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REVIEW ARTICLE

Treatment Options and Goals for Patients with Generalized Pustular Psoriasis

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Abstract

Generalized pustular psoriasis (GPP) is a rare, severe neutrophilic skin disorder characterized by sudden widespread eruption of superficial sterile pustules with or without systemic inflammation. GPP flares can be life-threatening if untreated due to potential severe complications such as cardiovascular failure and serious infections. Currently, there are no GPP-specific therapies approved in the USA or Europe. Retinoids, cyclosporine, and methotrexate are the most commonly used non-biologic therapies for GPP. The evidence that supports the currently available treatment options is mainly based on case reports and small, open-label, single-arm studies. However, recent advances in our understanding of the pathogenic mechanisms of GPP and the identification of gene mutations linked to the disease have paved the way for the development of specific targeted therapies that selectively suppress the autoinflammatory and autoimmune mechanisms induced during GPP flares. Several biologic agents that target key cytokines involved in the activation of inflammatory pathways, such as tumor necrosis factor-α blockers and interleukin (IL)-17, IL-23, and IL-12 inhibitors, have emerged as potential treatments for GPP, with several being approved in Japan. The evidence supporting the efficacy of these agents is mainly derived from small, uncontrolled trials. A notable recent advance is the discovery of *IL36RN* mutations and the central role of IL-36 receptor ligands in the pathogenesis of GPP, which has defined key therapeutic targets for the disease. Biologic agents that target the IL-36 pathway have demonstrated promising efficacy in patients with GPP, marking the beginning of a new era of targeted therapy for GPP.

Digital Features for this article can be found at https://doi.org/10.6084/m9.figshare.16823503.

Key Points

There are no generalized pustular psoriasis (GPP)-specific therapies approved in the USA or Europe for the treatment of GPP and management of GPP flares.

The evidence supporting the use of non-biologic and biologic therapies for the treatment of patients with GPP is limited and mainly based on case studies and small, open-label, single-arm studies.

Advances in our understanding of the pathogenesis of GPP have led to the development of targeted therapies, such as interleukin-36 receptor inhibitors, which have shown promising efficacy and acceptable safety in early-phase clinical trials.

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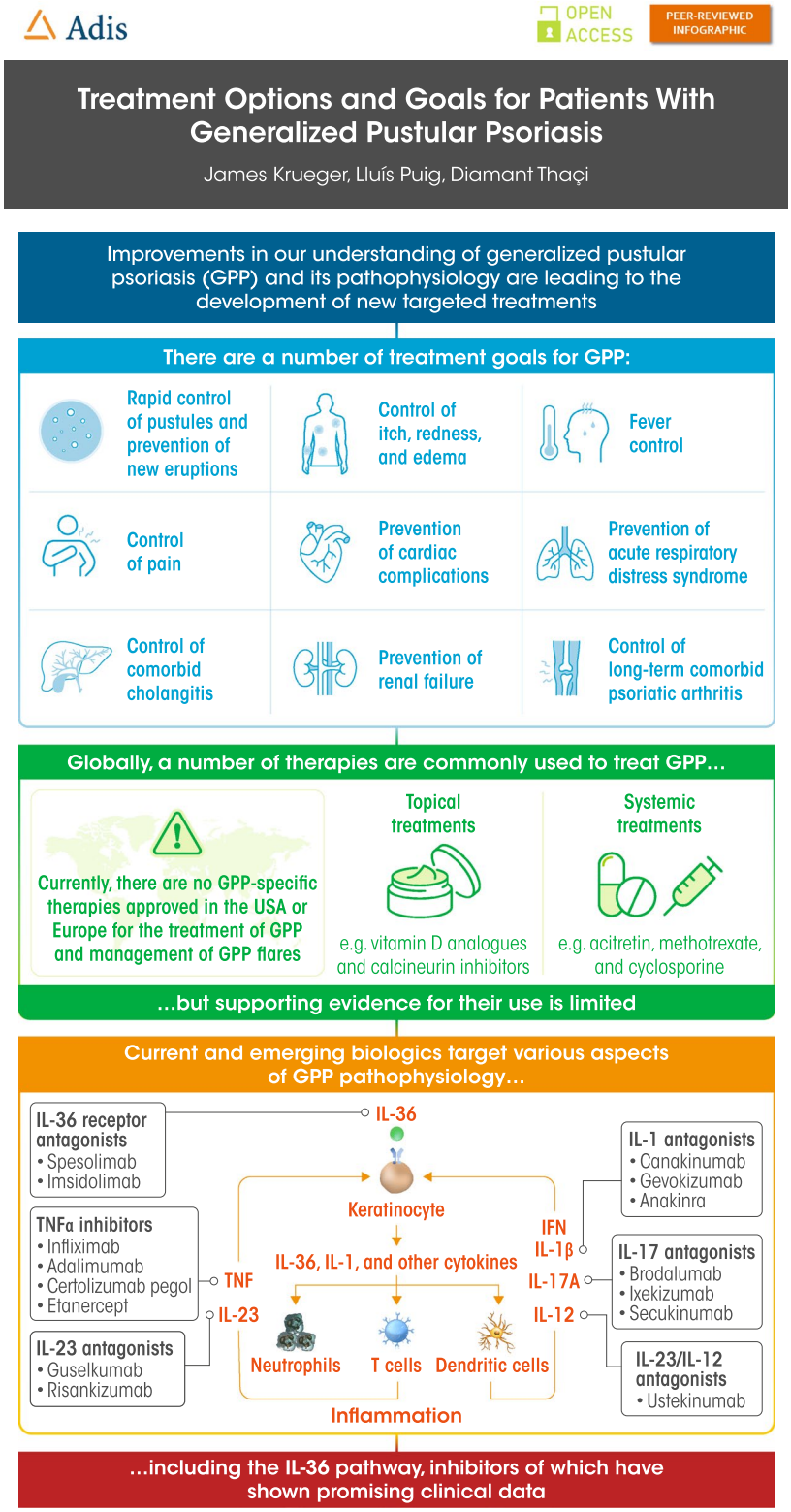
Graphical abstract



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1 Introduction

Generalized pustular psoriasis (GPP) is a rare, severe skin disease characterized by sudden widespread eruption of macroscopically visible primary sterile pustules on non-acral skin and may or may not be associated with systemic inflammation [1, 2]. Approximately 65% of patients diagnosed with GPP have a prior diagnosis of plaque psoriasis [3]. According to the European Rare and Severe Psoriasis Expert Network (ERASPEN), the clinical course of GPP can be relapsing, at least once, or persistent for more than 3 months [2]. GPP flares can be life-threatening if untreated due to potential systemic complications, such as bacterial infections [4], prerenal insufficiency [5], and cardiovascular failure [1]. GPP flares can be triggered by the use or discontinuation of corticosteroids [3, 6]. In addition, paradoxical incidence of GPP flares has been reported with the use of methotrexate, ustekinumab, and tumor necrosis factor (TNF)-α blockers [3, 7]. Upper respiratory tract infections, pregnancy, and stress have also been identified as triggers for GPP flares [4, 6, 8].

The pathogenic mechanisms of GPP flares are poorly understood. However, recent advances in our understanding of the biology and genetic mechanisms of autoinflammation and autoimmunity have led to the characterization of critical genetic mutations associated with the incidence and pathogenesis of GPP (these are discussed in greater detail in Chapter 2 [https://doi.org/10.1007/s40257-021-00655-y] of this supplement). Most notably, *IL36RN* mutations have been identified in cases of sporadic and familial GPP from around the world [9–14]. These loss-of-function mutations in the interleukin (IL)-36 receptor antagonist result in the hyperactivation of IL-36 signaling due to the unopposed stimulation of the IL-36 receptor by its ligands, IL-36α, IL36β, and IL-36γ. The increased production of IL-36 induces the production of chemokines by keratinocytes, leading to neutrophil epidermal accumulation, which drives the pathogenesis of GPP, and the formation of the characteristic spongiform pustules of Kogoj [3, 15, 16]. The proinflammatory functions of IL-36 cytokines can be further potentiated by a positive feedback loop with the IL-17/IL-23 axis. In addition, expression of IL-36γ has been found to correlate with disease activity in psoriasis and was suppressed by TNFα inhibition [17]. Accordingly, several potential therapeutic targets have been identified based on our understanding of these mechanisms. Inhibition of TNFα, IL-1, and IL-17A, which stimulate IL-36α, IL-36β, and IL-36γ synthesis in keratinocytes, may potentially disrupt inflammatory pathways in GPP (Fig. 1) [18]. Similarly, targeting the IL-23 pathway, which regulates the synthesis of IL-17, could potentially impact the IL-36 axis in patients with GPP [1]. Among these pharmacologic targets, inhibition of the IL-36 receptor is being evaluated for the treatment of GPP flares [19].

Advances in our understanding of the genetics and pathogenesis of GPP have revealed new opportunities to develop GPP-specific targeted therapeutic strategies. In this review, we highlight the currently available treatments and the emerging treatment options for GPP flares and long-term management of GPP, and provide recommendations for treatment goals.

2 Current Treatment Options for Patients with GPP

There are currently no GPP-specific treatments approved in the USA or Europe [1]. All treatments discussed herein have no prescribing label for GPP except in Japan, where several biologics are currently approved for treatment of the disease, including the TNFα-blocking agents adalimumab, infliximab, and certolizumab pegol; the IL-17/IL-17R inhibitors secukinumab, brodalumab, and ixekizumab; and the IL-23 inhibitors risankizumab and guselkumab [20–26]. Brodalumab is also approved in Taiwan and Thailand [20, 26, 27].

Current treatment options for GPP can be classified into biological and non-biological systemic agents. Based on the Japanese guidelines for the management of GPP and the Medical Board of the National Psoriasis Foundation, the most commonly used treatments for patients with GPP are retinoids, cyclosporine, and methotrexate (Table 1) [1, 20, 28–31]. However, the evidence that supports the use of current therapies for GPP is largely ill-defined and mainly based on small, open-label, single-arm studies and case reports. Care should be taken when basing treatment decisions on data from case reports to avoid the risk of overinterpreting the findings. It is also important to note the potential for publication bias, as positive treatment results are predominantly reported and may not truly reflect the number of cases of unsuccessful treatment. With no therapies approved outside of Japan, there is a lack of up-to-date and globally relevant GPP-specific treatment guidelines and goals despite the distinct pathologic and clinical features of the disease. Therefore, treatment of GPP flares and long-term management of patients with GPP remain urgent unmet medical needs.

2.1 Non-Biologic Systemic Therapies

2.1.1 Methotrexate

Methotrexate is a widely used drug for autoinflammatory and autoimmune conditions and is recommended for use in GPP according to the 2018 Japanese guidelines and the 2012 Medical Board of the National Psoriasis Foundation guidelines [20,

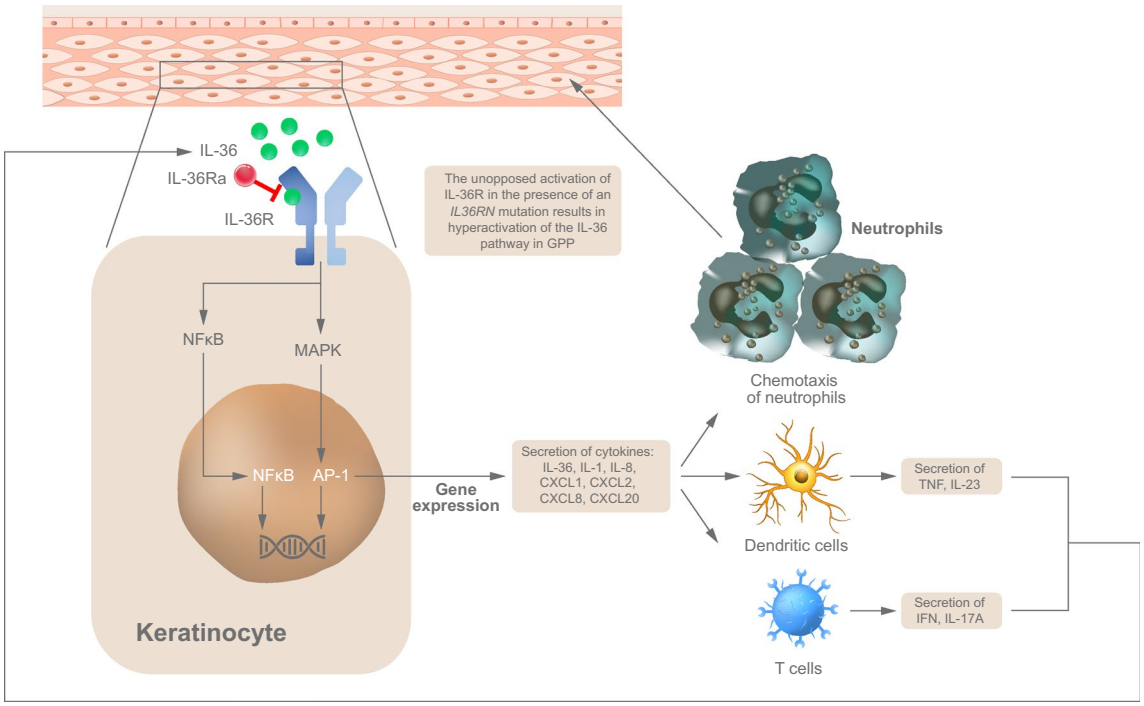

Fig. 1 Hyperactivation of IL-36 plays a central role in the pathogenesis of GPP by driving neutrophilic involvement. *GPP* generalized pustular psoriasis, *IFN* interferon, *IL* interleukin, *R* receptor, *TNF* tumor necrosis factor. Adapted from Zhou et al. [18]

28, 29]. However, there are no clinical studies that demonstrate the efficacy of methotrexate for the treatment or prevention of GPP flares. Although the mechanism of action of methotrexate for the treatment of GPP is not well defined, recent findings in psoriasis suggest that it restores the immunosuppressive function of regulatory T cells through inhibition of the mammalian target of rapamycin (mTOR) pathway [29, 32].

In patients with psoriasis, methotrexate has a slow onset of action. In a retrospective study that included 157 patients with several types of psoriasis, including 12 with GPP, methotrexate resulted in skin clearance in 31% of the enrolled patients within 3–5 months [29]. In this study, the treatment goal was to achieve adequate disease control rather than complete clearance. In a case study involving two patients with GPP, methotrexate was combined with anti-TNFα inhibitors such as infliximab and adalimumab for long-term control of GPP [33]. In this report, the Psoriasis Area and Severity Index (PASI), a disease measure established for plaque psoriasis, was used to assess treatment success in patients with GPP; however, it is worth noting that defined quantitative disease measures were not used. It is well known that methotrexate has an unacceptable safety profile in some patients, including liver toxicity that may lead to treatment discontinuation or limited use. Other adverse events associated with methotrexate include abnormal liver function, gastrointestinal symptoms, and increased risk of infection [29].

2.1.2 Calcineurin Inhibitors

Cyclosporine is commonly used to treat patients with GPP [28]. It acts as an immunosuppressive agent through the inhibition of calcineurin phosphatase signaling [30]. In a retrospective study of 102 patients with GPP, cyclosporine treatment resulted in a response in eight patients, but recurrence was common and the clinical disease measures were not defined [6]. Cyclosporine is associated with adverse events such as hypertension, nephrotoxicity, and increased risk of infection, limiting its long-term use for the maintenance treatment of GPP [6].

2.1.3 Retinoids

Retinoids are non-immunosuppressive drugs used for the treatment of psoriasis [34]; however, the evidence that supports the use of retinoids for the treatment of patients with GPP is limited. In a retrospective study that included 15 patients with pustular psoriasis, including 10 patients with GPP, acitretin resulted in a good response (defined as 60–90% clearance of skin lesions) based on prevention of new pustule formation within 3 days of treatment, and most

Table 1 Non-biologic systemic therapies for generalized pustular psoriasis

Drug	Mechanism of action	Efficacy and onset of action	General safety considerations
Methotrexate	The exact mechanism is unknown. It is proposed to suppress DNA synthesis and induce apoptosis of keratinocytes [1]	Efficacy in GPP has been demonstrated in several retrospective studies and case reports. Clearance of skin lesions could be achieved within 3–5 months [29]	Contraindicated during pregnancy [29] May cause hepatotoxicity and hematotoxicity [29]
Cyclosporine	Inhibits the production of inflammatory cytokines by T cells through inhibition of calcineurin [6, 77]	Efficacy is comparable with that of other non-biologics, based on case reports and retrospective studies [6, 30]	Pregnancy category C [1] Long-term use is associated with hypertension and renal dysfunction [6, 30]
Retinoids	Normalizes keratinization and epidermal cell proliferation and may suppress the production of proinflammatory cytokines, including TNFα, IL-1, and IL-6 [78]	The efficacy of acitretin has been demonstrated in case reports and retrospective studies. A retrospective study demonstrated that acitretin disrupted the formation of new pustules within 3 days, and skin lesion remission was observed within 5–7 days [35] In a retrospective study conducted in 1350 patients with GPP from a national Japanese registry, orally administered etretinate exhibited higher efficacy rates than cyclosporine, methotrexate, or corticosteroids; however, the efficacy measures were not defined [20]	Teratogenic; contraindicated in pregnancy [1] Long-term use may be associated with osteoarticular symptoms and adversely affect bone growth in children [1, 31]
MMF	Immunosuppressive agent that acts through inhibition of de novo purine synthesis [79]	MMF (2 g/day) improved the cutaneous status of patients within 1 week of treatment. The patients remained well, without requiring any treatment during follow-up for 4 months [25, 39]	The most commonly reported AEs associated with MMF are GI-related, including nausea, vomiting, diarrhea, abdominal cramps, constipation, soft stools, and frequent stools [79]
Hydroxyurea	Antimetabolite that is considered an effective treatment for chronic psoriasis [80]	The evidence that supports the use of hydroxyurea is limited. In a prospective, non-randomized study that included 80 patients with chronic plaque psoriasis and GPP with more than 20% body surface area involvement and psoriatic erythroderma, a good treatment response (up to 50% reduction in PASI score) was reported in 59/76 patients (77.6%) [40]	All patients showed lesional pigmentation [40]
Apremilast	Inhibits phosphodiesterase-4 in immune cells, leading to decreased levels of proinflammatory cytokines and chemokines [41]	In a case report, improvement of plaque psoriasis and GPP was noted after 2–3 weeks of treatment. Complete clearance of plaque psoriasis and GPP was noted 6 weeks after starting apremilast, with sustained remission of psoriatic plaques and pustular flares for 9 months at the time of this writing [41]	Mild-to-moderate AEs have been reported, including diarrhea, nausea, headache, and nasopharyngitis [41]

AE adverse event, *GI* gastrointestinal, *GPP* generalized pustular psoriasis, *IL* interleukin, *MMF* mycophenolate mofetil, *PASI* Psoriasis Area and Severity Index, *TNF* tumor necrosis factor

skin lesions resolved within 4–6 weeks [35]. However, it is important to note that relapse can be observed upon acitretin withdrawal [35].

All systemic retinoids are teratogenic [31] and may cause hepatotoxicity [36], mucocutaneous and skeletal toxicities, and hyperlipidemia [37]. Due to the potential toxicity of acitretin and the possibility of disease recurrence following its withdrawal, several study groups have attempted to identify reliable response biomarkers to predict benefit and recurrence following acitretin treatment. A recent study demonstrated that acitretin treatment resulted in a rise in plasma retinol and a reduction in PASI score, suggesting the potential use of plasma retinol as a biomarker of response to acitretin. Additional studies are needed to validate these findings [38].

2.1.4 Other Non-Biologic Agents

Several other non-biologic immunomodulatory agents have been used for the treatment of GPP. The evidence that supports their benefit is mainly based on case reports and non-randomized studies. Mycophenolate mofetil has demonstrated efficacy in a case study in which it improved the cutaneous status of a patient with GPP within 1 week of treatment. The patient remained in remission with no use of additional therapies for up to 4 months [39]. Hydroxyurea has also been used despite limited evidence of efficacy. In a prospective, non-randomized study that included 80 patients with chronic plaque psoriasis and GPP with > 20% body surface area involvement and psoriatic erythroderma, a good treatment response (up to 50% reduction in PASI score) was reported in 59/76 patients (77.6%) [40]. Apremilast, a phosphodiesterase-4 inhibitor approved for the treatment of moderate-to-severe plaque psoriasis, has also been used in a patient with GPP and resulted in improvement in GPP symptoms within 2–3 weeks of treatment, and complete skin clearance by Week 6, with sustained remission of psoriatic plaques and pustules for up to 9 months [41]; however, the evidence for its activity is based on a limited number of patients [42]. The positive use of colchicine for the treatment of patients with GPP has also been reported in two case studies [20, 43]; however, no clinical studies have been conducted to investigate the use of colchicine.

In certain cases, topical treatments such as calcipotriene and tacrolimus have been combined with systemic therapies to treat severe disease or used as monotherapy in patients with localized disease [28]. Topical treatments are not recommended for GPP flares; however, they have been proposed in Japanese guidelines for use as maintenance therapy after flares or as adjuvant therapy to manage psoriasis-like symptoms [20]. Alternative treatment modalities have also been used, including triamcinolone with wet body wraps and photochemotherapy using psoralen plus ultraviolet light [28]. In addition, granulocyte/monocyte adsorption apheresis has been used in Japan; however, evidence of its efficacy is mainly based on case reports [20].

2.2 Biologic Systemic Therapies

Increased understanding of the inflammatory and autoinflammatory mechanisms involved in the pathogenesis of GPP has provided the rationale for use of targeted biologics to treat GPP (Table 2) [7, 19, 21–23, 26, 33, 34, 44–61].

2.2.1 TNFα Blocking Agents

TNFα is a proinflammatory cytokine that plays a central role in the regulation and amplification of inflammatory pathways [62]. The TNFα inhibitors adalimumab, infliximab, and certolizumab pegol are currently approved in Japan for the treatment of GPP [20]. Several case reports have demonstrated the efficacy of TNFα inhibitors in the management of patients with GPP [63–65]. In a retrospective study that involved four patients experiencing GPP flares, treatment with 5 mg/kg infliximab intravenous infusion at Weeks 0, 2, and 6, followed by a monthly regimen, was effective. During the first 24 h after the infliximab infusion, the patients' condition stabilized, as evidenced by the resolution of pustules and suppression of eruption of new pustules within 24–48 h of infliximab infusion [66]. In an open-label study of infliximab that included 10 patients with GPP flares, the time to pustular clearance ranged 1–8 days [55].

Adalimumab was found to be effective and well tolerated for up to 52 weeks for the treatment of 10 Japanese patients with GPP, including those who did not respond to prior treatment with infliximab [67]. In another study that included three patients with GPP treated with adalimumab, time to remission was between 7 and 28 days [55]. Adalimumab has also shown efficacy in combination with acitretin and methotrexate in a case study of two patients [33]. In addition, case reports showed that etanercept was effective in patients with GPP [56], and a case series that included six patients with GPP showed that etanercept treatment normalized laboratory findings and markers of systemic inflammation and reduced PASI scores [68]. Paradoxically, cases of induction of pustular psoriasis flares by TNFα inhibitors have been reported; however, the mechanisms remain to be fully elucidated [7].

2.2.2 IL-17A and IL-17 Receptor Inhibitors

IL-17 is a key cytokine produced by T-helper 17 cells and plays an important role in the pathogenesis of inflammatory skin diseases. Moreover, IL-17A acts as a potent inducer of neutrophil recruitment [1]. Brodalumab, an IL-17 receptor antagonist approved in Taiwan and Thailand for

Table 2 Biologic systemic therapies for generalized pustular psoriasis

Drug	Efficacy and onset of action	General safety considerations
TNFα-blocking agents [55]		
Infliximab	Infliximab is reported to have a rapid onset of action (1–3 days) based on assessment of pustule clearance; however, the efficacy measures were not defined [30]	Increased risk of serious infections [81] Increased risk of lymphoma and other malignancies [60] May induce GPP flares [7] Immunogenicity may limit its efficacy [33]
Adalimumab	In a national, multicenter, retrospective study conducted among patients with GPP ($N = 11$) at a French university hospital, patients were treated with the TNFα inhibitors etanercept, infliximab, and adalimumab. For those treated with adalimumab, remission was achieved by two of three patients, and time to remission was 7–28 days. The efficacy of TNFα-blocking agents was based on the number of pustules and recurrence of GPP flares [55] In a study that included 10 Japanese patients with GPP, adalimumab treatment was effective and well tolerated for up to 52 weeks [67]	
Etanercept	Case studies demonstrated successful treatment of patients with GPP using etanercept [57, 59, 61, 68]	
IL-17 inhibitors [21, 22, 26]		
Brodalumab	In an open-label, multicenter, long-term, phase III study of 12 Japanese patients with GPP or erythrodermic psoriasis, brodalumab treatment was effective; by Week 12 of treatment, 83.3% of the patients were in clinical remission or experienced improvement in GPP symptoms, and by Week 52, 91.7% were in clinical remission or experienced improvement in GPP symptoms. Efficacy was defined using PASI, CGI, and Psoriasis Symptom Scale scores [26]	The most commonly reported AE was nasopharyngitis (33.3%). Five serious AEs occurred during the study; however, none were considered treatment-related [26]. Arthralgia, headache, and fatigue were the most common AEs associated with brodalumab [82]
Ixekizumab	In a phase III study that included five patients with GPP, ixekizumab treatment resulted in achievement of the study endpoints in 4/5 patients (80%). The clinical measures used were PASI, itch numeric rating scale, and Dermatology Life Quality Index [22, 53]	Ixekizumab is generally safe and effective in patients with GPP. The most frequently reported TEAEs associated with ixekizumab include nasopharyngitis, eczema, injection-site reaction, and seborrheic dermatitis [22, 53]
Secukinumab	In a phase III, multicenter, open-label trial, treatment with secukinumab resulted in improved CGI score in 83.3% of patients. Moreover, the area of erythema with pustules improved as early as Week 1 and resolved by Week 16 in most patients. The improvements were maintained throughout 52 weeks based on PASI, CGI, and JDA severity index scores [21]	Secukinumab is well tolerated with no unexpected safety signals. Nasopharyngitis, urticaria, diabetes mellitus, and arthralgia were the most frequent AEs reported [21]
IL-23 inhibitors [23]		
Guselkumab	Results from a phase III, multicenter, open-label study involving 10 patients with GPP showed guselkumab treatment resulted in rapid onset of action, with response observed within 1 week of treatment. The efficacy was assessed using CGI, PASI, and JDA severity index scores The median percentage improvement in PASI was 86.8% and the treatment success based on the JDA severity index was 100% [23]	The TEAEs reported overall were nasopharyngitis (6/21, 28.6%), gastroenteritis, nausea, arthralgia, and alopecia (2/21, 9.5% each) [23]

Table 2 (continued)

Drug	Efficacy and onset of action	General safety considerations
IL-23 and IL-12 inhibitors [50]		
Ustekinumab	In a case series of four patients with GPP, ustekinumab treatment induced sustained remission in all patients. This response was independent of *IL36RN* mutations and was consolidated by combination with low doses of the retinoid acitretin [70] In a case study of one patient, ustekinumab induced rapid resolution of symptoms within 4 weeks of treatment and the patient remained in remission for 2.5 years on a maintenance dose of ustekinumab 45 mg every 12 weeks [50]	Ustekinumab is well tolerated without any known complications or severe infections [50]
IL-1 inhibitors [45, 48, 49]		
Canakinumab	In a case report, 1-year treatment with canakinumab suppressed GPP symptoms and was well tolerated [49]	
Gevokizumab	In a case study of two patients with GPP, gevokizumab resulted in a 79% and 65% reduction in GPPASI scores at Weeks 4 and 12, respectively, with some improvements in quality-of-life instruments [48]	No notable AEs were related to gevokizumab, although one patient developed an abscess in a hematoma secondary to an injury [48]
Anakinra	In a 45-year-old patient who presented with a GPP flare following a GI tract infection that was resistant to adalimumab, treatment with anakinra suppressed the formation of new pustules by Day 9 and normalized the CRP level and leukocyte count [45]	
Future treatment options		
IL-36 receptor inhibitors [19, 51]		
Spesolimab (BI 655130)	In the phase I, proof-of-concept trial, a single, intravenous dose of 10 mg/kg spesolimab resulted in rapid (within 1 week) skin and pustule clearance that was sustained up to Week 20 [19]. In Effisayil™ 1, a 12-week, double-blind, randomized, placebo-controlled, phase II study in patients with a GPP flare, 53 patients were randomized 2:1 to receive a single 900 mg intravenous dose of spesolimab or placebo [52]. A GPPGA pustulation subscore of 0 at Week 1 was achieved by 19/35 patients (54.3%) receiving spesolimab versus 1/18 (5.6%) of those receiving placebo, and a GPPGA score of 0/1 at Week 1 was achieved by 15/35 patients (42.9%) receiving spesolimab versus 2/18 (11.1%) of those receiving placebo [52]. At Week 4, 16/35 patients (45.7%) receiving spesolimab achieved 75% improvement in GPPASI versus 2/18 (11.1%) of those receiving placebo [52]	Drug-related AEs were observed in 57.1% of patients; all AEs were mild or moderate [19]
Imsidolimab (ANB019)	Currently being developed for the treatment of GPP [44]	

AE adverse event, *CGI* Clinical Global Impression, *CRP* C-reactive protein, *JDA* Japanese Dermatological Association, *GI* gastrointestinal, *GPP* generalized pustular psoriasis, *GPPASI* Generalized Pustular Psoriasis Area and Severity Index, *GPPGA* Generalized Pustular Psoriasis Physician Global Assessment, *IL* interleukin, *PASI* Psoriasis Area and Severity Index, *TEAEs* treatment-emergent adverse events, *TNF* tumor necrosis factor

the treatment of GPP, has demonstrated efficacy in small clinical trials [26]. In an open-label, multicenter, long-term, phase III study of 12 Japanese patients with GPP or erythrodermic psoriasis, 83.3% of the patients treated with brodalumab achieved clinical remission or improved clinical status by Week 12 of treatment. By Week 52, 91.7% were in clinical remission or had improved clinical status. Similar trends were also observed in the PASI and Psoriasis Symptom Scale scores [26].

Secukinumab, a monoclonal antibody that targets IL-17A, has demonstrated efficacy in a phase III study of 12 patients with GPP in Japan. Secukinumab monotherapy and co-therapy resulted in 9/12 patients (75%) achieving a Clinical Global Impression (CGI) score of 'very much improved' at Week 12, and 7/12 patients (58.3%) achieving this at Week 52 [21]. PASI 75 was achieved by 8/12 patients (72.7%) at approximately Weeks 3–4, which reached the maximum at approximately Week 16 (10/12 patients [83.3%]) and was sustained until Week 52 [21].

Ixekizumab, an IL-17A antagonist, has demonstrated efficacy in patients with GPP in three phase III, open-label, multicenter studies, which included Japanese patients with GPP as a subset [22]. Of the five patients with GPP who were included in the study, four achieved a PASI 75 response, and two had completely clear skin by Week 12; the response was maintained for the 52-week treatment period [22]. In the 3-year long-term follow-up study, all five patients with GPP had a Global Improvement Score of resolved or improved from Week 12 onwards. In addition, all patients experienced improvement in PASI scores [69]. The mean PASI score was 12.8 at baseline and 1.8 and 1.6 at Weeks 52 and 244, respectively [69].

2.2.3 IL-23 and IL-23/IL-12 Inhibitors

Guselkumab, a monoclonal IL-23 inhibitor, was found to be effective in patients with GPP. In a phase III, multicenter, open-label study in Japan involving 10 patients with GPP, treatment success (defined as a CGI score of 'very much improved', 'much improved', or 'minimally improved') was observed with guselkumab within 1 week in five patients (50%) with GPP [23]. In this study, guselkumab 50 mg was administrated subcutaneously at Weeks 0 and 4, and every 8 weeks thereafter until Week 52. At Week 52, treatment success was achieved by all eight patients who completed the study [23].

Risankizumab, which targets the p19 subunit of IL-23, is another monoclonal antibody that is approved in Japan for the treatment of patients with GPP [56]. In addition, ustekinumab, a monoclonal antibody targeted against IL-23 and IL-12, has been reported to be effective in a case series of four patients with treatment-refractory GPP regardless of *IL36RN* mutation status [70], but no specific disease measures were mentioned.

2.2.4 IL-1β and IL-1R Inhibitors

Canakinumab, a monoclonal antibody that targets IL-1β, has shown efficacy in a patient who experienced hypersensitivity to the IL-1R antagonist anakinra. Canakinumab treatment resulted in relief of the patient's symptoms based on complete skin clearance and prevention of future recurrence of systemic symptoms [49]. In addition, absolute eosinophil count and liver tests were normalized [49]. Gevokizumab, another monoclonal antibody that blocks the activation of IL-1β receptors, has shown encouraging results in an open-label, expanded-access study in two patients with severe, recalcitrant GPP. Two patients treated with gevokizumab had a respective 79% and 65% reduction in Generalized Pustular Psoriasis Area and Severity Index scores at Week 4 and 12, with some improvements in quality-of-life instruments [48]. Anakinra is an IL-1R antagonist that has the potential to be an effective treatment for GPP. In a case report of a 45-year-old patient who presented with a GPP flare following a gastrointestinal tract infection that was resistant to adalimumab, treatment with anakinra suppressed the formation of new pustules by Day 9 and normalized the C-reactive protein level and leukocyte count [45]. Although these reports demonstrate encouraging results, large, prospective, randomized clinical trials in patients with GPP are needed to confirm the broad efficacy and safety of IL-1-targeted therapies for the treatment of GPP flares.

3 Future Treatment Options

3.1 IL-36 Pathway Inhibitors

Understanding the central role of the IL-36 pathway in the pathogenesis of GPP has paved the way for the development of novel targeted anti-IL-36 therapies for the treatment of patients with the disease. Spesolimab (BI 655130), a selective, humanized antibody against the IL-36 receptor that blocks its activation and suppresses downstream proinflammatory signaling, has demonstrated efficacy in a phase I, proof-of-concept trial. A single intravenous dose of spesolimab 10 mg/kg was associated with rapid (within 1 week) clearance of skin and pustules up to Week 20. In seven patients presenting with a GPP flare, spesolimab was associated with rapid and sustained improvements in clinical symptoms. A Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 was achieved within 1 week of treatment by five patients (71.4%) and maintained up to Week 20. Rapid improvements in the signs and symptoms of GPP

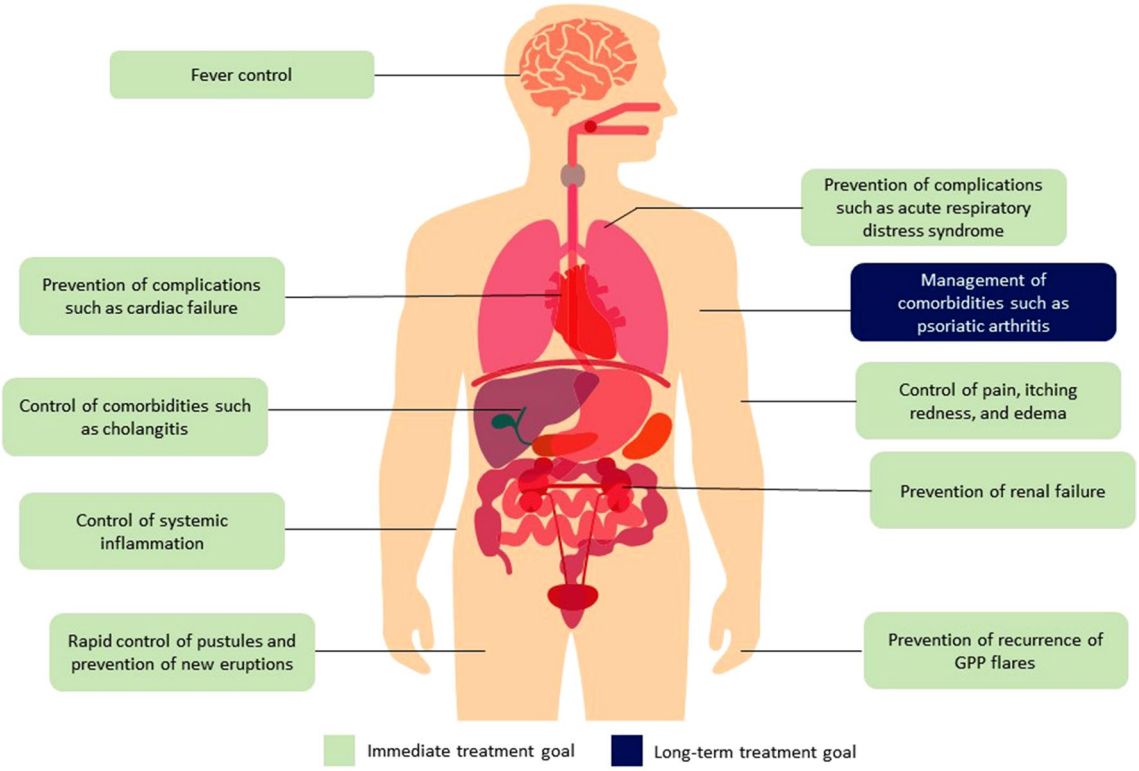

Fig. 2 Treatment goals in patients with GPP. GPP is a systemic disease with manifestations that affect several organs. Treatment goals should focus on improving skin-related symptoms and systemic inflammation. *GPP* generalized pustular psoriasis

after treatment with spesolimab were achieved according to patient-reported outcomes [19]. Spesolimab was effective regardless of *IL36RN* mutation status, which indicates that the IL-36 pathway is critical to the pathogenesis of GPP irrespective of a patient's genetic background [19].

These findings were confirmed by the results of the Effisayil™ 1 study, a 12-week, double-blind, randomized, placebo-controlled, phase II study in patients with a GPP flare. A total of 53 patients were randomized 2:1 to receive a single 900 mg intravenous dose of spesolimab or placebo [52]. A GPPGA pustulation subscore of 0 at Week 1 was achieved by 19/35 patients (54.3%) receiving spesolimab versus 1/18 (5.6%) of those receiving placebo (one-sided $p = 0.0004$) [52]. These results were sustained throughout the 12-week study. Spesolimab had a tolerable safety profile, and most adverse events were mild to moderate and comparable to those in the placebo arm [52]. Spesolimab is currently being evaluated for the prevention of GPP flares in Effisayil™ 2, a phase IIb, dose-finding study [71].

Several other anti-IL-36 therapies are currently under development. Imsidolimab (ANB019) is a monoclonal antibody targeted against the IL-36 receptor that is currently being developed for several skin indications, including GPP. Positive results of a single-arm, open-label, phase II trial of imsidolimab in eight patients with GPP were recently reported [72]. Based on these data, a phase III trial, GEMINI-1, will be conducted, in which 45 patients with GPP flares will be enrolled to receive a single dose of 750 mg intravenous imsidolimab, 300 mg intravenous imsidolimab, or placebo. The primary endpoint of this trial is the proportion of patients achieving clear or almost clear skin as determined by a GPPGA score of 0 or 1 at Week 4 [51]. Patients will subsequently be enrolled in the GEMINI-2 trial to receive monthly doses of 200 mg subcutaneous imsidolimab or placebo based on their response to treatment in the GEMINI-1 trial [51]. Similarly, A-552, a small molecule antagonist of IL-36γ, was recently identified using high-throughput screening and is being evaluated for the treatment of plaque psoriasis and potentially other inflammatory skin diseases [73].

4 Establishing Treatment Goals in GPP

Treatment goals in GPP are not well defined due to the rarity of the disease, its heterogeneous symptoms, and the lack of consistent treatment guidelines and therapeutic monitoring strategies. Clinically relevant treatment goals for GPP flares involve the cessation of pustulation and the resolution of erythema and edema. Several treatment goals can be proposed

based on the recent advances in our understanding of disease pathogenesis and the development of novel, effective biologics (Fig. 2). Proposed treatment goals can be divided into immediate and long term.

4.1 Immediate Treatment Goals

The main immediate therapeutic goals during a GPP flare are to improve skin symptoms and reduce the burden of systemic manifestations to prevent potential complications [56]. Rapid control of skin symptoms, within a week of treatment, is a feasible treatment goal based on the results of spesolimab clinical trials [19]. Short-term treatment goals should also focus on the prevention of further complications such as neutrophilic cholangitis, uveitis, acute respiratory distress syndrome, cardiovascular aseptic shock, heart failure, prerenal kidney failure, and severe infections.

4.2 Long-Term Treatment Goals

In the long-term management of GPP, treatment goals should focus on the prevention of new flares or disease worsening and the treatment of GPP comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, osteoarthritis, and cholangitis, with the ultimate goal of improving patients' quality of life [15, 74]. Specific long-term treatment goals are not well defined in clinical trials; however, the results of a recent survey of Corrona Registry dermatologists indicated that in > 80% of patients, symptoms still persist in between flares, and many treatments are not effective at preventing flares [75]. These findings highlight the need for rigorous real-world studies to further evaluate current and emerging GPP treatment options and define feasible long-term goals to improve patients' quality of life.

4.3 Other Treatment Goals

During pregnancy, GPP flares should be treated promptly to prevent any further complications that may impact the well-being of the mother and fetus [76]. In addition, treatment goals of infantile and juvenile pustular psoriasis should focus on preventing recurrences, which have been reported to occur annually [3]. Furthermore, treatment of geriatric patients with GPP may pose substantial challenges due to comorbidities and potential exposure to medications that could trigger flares.

The identification of patient-desired treatment goals is needed to improve patients' quality of life and alleviate the emotional burden caused by the psychological or physical pain associated with a GPP diagnosis (these are discussed in greater detail in Chapter 7 [https://doi.org/10.1007/s40257-021-00663-y] of this supplement).

5 Conclusions

International treatment guidelines for patients with GPP are lacking and most available treatments are used off-label based on efficacy in plaque psoriasis or limited evidence derived from case reports and small, uncontrolled, open-label, single-arm trials in GPP. Recent advances in our understanding and treatment of GPP offer several opportunities to improve patient care. Moreover, there is a lack of consensus regarding the definition of treatment success or failure and the optimal time to switch patients to an alternative treatment. With the emergence of new and effective therapeutic interventions, patient care will continue to evolve towards improving therapeutic outcomes and quality of life.

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