	Primary endpoint: improvement in CGI at week 16 Secondary endpoints included improvements in the JDA total score, JDA component scores, and PASI scores at week 52	10/12 patients achieved the primary endpoint Efficacy of secukinumab was sustained until week 52 Acceptable safety profile Most common AEs (52 weeks): nasopharyngitis, urticaria, diabetes mellitus, and arthralgia

Table 2 continued

Biologic agent	Study design	Population	Endpoints	Clinical outcomes
Brodalumab	Open-label, multicenter, single-arm, phase III, 52-week trial Dose 140 mg, s.c. Treatment at day 1, week 1, and week 2, and then every 2 weeks until week 52	Japanese patients with GPP (<i>N</i> = 12) or psoriatic erythroderma (<i>N</i> = 18) Mean ± SD age (years): 43.1 ± 16.8	Primary endpoint: CGI remission or improvement Secondary endpoints included improvements in PASI scores and the Pustular Symptom Score through 52 weeks	11/12 patients with GPP had CGI remission or improvement Favorable safety profile Most common AE (52 weeks): nasopharyngitis
Ixekizumab	Open-label, multicenter, single-arm, phase III, 52-week trial Administered at week 0 (dose 160 mg), week 2–12 (80 mg every 2 weeks), and week 16–52 (80 mg every 4 weeks), s.c.	Japanese patients with plaque psoriasis (<i>N</i> = 78), erythrodermic psoriasis (<i>N</i> = 8), and GPP (<i>N</i> = 5) Mean ± SD age (years): 48.2 ± 15.6	Key endpoints included improvements in PASI scores, sPGA, and global improvement scores	All five patients with GPP had resolved or improved symptoms Most common treatment-emergent AEs (52 weeks): nasopharyngitis, eczema, seborrheic dermatitis, urticaria, and injection site reactions
IL-23 inhibitor				
Guselkumab	Open-label, multicenter, single-arm, phase III, 52-week trial Dose 50 mg, s.c. Treatment at week 0 and 4, and then every 8 weeks until week 52	Japanese patients with GPP (<i>N</i> = 10) or erythrodermic psoriasis (<i>N</i> = 11) Mean ± SD age (years): 42.6 ± 8.97	Primary endpoint: improvement in CGI score at week 16 Secondary endpoints included improvements in PASI, JDA severity index total score, and IGA score through 52 weeks	7/9 patients achieved the primary endpoint Treatment effect of guselkumab was observed within 1 week after treatment in 50% (5/10) of patients Favorable safety profile Most common treatment-emergent AE (52 weeks): nasopharyngitis

AE adverse event, *CGI* Clinical Global Impression, *CR* clinical response, *DLQI* Dermatology Life Quality Index, *GPP* generalized pustular psoriasis, *GPPGA* Generalized Pustular Psoriasis Physician Global Assessment, *IL* interleukin, *JDA* Japanese Dermatological Association, *IGA* Investigator’s Global Assessment, *i.v.* intravenously, *PASI* Psoriasis Area and Severity Index, *s.c.* subcutaneously, *SD* standard deviation, *sPGA* Static Physician Global Assessment, *TNF-α* tumor necrosis factor-α

CLINICAL TRIALS OF OTHER BIOLOGIC AGENTS IN PATIENTS WITH GPP

TNF-α Inhibitor

Adalimumab was investigated in an open-label, multicenter, single-arm, phase III trial that enrolled ten Japanese patients with GPP.

Patients received adalimumab (80 mg) at week 0, then 40 mg every 2 weeks until week 50. The primary endpoint was CR (remission or improvement from baseline) at week 16, and secondary endpoints included improvements in the Psoriasis Area and Severity Index (PASI) response rates and DLQI through 52 weeks. Of the ten patients, seven achieved CR by week 16, and five achieved CR by week 52. Adalimumab showed an acceptable safety profile over

52 weeks; nasopharyngitis, pruritus, and hypoalbuminemia were the most common adverse events (AEs) experienced [14] (Table 2).

IL-17/IL-17 Receptor (IL-17R) Inhibitors

Secukinumab, brodalumab, and ixekizumab were each investigated in open-label, multicenter, single-arm, phase III, 52-week trials that enrolled Japanese patients with GPP. The dose and frequency of the IL-17/IL-17R inhibitors for patients receiving the biologic agents varied by trial (Table 2). In these three trials, the number of patients with GPP in the treatment arms was low with only 12, 12, and 5 patients, respectively. Primary and secondary endpoints used to evaluate the efficacy of the biologic agents in the three trials were also different. The Clinical Global Impression (CGI) of improvement at week 16 was assessed as a primary endpoint in patients treated with secukinumab; the CGI remission or improvement at week 12 and week 52 was assessed in patients treated with brodalumab; and key endpoints for patients treated with ixekizumab included improvements in the PASI, static Physician Global Assessment, and global improvement scores. All three trials reached the efficacy endpoints and demonstrated acceptable safety profiles for these IL17/IL-17R inhibitors. Nasopharyngitis, urticaria, diabetes mellitus, and arthralgia were the most common AEs in patients treated with secukinumab; nasopharyngitis was the most common AE in patients with GPP who received brodalumab; and the most common treatment-emergent AEs reported by patients with GPP who received ixekizumab were nasopharyngitis, eczema, seborrheic dermatitis, urticaria, and injection site reactions [15–17] (Table 2).

IL-23 Inhibitor

Guselkumab was studied in an open-label, multicenter, single-arm, phase III trial that enrolled ten Japanese patients with GPP. Patients received guselkumab (50 mg) at week 0 and 4, and then every 8 weeks until week 52. The improvement in CGI score at week 16 was assessed as a primary endpoint, and secondary

endpoints included improvements in PASI, Japanese Dermatological Association (JDA) severity index total score, and Investigator's Global Assessment score through 52 weeks. Of the patients, seven achieved the primary endpoint, and the treatment effect of guselkumab was observed in 50% (5/10) of patients within 1 week post treatment. Guselkumab showed a favorable safety profile, and the most common treatment-emergent AE was nasopharyngitis [18] (Table 2).

SUMMARY AND EXPERT COMMENTS

GPP is an autoinflammatory, neutrophilic disease, with a complicated pathogenesis that to date has not been fully understood [1]. Studies have shown that messenger RNA (mRNA) levels of IL-1, IL-17A, IL-36, IL-22, TNF- α , and interferon- γ were elevated in skin biopsies of patients with GPP, compared with normal skin, suggesting that multiple cytokines were involved in the inflammatory responses [7]. Among the cytokines identified, IL-36 plays a central role in GPP [7]; however, previous clinical trials mostly investigated biologic agents that target TNF- α , IL-17, and IL-23 cytokines [3].

Effisayil 1 is the first randomized, double-blind, placebo-controlled trial that enrolled the largest sample size of patients with GPP ($N = 53$) to date. Twelve countries across Europe, North America, North Africa, and Asia participated in the study; 54.7% (29/53) of the patients were Asian [11], including Chinese patients (a publication based on this Chinese subpopulation is currently under development). The study utilized clinically relevant GPP-specific endpoints to evaluate the efficacy of spesolimab, which will help establish the utility of GPPGA as a clinically meaningful assessment tool in practice. In addition, the study used PRO questionnaires to further evaluate the efficacy of spesolimab from the patient's perspective. A significantly greater proportion of patients in the spesolimab group achieved the primary and key secondary endpoints, compared with the placebo group. The clinical improvements with spesolimab were sustained over the observation

period. The treatment effects could be observed within 1 week after receiving spesolimab, indicating its rapid onset of action [11].

In comparison with the other biologic agents, spesolimab targets the IL-36 signaling pathway that plays a central role in the pathogenesis of GPP. The Effisayil 1 trial recruited patients who experienced GPP flare, while the other trials included patients with milder disease that did not necessarily present flare. In addition, the inclusion criteria for patients differed between Effisayil 1 and the other clinical trials; the diagnostic criteria of GPP in Effisayil 1 were defined by the European Rare and Severe Psoriasis Expert Network [13], whereas GPP criteria in the other trials were defined by different guidelines. For example, the diagnostic criteria of GPP were defined by the JDA in the trials with secukinumab, guselkumab, and adalimumab [14, 15, 18], while the trial with brodalumab followed criteria defined by the therapeutic guidelines for the treatment of GPP in Japan [16]. Dosing frequencies for patients with GPP receiving biologic agents in the clinical trials also differed, with patients receiving a single dose of spesolimab on day 1, followed by an open-label dose or rescue therapy in Effisayil 1 [11], while in the other trials patients received biologic agents for several weeks in a continuous manner [14–18]. Furthermore, the sample size in Effisayil 1 was the largest compared with the numbers enrolled in the other GPP trials, and Effisayil 1 included a population that was more diverse than that of the other trials [11]. The randomized, double-blind and placebo-controlled study design of Effisayil 1 provided an accurate evaluation of the efficacy and safety of spesolimab in patients with GPP.

Although the primary endpoints differed between the clinical trials described above, all achieved their primary endpoints, and improvements in several secondary endpoints in each trial were also observed. All the biologic agents showed acceptable safety profiles during the treatment periods.

EXPERT OPINIONS

Activated IL-36 pathway has been shown to cause a positive feedback loop of uncontrolled signaling that induces excessive production of numerous inflammatory cytokines, subsequently resulting in chemokine secretion and neutrophil recruitment in the epidermis [1]. The abnormal activation of neutrophils also contributes to neutrophil-filled pustule formation and GPP development [1, 19]. The IL-36–neutrophil axis plays a critical role in the autoinflammatory responses in GPP, whereas in comparison with GPP, the IL-23/IL-17 signaling pathway drives the progression of plaque psoriasis [1, 19]; GPP and plaque psoriasis are distinct in terms of their pathophysiological mechanism. Therapy targeting the IL-36 signaling pathway could be a novel and important treatment for GPP, and Effisayil 1 showed the significant clinical benefits of spesolimab in patients with GPP flare.

Studies on different biologic agents for treatment of GPP have used many different endpoints to assess disease severity, such as CGI, PASI, GPPGA, and GPPASI, which suggests that there is an unmet need for comprehensive clinical disease measures for monitoring patients with GPP in routine clinical practice. In addition, there are discrepancies in diagnostic criteria, and delayed diagnosis as well as differential diagnosis of GPP are ongoing challenges in the clinic; hence, standardized international criteria need to be developed to improve the diagnosis of GPP. In Effisayil 1, PROs, including PSS, DLQI, pain VAS, and FACIT-fatigue scale, are recommended for evaluating the treatment efficacy of biologic agents in patients with GPP.

Treatments with rapid onset of action for patients with GPP flare, as well as long-term management of GPP, remain major challenges and unmet needs for dermatologists. A randomized, double-blind, placebo-controlled, phase II trial (Effisayil 2, NCT04399837) is currently underway to investigate prevention of GPP flare in patients who have history of GPP but whose skin is clear or almost clear at study entry, which will provide more evidence on spesolimab for long-term treatment of GPP.

Currently, the completed clinical studies in GPP with other biologics have limitations, including study design (such as single-arm), small sample size, and short duration of study. Effisayil 1 is the first multinational, randomized, double-blind, placebo-controlled, phase II trial targeting the IL-36 receptor that shows promising clinical outcomes in patients with GPP flare. In addition, more randomized clinical trials and real-world studies are warranted to further investigate the efficacy of biologic agents in patients with GPP, and to explore optimized treatment strategies for patients with GPP in the future.

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