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COMMENTARY

Commentary: Unmet Needs in Generalized Pustular Psoriasis in Clinical Practice

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Key Summary Points

Generalized pustular psoriasis (GPP) is a rare, severe skin condition with recurrent pustules and unpredictable flares, causing discomfort and potentially life-threatening complications.

Compared to patients with plaque psoriasis, patients with GPP have a higher burden of illness and suffer from increased psychological distress.

Unmet needs in GPP management include limited awareness, misdiagnosis, and the lack of guidelines for treatment selection.

Raising awareness, educating patients, and streamlining the patient journey can optimize GPP management.

Introduction of novel therapies, like spesolimab, offers hope for effective treatment, potentially reducing mortality and hospitalization.

INTRODUCTION

Generalized pustular psoriasis (GPP) is a rare and chronic inflammatory skin disease characterized by recurrent flares of pustulation with or without systemic inflammation that can be life-threatening if not appropriately treated [1–4]. GPP predominantly affects female individuals and can manifest at any age, including during childhood as juvenile GPP. Nevertheless, the majority of cases are observed in individuals during their fifth decade of life [5].

GPP may be associated with preexisting plaque psoriasis but can also develop independently, and is now recognized as a genetically, histologically, and clinically distinct entity from plaque psoriasis with a different pathophysiological mechanism [6].

GPP carries a significant burden both in terms of clinical impact and patient-reported experiences, making it a recognized difficult-to-treat condition. Currently, a consensus guideline for GPP management is lacking. GPP treatment is typically based on the use of immunosuppressants, such as cyclosporine and methotrexate, immunomodulators, systemic corticosteroids, and retinoids. Further investigated treatments include tumor necrosis factor (TNF) inhibitors (adalimumab, infliximab, and etanercept) and other biologics, although these are based on very weak evidence such as case reports and small, open-label, single-arm studies [2, 7–11].

In dermatological practice, the treatment strategy for GPP often follows a similar approach to that used for more severe cases of plaque psoriasis. However, GPP is a genetically and phenotypically distinct condition from plaque psoriasis, highlighting a potential unmet need for this specific patient population, as GPP requires tailored treatment strategies that address its unique characteristics. Indeed, while the adaptive immune system and the interleukin (IL)-23/IL-17 axis play a central pathogenic role in plaque psoriasis, GPP appears to be driven by an inflammatory response resulting from hyperactivation of innate immunity, with predominant participation of the IL-36 axis [12].

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 [12, 13].

We reviewed the available clinical evidence and guidelines related to GPP treatment, aiming to discuss the challenges faced in the management of patients with GPP and the identification of unmet educational needs.

CLINICAL MANIFESTATIONS AND BURDEN OF DISEASE

GPP is an unpredictable disease with a highly variable course and is currently considered a phenotypically and genetically separate disease entity to plaque psoriasis. A key characteristic of GPP is the recurrence of the acute phase of generalized sterile pustule formation, widespread inflammation, and erythema, with

partial or complete remission between episodes [1–4].

In the acute setting, patients with GPP complain of burning sensation in skin associated with some pain, usually without any triggering factor, and consequently with a severe impact on their quality of life [14].

GPP flares may be associated with systemic inflammation and symptoms such as fever, joint pain, risk of sepsis, general distress, fatigue, and in some cases an electrolyte imbalance, cholangitis, and leukocytosis. GPP flares vary in frequency, severity, and length between patients and between flares in the same patient and may occur de novo or be triggered by external factors, including stress, infections, and withdrawal medication [15].

GPP flares can be life-threatening if untreated because of potential severe complications, including sepsis, acute renal failure, congestive heart failure, and acute respiratory distress syndrome, and comorbidities include metabolic, cardiac, and neurologic disorders. Mortality data from studies of patients with GPP are limited, but the reported mortality rates range from 2% to 16% [2, 4, 15–23].

Real-world evidence from a large claims-based dataset showed that GPP has a high burden of illness that differs from patients with plaque psoriasis. Given the higher occurrence of comorbidities in patients with GPP, it is not surprising that these patients have an increased medication burden compared with those with plaque psoriasis [14].

Notably, the greater prevalence of anxiety and depression in patients with GPP indicates that they experienced a greater emotional burden compared with patient with plaque psoriasis. Therefore, patients with GPP may require a multidisciplinary strategy to manage both the psychological and physical manifestations of the disease [14].

The increased utilization of opioid pain medication in the GPP cohort (almost twice that of the plaque psoriasis cohort) suggests a more likely experience of severe pain in patients with GPP than those with plaque psoriasis. One explanation for the increased use of opioids in patients with GPP could be the presence of systemic symptoms, which can cause significant pain and/or inflammation-induced joint pain [14].

A real-world retrospective cohort study analyzing evidence from the Japanese Medical Data Center database compared demographics, comorbidities, and medication use between patients with GPP and plaque psoriasis, demonstrating a higher disease burden in patients with GPP, including the presence of comorbidities and healthcare resource utilization, compared with those affected by plaque psoriasis [24].

The prognosis of GPP in older patients may be poorer than in younger patients as a result of the systemic complications of the disease [2, 4].

OVERVIEW OF CURRENT THERAPIES IN GPP

Patients affected by GPP may have a variable number of flares per year, which commonly last 2–5 weeks but they may persist longer than 3 months; and approximately 50% may require hospitalization.

During the acute phase of a GPP flare, the treatments goals consist of improving skin symptoms and reducing the burden of systemic manifestations to prevent potential complications: rapid control of pustules and prevention of new eruptions; control of pain, fever, concomitant cholangitis, concomitant psoriatic arthritis, itch, redness, and edema; prevention of cardiac complications, failure, and acute respiratory distress syndrome.

Current guidelines for GPP management are lacking. Non-biologic systemic therapies, including corticosteroids, acitretin, cyclosporine, and methotrexate have been typically used as first-line treatments for patients with GPP although evidence supporting this therapeutic strategy is limited. Other non-biologic agents that have been used for the treatment of GPP include mycophenolate mofetil, hydroxyurea, apremilast, and colchicine. Given the acute life-threatening features of GPP flares, cyclosporine sometimes is preferred owing to its rapid onset of action [4, 25, 26]. Some biologic agents that target key cytokines involved in the activation of inflammatory pathways have been used as

treatments for GPP (Table 1). In Japan and other Asian countries, several biologics are approved for treatment of the disease, including TNF inhibitors (infliximab, adalimumab, and certolizumab pegol), IL-17/IL-17R inhibitors (secukinumab, brodalumab, bimekizumab, and ixekizumab), and IL-23 inhibitors (risankizumab and guselkumab) [4, 18]. However the utilization of various non-specific treatments for GPP usually results in partial control of the disease.

Recently, spesolimab, an IL-36R antagonist, has been approved in the USA, Japan, and Europe for the treatment of GPP flares in adults. The IL-36 pathway has recently emerged as a central axis driving the pathogenic inflammatory mechanisms of GPP. Biologic agents that inhibit the IL-36 pathway have shown efficacy and a favorable safety profile in patients with GPP and thus represent novel potential therapeutic options for this patient population [12, 27–32].

In addition, double-blind, placebo-controlled, global multicenter phase III trials are currently evaluating imsidolimab, an anti-IL-36R monoclonal antibody, as a promising approach to GPP treatment.

METHODOLOGY

A panel of nine Italian GPP experts attended a meeting in Milan in November 2022. The main methodological aspects were as follows: (1) a professional facilitator presented the main literature on GPP therapies and management to the experts as a trigger to encourage discussion; (2) the experts commented on the evidence reported in the literature and provided their opinion on current unmet needs in GPP. They examined the diagnostic and assessment challenges related to GPP flares and evaluated the adequacy of treatment options currently considered for GPP management.

No formal techniques for discussion and/or for achieving a consensus agreement were adopted. A preliminary outline of this manuscript was critically revised by two panelists, appointed at the meeting. All other panelists reviewed the outline, which was then developed into the current manuscript with the contribution of all participants.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EXPERT OPINION

Unmet Needs in the Management of GPP

Limited GPP awareness, due to the rarity of this disease and, consequently, to a limited number of studies on GPP compared with those on plaque psoriasis, combined with inaccurate diagnosis and similarity to other variants of psoriasis, has classically complicated the patient journey in GPP.

Differentiation of GPP from other similar diseases is crucial. As a result of its rarity, many healthcare professionals have a lack of experience and knowledge of GPP. GPP is often misdiagnosed as an infection or other skin disorders, delaying specialist referral. GPP can be life-threatening without prompt and adequate treatment.

A further unmet need in GPP concerns the lack of patient awareness, though more awareness can be observed in patients with a history of plaque psoriasis preceding the GPP who are aware of the clinical features and course of psoriatic conditions. In contrast, in other individuals GPP occurs as the sole phenotype without manifestations of plaque psoriasis at any time. These patients must be supported in understanding their disease.

Fortunately, not all cases of GPP necessitate a visit to the emergency department or hospitalization due to systemic complications. Indeed, there are also more mild cases and/or more localized forms of pustular psoriasis.

In daily clinical practice, managing patients with a severe form of GPP can be challenging, particularly when they present with painful pustules but without severe overall symptoms. These patients often experience intense pain, even in areas without visible pustules, due to dysesthesia or heightened sensitivity of the skin. This significant pain has a notable impact

Table 1 Biologic systemic therapies for generalized pustular psoriasis

Drug class	Drug
TNFα-blocking agents	Infliximab
	Adalimumab
	Etanercept
IL-17 inhibitors	Brodalumab
	Ixekizumab
	Secukinumab
	Bimekizumab
IL-23 inhibitors	Guselkumab
IL-23 and IL-12 inhibitors	Ustekinumab
IL-1 inhibitors	Canakinumab
	Gevokizumab
	Anakinra
IL-36 receptor inhibitors	Spesolimab
	Imsidolimab

on the quality of life for patients with GPP and is typically not observed in cases of plaque psoriasis. Pruritus, burning, pain, and other dysesthetic symptoms are frequently reported. Depression, anxiety, anger, and feelings of futility and helplessness are commonly reported by patients with GPP. They are often sad and anxious about the way their skin looks, feels, and behaves.

The lack of guidelines to support GPP treatment selection is a crucial unmet need in optimizing disease management. Until now, the treatment of flares has been quite heterogeneous due to the lack of specific treatments for GPP.

Historically, in clinical practice, the management of GPP has been based largely on strategies optimized for managing plaque psoriasis, despite limited evidence demonstrating their efficacy in pustular psoriasis.

A relevant critical aspect in GPP management is related to frequent switching to a new treatment due to the repeated failures. This therapeutic approach has a negative impact on the clinician and patient but also on the care system in terms of costs.

In the case of a patient with an acute flare of GPP seeking medical care in the emergency department, treatment typically involves initiating a systemic corticosteroid agent. In patients with GPP and several acute episodes, clinicians often use cyclosporine or acitretin as first-line agent; in case of inefficacy, switching to a biological agent is performed.

A patient with an acute flare of GPP is closely monitored. The switch to the biological agent is made if the patient has not responded or in case of poor tolerability or side effects to acitretin or cyclosporine therapy and to prevent a subsequent flare. In other words, the treatments, used before a specific therapy for GPP was available, allowed only a partial and non-lasting remission of the disease, characterized by the persistence of symptoms.

Overall Considerations to Improve the Patient Journey in GPP

Improved recognition and understanding of GPP is essential and current gaps existing in different aspects of medical education should be filled to optimize the management of patients with GPP.

While it shares some signs and symptoms with other forms of psoriasis, GPP is a separate condition and requires an accurate diagnosis, which should lead to distinct management approaches. Timely GPP diagnosis is critical to ensure prompt and appropriate treatment.

There are several common laboratory anomalies that may differentiate GPP from plaque psoriasis, including leukocytosis with neutrophilia and elevated erythrocyte sedimentation rate or C-reactive protein, as well as increased alkaline phosphatase, transaminase, and bilirubin levels.

Unlike plaque psoriasis, monitoring the progression of GPP involves not only clinical assessments but also the measurement of systemic inflammation markers and skin biopsies. Therefore, it is crucial to incorporate an understanding of the disease's pathology in terms of

clinical pathogenesis, utilizing appropriate scoring systems for diagnosis and markers for disease follow-up and monitoring of comorbidities. This emphasizes the need for a more structured and collaborative dialogue on GPP between dermatologists and pathologists, promoting a deeper understanding of the disease and its management. Pain should be properly managed as it can be associated with anxiety and depression disorders. In some cases, the flares are induced by the patients' emotional state. Psychological follow-up is a relevant aspect of long-term care for patients with GPP [33, 34].

It may be important to consider the provision of psychological support to accompany patients with GPP during the management of flare episodes. The psychological impact of GPP, including depression, anxiety, and feelings of helplessness, can significantly affect patients' well-being and quality of life. Offering psychological support can help patients cope with the emotional challenges associated with GPP and provide them with the necessary tools and resources to manage flare episodes effectively. In addition, patients with GPP need to be able to recognize their disease. Consequently, educating patients on their role in disease management is key to delaying the occurrence of GPP flares.

Awareness is essential for early detection and for the introduction of indicated therapies and is key to ensuring optimal management in GPP.

The aspect of patient access is also fundamental. A shortened and facilitated patient journey would improve the management of GPP. This could be achieved by involving, for example, emergency, internal medicine, and infectious disease departments.

Role of New Therapies in Facing Unmet Needs in GPP Management

Until a few years ago, people living with GPP had no specific therapeutic options that could help them manage their unpredictable disease. Treatment goals in GPP have not been well defined because of a lack of consistent treatment guidelines. Therefore, immediate treatment of GPP flares and long-term management of patients with GPP have been riddled with uncertainty.

Spesolimab has recently been approved as a treatment for GPP flares and new treatment options are available, such as in the USA, China, Japan, and the EU. Therefore, it is necessary to understand how to optimize the management of patients with GPP in clinical practice and to update current GPP treatment guidelines.

Given the life-threatening nature of GPP episodes, the use of drugs that rapidly achieve disease resolution is required. While previous treatments were not evidence based, and could be slow to act or ineffective, an effective, evidence-based treatment, spesolimab, is now available in many countries. Adoption of more effective therapies is essential to fulfill the unmet needs in GPP management and ensure best practice for patients. It would be desirable, for example, to have a day hospital regimen for the management of the therapy with spesolimab.

Given GPP is a life-threatening condition, effective treatments may reduce mortality, shorten hospitalization, and reduce morbidity.

CONCLUSION

Generalized pustular psoriasis is a dermatological emergency and a life-threatening condition that poses multiple diagnostic and management challenges to dermatologists. A lack of disease awareness combined with clinical similarities to other types of psoriasis have historically complicated the diagnosis of GPP. It is now clear that GPP requires a distinct diagnosis from plaque psoriasis and other dermatological conditions, and better understanding of the genetic characteristics underlying GPP may improve the accuracy of diagnoses.

Optimization of GPP management requires multilevel support. Indeed, a support is needed for (i) dermatologists to increase their understanding of GPP management; (ii) emergency medicine doctors, infectious disease specialists, internists, and general practitioners to recognize GPP as a potentially life-threatening autoinflammatory skin disease needing urgent

specialist referral and treatment; (iii) patients to feel empowered to take an active role in managing GPP, avoiding triggers and adhering to treatment plans; (iv) industry and regulatory organizations to share robust clinical trial information and consistent treatment guidelines; (v) healthcare organizations to improve communication, cooperation, and definition of roles and responsibilities among multidisciplinary teams.

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Declarations

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