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REVIEW

Considerations for Treating Generalized Pustular Psoriasis (GPP): A Narrative Review

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ABSTRACT

Generalized pustular psoriasis (GPP) is a rare, chronic dermatological condition characterized by widespread pustulation that may be associated with other cutaneous and systemic manifestations. If left untreated, it may be life-threatening. Therapies developed for plaque psoriasis have been used to treat GPP with limited efficacy; however, these therapies do not target the interleukin (IL)-36 pathway, which is the most common pathway implicated in the pathogenesis of GPP. A systemic biologic targeting the IL-36 receptor for the treatment of GPP is currently the only approved treatment for GPP and allows for an opportunity to improve patient outcomes. This manuscript outlines practical considerations that aim to provide guidance on personalizing the treatment of GPP.

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Key Summary Points

Generalized pustular psoriasis (GPP) is a rare disease which may be life-threatening if left untreated.

Several factors including rarity, variation in disease severity and clinical presentations, and ineffective treatment options have complicated the management of patients with GPP.

This manuscript aims to provide guidance to optimize GPP treatment, presenting a clear overview of factors dermatologists should consider when treating patients with GPP including pharmaceutical and non-pharmaceutical options.

Continued exploration of the treatment and management of this rare disease will enhance the understanding of therapeutic options for patients with GPP and improve GPP patient outcomes/experience.

INTRODUCTION

Generalized pustular psoriasis (GPP) is a rare, chronic autoinflammatory skin disease characterized by the eruption of sterile, macroscopically visible pustules, typically 2–3 mm in diameter, which may coalesce into larger lakes of pus [1, 2]. Pustules most often develop on the trunk and limbs but may simultaneously appear on acral skin [3]. Other common cutaneous findings

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include erythema and scaling [2]. Erythema, an inflammatory response, results from dilation of cutaneous blood vessels and can affect large areas of the body. Scaling results from inflammatory responses that accelerate keratinocyte proliferation, while ruptured pustules contribute to widespread collarettes of desquamation. See the previous article in this series, "Considerations for Defining and Diagnosing Generalized Pustular Psoriasis", for details on diagnosis [4].

Patients may experience singular or recurrent episodes of GPP. Each episode significantly impacts a patient's quality of life [5, 6]. More severe eruptions may be life-threatening [5, 6]. GPP may be induced by a number of internal and external pathogenic factors including exposure to certain drugs [7], respiratory tract infections [8], and pregnancy [1], all mediated by genetic predisposition [9–12]. GPP typically affects adults 40–59 years of age, although cases have been reported in pediatric, young adult, and elderly populations [13–15]. Women may be at a greater risk of developing GPP [16].

This manuscript provides an overview of factors dermatologists should consider when treating patients with GPP. Currently available pharmaceutical options are reviewed to help optimize treatment, and non-pharmaceutical options are discussed (Fig. 1). These considerations were established using published evidence and expert opinions from Canadian dermatologists with clinical expertise in treating GPP.

METHODS

A comprehensive literature search was conducted on March 30, 2021 using the OvidSP platform to access EMBASE (1974 to March 26, 2021) and MEDLINE® (1946 to March

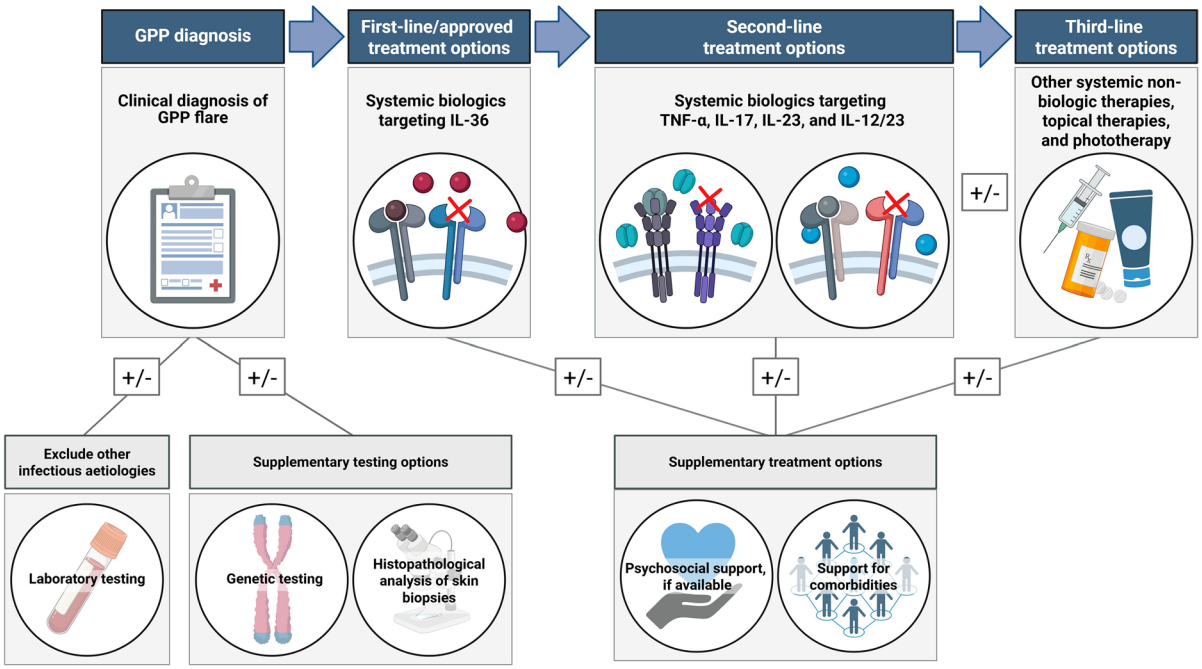

Fig. 1 Treatment guidance for generalized pustular psoriasis. After GPP is diagnosed, first-line therapy should ideally be a systemic biologic targeting interleukin (IL)-36 signalling. Second-line therapies include systemic biologics targeting cytokines other than IL-36, while third-line therapies include systemic non-biologic therapies, topical therapies, and phototherapy. Psychosocial support and support for comorbidities may not be required for each patient but should be considered. Clinicians may consider using systemic biologics that target tumour necrosis factor alpha (TNFα), IL-17 or IL-23 and/or traditional systemic non-biologic therapies, such as corticosteroids or cyclosporine in pregnant patients as IL-36R inhibitors have not been studied in this population. Created with BioRender.com. *GPP* generalized pustular psoriasis, *IL* interleukin, *TNFα* tumour necrosis factor alpha

26, 2021; including Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions®; Fig. 2). The search strategy included both controlled vocabularies, Emtree and MeSH terms, and free-text terms related to GPP, diagnosis, disease course, comorbidities, treatment approaches, systemic therapies, clinical practice guidelines, and quality of life. Boolean operators and proximity operators were used to combine concepts and enhance retrieval sensitivity. The search was limited to English-language articles. Following de-duplication and screening for relevance/full-text accessibility, 237 publications were exported for inclusion. This search strategy was repeated to expand the date of publication to December 1, 2024, and authors were given the opportunity to provide additional publications to supplement the results of these searches, yielding 79 new results. A summary package of the literature was generated by a professional medical writer with dermatology expertise and distributed to all authors for review.

The steering committee chairs (CL, VP, and KP) convened synchronously to highlight areas of particular importance. These areas of importance were expanded upon in a subsequent working group meeting with all authors to define specific topics and nuances for inclusion in the final manuscript. Publications pertaining to the definition and diagnosis of GPP were allocated to the previously published companion to this article [4], while those pertaining to the treatment of GPP were allocated to the present publication. Ethics approval was not required, as the nature of this work did not involve human or animal subjects. Where tools have been used for the creation of figures/images/tables/other material in the submission, the appropriate licenses/permissions have been obtained to allow publication in this journal and to permit

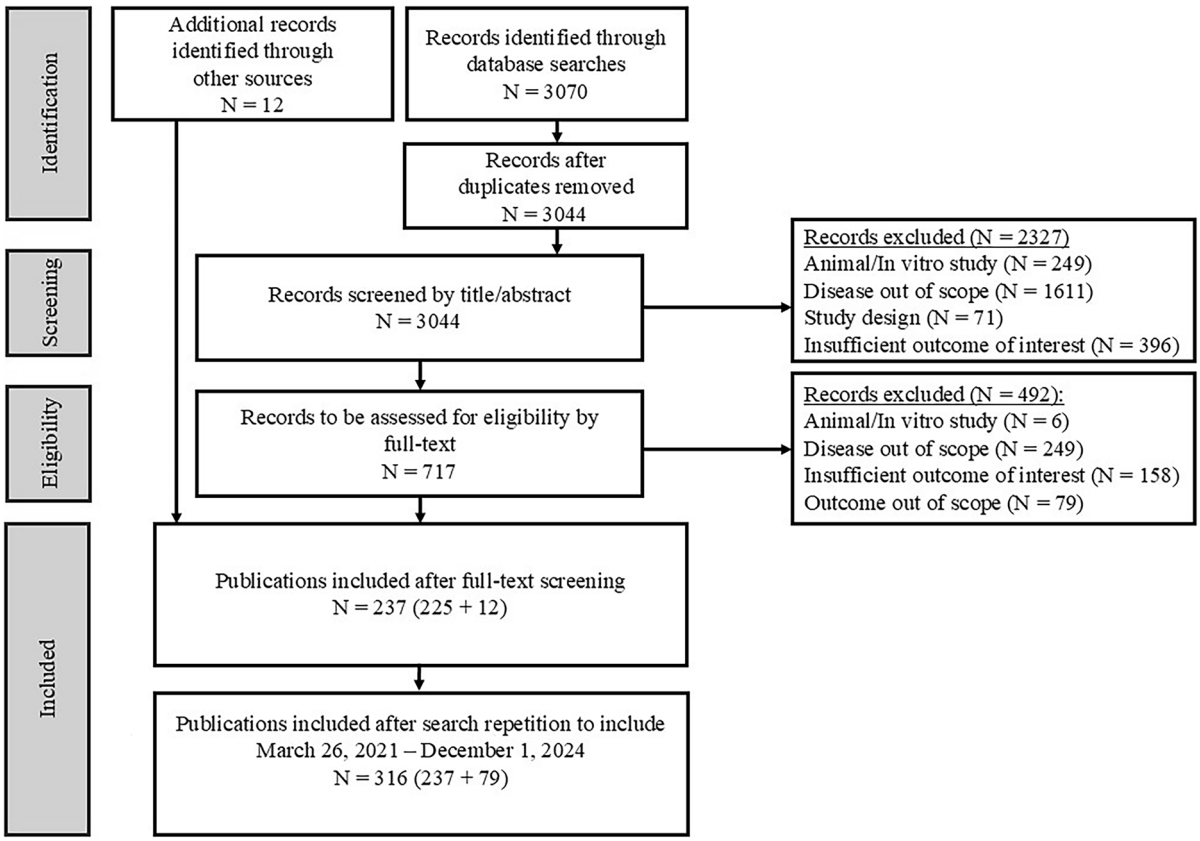

Fig. 2 PRISMA flow diagram outlining the study selection process

PHARMACEUTICAL MANAGEMENT OF GPP

There is a Lack of Strong Evidence Supporting the Efficacy of Off-Label Systemic Non-biologic Therapies in GPP Treatment

Given the rarity of GPP and the history of limited effective therapies, treatment guidelines have been slow to develop. Until recently, there was no approved GPP treatment and treating physicians would often begin with accessible systemic non-biologic therapies, such as corticosteroids (prednisone/prednisolone), cyclosporine, methotrexate, or acitretin, after which the patient may transition to a systemic biologic if disease control is not achieved [17].

A retrospective analysis of 102 adult patients with GPP determined several characteristics of the GPP population. The mean duration of follow-up after GPP diagnosis was 5 years (range 22 days to 22 years). Despite ongoing systemic therapy with plaque psoriasis treatments (corticosteroids, cyclosporine, methotrexate, and retinoids), 22% of patients experienced persistent pustules from GPP affecting 10–30% of body surface area (BSA), 50% of patients experienced persistent plaque psoriasis, and only 4% of patients were cleared [18]. Another retrospective analysis of 82 pediatric and adult patients with GPP found that 18 patients (22%) experienced residual pustules after systemic non-biologic therapy with plaque psoriasis treatments (corticosteroids, cyclosporine, methotrexate, and retinoids), with seven (9%) of these patients having no clinical response [19].

Systemic Biologic Therapies That Target the IL-36 Pathway, the Predominant Pathway Involved in the Pathogenesis of GPP, are Recommended and Considered First-Line Therapy for the Treatment of GPP

The predominant cytokine involved in the pathogenesis of GPP is interleukin (IL)-36, a neutrophil-stimulating cytokine found upstream of IL-17 and tumour necrosis factor alpha (TNFα) [11, 20, 21]. Since 2022, spesolimab, a targeted IL-36 receptor (IL-36R) inhibitor, has been approved in 53 countries for the treatment of adult patients with GPP flares [11, 22]. In 2024, the spesolimab indication was expanded to also include the treatment of GPP flares and prevention of GPP flares in adult and pediatric patients aged ≥ 12 years with weight ≥ 40 kg in Canada [23, 24], the USA [23, 25], China [25], and Europe [26].

A global Delphi consensus, with a panel composed of 30 dermatologists and three patient representatives, determined that short-term goals for GPP treatment should include pustular clearance within 7 days and prevention of new pustules within 2–3 days of treatment initiation [27], while long-term goals for GPP treatment should focus on minimizing disease severity, preventing flares, and controlling signs and symptoms between flares. The panel cautioned against discontinuing treatment prematurely [27]. In an Asia–Pacific consensus publication, 20 dermatologists with expertise in GPP collaborated and all agreed that spesolimab is the preferred treatment for severe GPP flares (BSA ≥ 10% or Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total and/or pustulation score ≥ 3 with or without systemic symptoms, or any cutaneous severity with systemic symptoms) owing to the rapid improvements in skin signs and symptoms with a single dose [28]. The Taiwanese Dermatological Association consensus publication recommends using injectable spesolimab or an oral retinoid for the first-line treatment of GPP flares and maintenance in adults [29]. An Italian consensus did not find agreement on preferred treatment for GPP flares or maintenance; however, the data was collected in 2022, prior to spesolimab approval in Europe [30].

Spesolimab acts more rapidly and effectively than previously used off-label systemic biologics, completely clearing pustules in a significant proportion of patients within 1 week [11]. Effisayil™ 1 (NCT03782792) was a multicentre, randomized, double-blinded, placebo-controlled, phase II clinical trial that evaluated a

single 900 mg intravenous (IV) dose of spesolimab or placebo in 53 adult patients with GPP flares. Results were evaluated at 1 week, after which rescue medications could be used. After the first week, 54% of patients receiving spesolimab had a pustulation sub-score of 0 on the GPPGA, compared with 6% of patients receiving placebo; in addition, 43% of spesolimab-treated patients had a GPPGA total score of 0 or 1, compared with 11% of placebo-treated group [11]. After 1 week of treatment, 38% of spesolimab-treated patients required a rescue dose of spesolimab (900 mg IV) because of persistent signs and symptoms, compared with 88% of placebo-treated patients. In addition, 13% and 24% of spesolimab- and placebo-treated patients, respectively, required standard-of-care escape treatment when they experienced worsening of disease during week 1 or were ineligible to receive spesolimab after week 1 [11].

After 12 weeks, 82% of spesolimab-treated patients had experienced an adverse event (AE), 10% of which were grade 3 or 4 in severity. The most common AE was infection, experienced by 47% of spesolimab-treated patients (17% during the first week of treatment, compared with 5.6% of placebo-treated patients), followed by pyrexia, experienced by 10% of spesolimab-treated patients at week 12. Twelve per cent of spesolimab-treated patients sustained serious AEs (6% within 1 week of treatment). There were two potential cases (4%) of a drug reaction with eosinophilia and systemic symptoms (DRESS) [11]. A subsequent review showed that the RegiSCAR DRESS scores for the two cases were assessed as "no DRESS" and "possible DRESS" [11].

Spesolimab has also been studied in flare prevention and is indicated as a prevention of flares for GPP. Effisayil™ 2 (NCT04399837) was a multicentre, randomized, placebo-controlled, phase IIb clinical trial that evaluated efficacy and safety of subcutaneous (SC) spesolimab for GPP flare prevention over 48 weeks [31]. Adult patients were assigned to one of four treatment groups: placebo ($n=21$), low-dose spesolimab ($n=31$; 300 mg SC loading dose, followed by 150 mg SC every 12 weeks), medium-dose spesolimab ($n=31$; 600 mg SC loading dose, followed by 300 mg SC every 12 weeks), or high-dose spesolimab ($n=30$; 600 mg SC loading dose, followed by 300 mg SC every 4 weeks). The estimated probability of first GPP flare was significantly reduced with spesolimab treatment compared with placebo, as demonstrated by hazard ratios (0.35, 0.47, and 0.16 in low-, medium-, and high-dose spesolimab-treated groups, respectively). After 48 weeks of treatment, 35 patients experienced GPP flares, including 22.6% ($n=7/31$), 29.7% ($n=9/31$), and 12.7% ($n=3/30$) of patients in the low-, medium-, and high-dose spesolimab-treated groups as well as 51.6% ($n=16/31$) of placebo-treated patients. In terms of safety, AEs, including infection rates, were similar between treatment groups [31].

The efficacy and safety of another IL-36R antagonist, imsidolimab, were investigated in adult patients in an open-label, single-arm, multiple-dose, phase II clinical trial (GALLOP [NCT03619902]). The dose of imsidolimab investigated was 750 mg IV on day 1, followed by 100 mg SC every 4 weeks [32]. At week 4, 75% of imsidolimab-treated patients (6 of 8 patients) were much improved ($n=2$) or very much improved ($n=4$) according to the Clinical Global Impressions (CGI) scale. At week 16, 75% of imsidolimab-treated patients were minimally improved ($n=1$), much improved ($n=1$), or very much improved ($n=4$). Improvement was seen in GPP signs and symptoms, including pustules, erythema, and dermal edema [32]. Seventy-five per cent of imsidolimab-treated patients ($n=6$) experienced at least one treatment-emergent AE (TEAE), which resulted in one patient discontinuing treatment.

Imsidolimab was further studied in two randomized, double-blind, placebo-controlled, phase III clinical trials for adult patients experiencing moderate-to-severe GPP flares (GEMINI-1 [NCT05352893] and GEMINI-2 [NCT05366855]) [33, 34]. GEMINI-1 found that 53% of patients ($n=8$) who received a single dose of 750 mg IV imsidolimab achieved a GPPGA score of 0/1 (clear or almost clear skin) at week 4, compared with 13% of placebo patients ($n=2$) [35]. Fifty-three per cent of patients who received a single dose of 300 mg IV imsidolimab ($n=8$) also achieved a GPPGA score of 0/1 at week 4. GEMINI-2 randomized the 16 responder patients from GEMINI-1 to a monthly maintenance dose

of 200 mg SC imsidolimab or placebo for at least 24 weeks, up to 92 weeks. All of the patients who received 200 mg SC imsidolimab maintenance therapy ($n=8$) maintained a GPPGA score of 0/1 compared with 25% of placebo patients ($n=2$). No maintenance therapy patients experienced a flare compared with 63% of placebo patients ($n=5$). Both studies demonstrated a favourable safety and tolerability profile; no treatment-related serious adverse events (SAEs) or SAEs leading to discontinuation were reported in imsidolimab-treated patients [35].

Imsidolimab is not yet approved for the treatment of GPP. However, the development and availability of multiple advanced targeted systemic therapies aimed at treating GPP holds promise for significantly improving the treatment and management of this challenging disease [36, 37].

Systemic Biologics That Target the Predominant Cytokines in Plaque Psoriasis Should Be Considered Second-Line Therapy for the Treatment of GPP

While a treatment that blocks IL-36 signalling is preferred, treatment should be prioritized because of the urgent nature of GPP. Therefore, in cases where direct inhibition of the IL-36 pathway is inaccessible or ineffective, second-line therapy should incorporate other systemic biologics. The levels of evidence were assessed for systemic biologics used to treat GPP [36]. Those agents that target the predominant cytokines in plaque psoriasis were found to have limited-research-based evidence or no evidence to support their use in the treatment of GPP [36].

TNFα inhibitors were approved in Canada to treat plaque psoriasis prior to 2010 [38]. These were the first systemic biologics used off-label to treat GPP and three agents in this class (adalimumab, infliximab, and certolizumab pegol) were subsequently approved in Japan for the treatment of adult patients with GPP [39]. Data from randomized controlled trials on the efficacy of TNFα inhibitors in GPP are limited [36], but one small study ($n=10$) showed clinical improvement of GPP in adult patients (Table 1); adalimumab treatment improved total GPP score, which measures erythema with pustules, total erythema, edema, and systemic/laboratory findings [40]. Clinical trial data are lacking for infliximab, but case reports and case series suggest that it may completely or partially resolve GPP in adult patients (Supplementary Table 1). In a small study ($n=7$), most adult patients treated with certolizumab pegol ($n=6$) achieved CGI responses of 'improved' or 'remission' and all had an improved Japanese Dermatological Association Severity Index of GPP (JDA-GPPSI) score, which measures erythematous area, erythematous area with pustules, and edematous area [41]. Clinical trial results (Table 1) are supported by case reports and case series that recount treatment with TNFα inhibitors (Supplementary Table 1). Given the limited direct evidence, the use of TNFα inhibitors as second-line therapy for GPP requires additional studies to support treatment decisions.

Data supporting the use of IL-17 and IL-23 inhibitors for the treatment of GPP are limited (Table 1), although case reports and case series in adults provide some insight into treatment efficacy (Supplementary Table 1). Responses to secukinumab (as monotherapy and in combination with systemic non-biologic therapy), ixekizumab, brodalumab, guselkumab, and risankizumab are encouraging, though mixed [42–51]. There is a lack of clinical trial data for ustekinumab and tildrakizumab, although case reports indicate that ustekinumab has efficacy in adult patients [52, 53]. A single case report found that bimekizumab in combination with granulocyte monocyte adsorption apheresis successfully treated GPP [54]. Further research is needed on newer-generation systemic biologics to establish a more comprehensive understanding of their role in the treatment of GPP.

Systemic Non-biologic Therapies, Topical Therapies, and Phototherapy Should Be Considered Third-Line Therapy for the Treatment of GPP

Third-line systemic non-biologic therapies used to treat GPP include corticosteroids [55], cyclosporine [56], methotrexate [57], and retinoids

Table 1 Summary of randomized controlled trials and cohort studies investigating plaque psoriasis-approved systemic biologics for the treatment of GPP

Target pathway	Treatment	Clinical trial	Treatment method	Result(s)
TNFα	Adalimumab [40]	NCT02533375; phase III, multicentre, open-label single-arm randomized control trial (adults) 52 weeks *N* = 10 Japan	SC injection: 80 mg at week 0, followed by 40 mg every other week starting at week 2; dose escalation (80 mg) was allowed for participants who did not have an adequate response by week 8	70% of patients (*n* = 7) achieved remission or improvement from baseline by week 16 JDA severity index was improved at 52 weeks (mean = 7.5 at week 0 and 1.5 at week 52)
	Certolizumab pegol [41]	NCT03051217; phase II/III, multicentre, randomized, double-blind, parallel group, placebo-controlled trial (adults) 52 weeks *N* = 7 Japan	SC injection: 400 mg (Q2W) or 200 mg (Q2W with 400 mg at weeks 0, 2, and 4) for 16 weeks; "much improved" patients continued for 52 weeks	86% of patients (*n* = 6) achieved CGI-I improved or remission 57% of patients (*n* = 4) achieved DLQI 0/1 29% of patients (*n* = 2) achieved INRS 0 86% of patients (*n* = 6) achieved reduced JDA severity index from baseline
IL-17	Secukinumab [44]	NCT01952015; phase III, multicentre, open-label randomized control trial (adults) 52 weeks *N* = 12 Japan	SC injection: 150 mg weekly for 4 weeks, then Q4W; two non-responders were dose escalated to 300 mg	83% of patients achieved CGI 'very much improved' (*n* = 9) or 'much improved' (*n* = 1) at week 16 and was sustained until week 52
	Ixekizumab [45–47]	NCT01624233; phase IV, multicentre, open-label randomized control trial (adults) 52 weeks *N* = 5 Japan	SC injection: 160 mg at baseline, 80 mg from weeks 2–12 (Q2W), and 80 mg from weeks 16 to 52 (Q4W)	100% of patients resolved (*n* = 2) or improved (*n* = 3) by week 52, measured using global improvement scores Average DLQI score was improved by 5.8 points from baseline

Table 1 continued

Target pathway	Treatment	Clinical trial	Treatment method	Result(s)
		Cohort study (adults) Average treatment length = 10.1 ± 4.2 months *N* = 10 Japan	SC injection: 80 mg Q4W	At week 12, 100% of patients (*n* = 9) achieved PASI 75, 67% of patients (*n* = 6) achieved PASI 90, and 22% of patients (*n* = 2) achieved PASI 100
		NCT03942042; cohort study (adults) 12–20 weeks *N* = 7 Japan	SC injection: 160 mg at baseline, 80 mg Q2W until week 12	86% of patients resolved (*n* = 4) or improved (*n* = 2) by week 12, measured using global improvement scores Average DLQI score was improved by 5.0 points from baseline (at week 12)
	Brodalumab [48]	NCT01782937; phase III, open-label, multicentre, long-term randomized control trial (adults) 52 weeks *N* = 12 Japan	SC injection: 140 mg at weeks 0, 1, and 2, then Q2W until week 52	83% of patients achieved CGI 'improved' (*n* = 7) or 'remission' (*n* = 3) at week 12 92% of patients achieved CGI 'improved' (*n* = 4) or 'remission' (*n* = 7) at week 52 92% of patients (*n* = 11) had a pustular symptom score of 0/1 at week 52

Table 1 continued

Target pathway	Treatment	Clinical trial	Treatment method	Result(s)
IL-23	Guselkumab [49]	NCT02343744 Phase III, multicentre, open-label study (adults) 52 weeks *N* = 10 Japan	SC injection: 50 mg at baseline and week 4; participants then received 50 or 100 mg (depending on response) Q8W until week 52	79% of patients achieved CGI score 'very much improved' (*n* = 2), 'much improved' (*n* = 2) or 'minimally improved' (*n* = 3) at week 16 Response was maintained in all patients who completed the trial (*n* = 8; week 52) Average JDA score was reduced by 3 points at 52 weeks 75% of patients (*n* = 6) reduced DLQI score by ≥ 5 points at 52 weeks
	Risankizumab [50]	NCT03022045 Phase III, randomized, open-label study (adults) 180 weeks *N* = 8 Japan	SC injection: 75 or 150 mg at baseline and week 4, then Q12W until week 160	100% of patients achieved clinical response at week 16 (*n* = 8) 75% of patients achieved DLQI 0/1 at week 16 (*n* = 6) 100% of patients who completed the study (*n* = 3) sustained clinical response at week 160

The JDA severity index examines skin score (erythema [with and without pustules] and edema) and laboratory test score. CGI and CGI-I are seven-point scales assessing the improvement or worsening of a patient's illness, relative to baseline at the start of intervention. The DLQI measures the impact of skin disease on patient quality of life using a 10-question questionnaire. The INRS asks patients to rate the intensity of their itch using a numeric scale

CGI Clinical Global Impression, *CGI-I* Clinical Global Impression Improvement, *DLQI* Dermatology Life Quality Index, *GPP* generalized pustular psoriasis, *IL* interleukin, *INRS* Itch Numeric Rating Scale, *JDA* Japanese Dermatological Association, *PASI* Psoriasis Area and Severity Index, *SC* subcutaneous, *TNFα* tumour necrosis factor alpha

[58]. These agents have limited efficacy against GPP, are associated with frequent relapses, and may cause significant adverse events (AEs), as systemic corticosteroids have been shown to precipitate GPP episodes [18, 57, 59–61]. Clinical trial data for the treatment of GPP with these medications are lacking. The levels of evidence for systemic non-biologic therapies were analysed [36]. Retinoids were found to have moderate evidence or limited research-based evidence [36]. Hydroxyurea demonstrated limited research-based evidence [36]. There is no evidence to support the use of other systemic non-biologic therapies, including corticosteroids, cyclosporine, methotrexate, fumarates, and phosphodiesterase 4 (PDE4) inhibitors for the treatment of GPP [36]. Although these agents have known limitations, they remain in use, particularly in regions where access to new targeted therapies is limited as a result of their relative affordability and familiarity of use.

While topical corticosteroids are often used in combination with other therapies to treat GPP, a recently published review recommended they not be used [17]. In contrast, Japanese guidelines on the management of GPP suggest that topical corticosteroids may be considered in some cases for maintenance or adjunctive therapy [39]. While their use may relieve inflammatory signs and symptoms, such as pruritus and pain, the patient usually requires additional treatment to resolve the GPP flare. Further, if the disease is extensive, any topical therapy, including corticosteroids, calcineurin inhibitors, and vitamin D_3 analogues, will be insufficient to resolve the signs and symptoms [62].

Despite a lack of evidence indicating efficacy for topical therapies, they are considered safe when used in combination with systemic therapies. Patients with GPP may have a history of plaque psoriasis and may be on an advanced systemic therapy to control that condition when experiencing a GPP flare, which should be considered when determining treatment options [62, 63].

In cases where monotherapy using plaque psoriasis therapies is not sufficiently effective, treatment can be optimized through modifications of the dose and/or interval of the current systemic therapy. Combination therapy has been used in both pediatric and adult patients with GPP [42, 43].

Frequency of Monitoring for Patients Experiencing a GPP Flare Depends on Disease Severity and Treatment

Patient follow-up is recommended to monitor GPP. As with most other aspects of GPP, patient monitoring varies according to several factors (Fig. 3), including level of disease control and frequency of flares. Hospitalized patients with GPP are monitored daily as mortality rates are highest during the acute phase of the disease [18]. During GPP flares, physicians should consider performing laboratory investigations and physical examination assessments because of the systemic manifestations of the disease, which can include organ dysfunction and treatment-related AEs such as infections [11, 32, 39]. Once the disease is controlled, monitoring and testing frequency can be reduced.

The unpredictability of GPP episodes between and within patients requires the treatment setting to be individualized for each episode. Some patients will require hospitalization, while others may be appropriately managed as outpatients, depending on their stability and disease severity [55, 64, 65]. Healthcare systems differ in resource availability, which affects the types of treatment that are accessible for each patient. Patients who are unable to access effective therapies may be more likely to require hospitalization or prolonged hospitalization as well as other disease-related complications due to deteriorating disease state [66].

NON-PHARMACEUTICAL MANAGEMENT OF GPP

Current Patient-Reported Outcome (PRO) Assessments are Not Sufficient to Influence Treatment Choice for a Patient with GPP

There is no PRO assessment developed specifically for GPP. A validated PRO developed for plaque

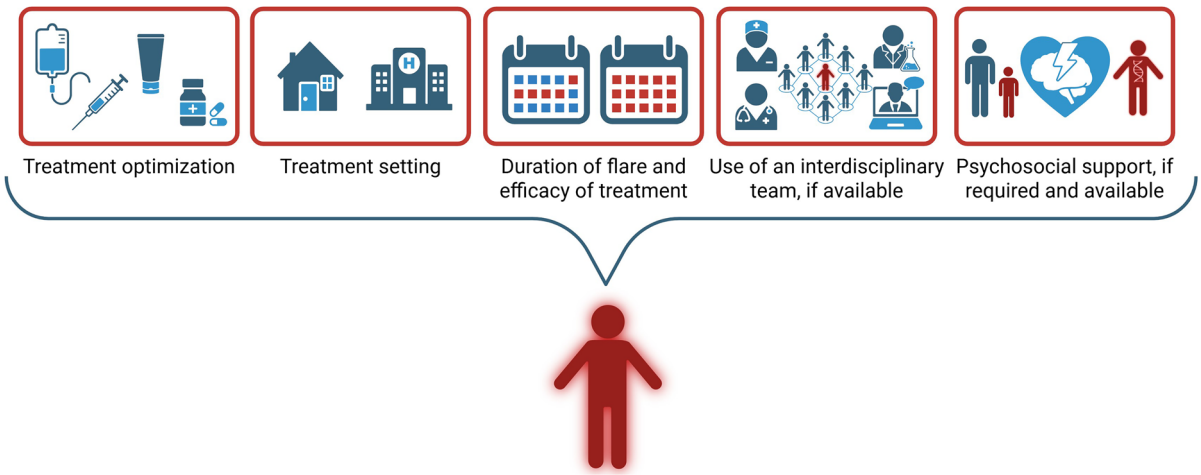

Fig. 3 Overall treatment considerations for generalized pustular psoriasis. Treatment of generalized pustular psoriasis should be individualized for each patient. Treatment optimization and setting may depend on disease severity, signs, and symptoms, as well as available medications. Flare duration and treatment efficacy will vary by patient. The use of an interdisciplinary team may depend on resource availability, as well as the need for specialists as a result of comorbidities experienced by the patient. Created with BioRender.com

psoriasis, the Psoriasis Symptom Scale (PSS), has been used in GPP clinical trials [6], but without a GPP-specific PRO assessment, it is not recommended that these are considered when choosing treatment. In interviews, seven patients with GPP provided positive feedback on the PSS, which asks about plaque psoriasis-specific signs and symptoms, including pain, burning, itch, and redness, but not pustules [6]. Development of a GPP-specific PRO that includes questions about pustules would be valuable.

Patient Education on Disease Management and Flare Triggers is Recommended to Help Prevent or Delay GPP Flares

Patients with GPP should be educated on disease management and flare triggers to help prevent or delay future flares, especially during the first acute episode. Many triggers are unknown and may be unavoidable, such as upper respiratory tract infection [8] and pregnancy [1]. Patients may find tracking their flares helpful in detecting patterns, and after experiencing several flares, some patients may be able to estimate when their next episode will occur. It is crucial that patients understand the importance of contacting their dermatologist as soon as they develop any signs or symptoms of a flare. Patients should also be encouraged to contact their dermatologist if they develop other skin conditions that may require additional treatment, such as a secondary cutaneous infection [67].

It is Recommended That Patients with GPP are Educated on Genetics and Heritability to Better Understand Their Condition and Its Potential Familial Implications

Some patients may be interested in education around the genetics and heritability of GPP. In these instances, connecting the patient with a genetic counsellor is recommended. Individuals with GPP who have or hope to have children may find it beneficial to learn what is known about the heritability of GPP. Close relatives may also be encouraged to be tested for genetic mutations if they know that they may be predisposed to this disease. It should be emphasized to these patients that genetic testing may not reveal a genetic mutation, even in an individual who has developed or will develop GPP [11]. Loss-of-function mutations in *IL-36RN* and other

known associated genes are not required for the development of GPP. The Effisayil™ 1 clinical trial tested participants for genetic mutations in *IL-36RN*, *CARD14*, and *AP1S3* and found that a minority of participants exhibited known genetic mutations (*IL-36RN*, 13%; *CARD14*, 9%; *AP1S3*, 2%), although many countries were not represented in this clinical trial. Importantly, patients responded to spesolimab treatment irrespective of whether they were found to have a genetic mutation [11].

Evidence suggests that genetic predispositions may be associated with distinct aetiologies of GPP. The *IL-36RN* loss-of-function mutation is associated with more severe outbreaks than average from an earlier age and cases typically present without concomitant plaque psoriasis [68–70]. The *CARD14* gene helps to regulate the NF-κB pathway, which increases expression of proinflammatory molecules (e.g. TNFα, IL-1, IL-6, and IL-8), and plays a role in keratinocyte differentiation and proliferation [71]. *CARD14* gain-of-function mutations are more prevalent in cases with concomitant plaque psoriasis [72, 73]. Mutations to the *AP1S3* gene affect autophagy-mediated inflammatory cytokine production, with upregulation of TNFα, IL-1, and IL-36α [10, 74]. *AP1S3* loss-of-function mutations do not appear to affect age of onset or plaque psoriasis concurrence; however, there is a non-significant trend for patients with *AP1S3* gene mutations to be female, suggesting a possible influence of sex-specific factors [16].

Additional genes associated with the development and progression of GPP include myeloperoxidase (*MPO*) and serine protease inhibitor A3 (*SERPINA3*). *MPO* mutations upregulate the accumulation and activity of neutrophils, which increase activation of the IL-36 cytokine pathway [74]. *SERPINA3* mutations prevent the inhibition of various proteases, including the enzyme that activates IL-36β precursors [75]. Other members of the *SERPIN* family are also implicated in the development of GPP [76, 77]. While it may be beneficial for a patient to understand the potential distinct manifestations of GPP associated with their genetic mutation, it should be emphasized that GPP has a multifactorial disease course, of which genetic mutations are only one influencing factor, and treatment choice is unlikely to be altered.

Patients May Experience Physical and Psychosocial Comorbidities Associated with GPP and May Require Support From Non-dermatology Specialties

Considering the array of physical and psychosocial comorbidities associated with GPP, involvement of an interdisciplinary team is recommended, although the availability of specialists will depend on local resources. Most patients with GPP develop psychosocial issues, and it is likely that they will benefit from psychosocial support and should be offered this resource, if available [5].

Factors playing a role in the psychosocial wellbeing of patients with GPP include admission to the hospital, especially the intensive care unit (ICU), which may lead to post-traumatic stress disorder (PTSD). Irrespective of disease, patients admitted to the ICU exhibited moderate-to-severe symptoms of anxiety (38%), depression (32%), and/or PTSD (18%) up to 1 year after discharge [78]. A high proportion of patients with GPP experience feelings of fear/anxiety (67%) and depression/hopelessness (59%) [5], despite relatively low ICU admission numbers (4% and 6.1% of GPP-related hospitalizations resulted in ICU admission in the USA and Spain, respectively) [79, 80]. These data suggest that the psychosocial effects exhibited by patients with GPP likely arise as a result of disease state, and are exacerbated by more severe disease and resultant hospitalization [5, 6].

Patients who may particularly benefit from psychological support include those who have experienced or are experiencing juvenile-onset GPP [81], parents or caregivers of pediatric patients with GPP [82], and patients with GPP who tested positive for genetic mutations. Evidence has demonstrated a negative psychological impact caused by genetic testing for other severe diseases due to perception of risk and beliefs about disease controllability [83]. However, this negative effect may be blunted by the availability of an effective treatment for GPP [11, 32, 83].

Ideally, patients should be connected with a mental health professional and/or support groups for patients with rare diseases. Patient advocacy groups, such as the International Psoriasis Council and the International Federation of Psoriasis Associations, can share international and local resources [84]. Websites, discussion forums, and support groups can provide patients and caregivers with knowledge and support, as well as a sense of empowerment, as they take an active role in their disease.

CONCLUSION

Several factors, including rarity of the disease, varying disease severities and clinical presentations, and ineffective treatments have led to challenges in managing patients with GPP. Novel treatments targeting IL-36 are effective at preventing and resolving GPP flares in a timely manner. Individualized treatment, taking patient input into account, is recommended because of the multifactorial pathogenesis of GPP. The treatment considerations described in this manuscript aim to provide guidance to optimize treatment of GPP and improve the patient experience.

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