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Update on Generalized Pustular Psoriasis

Atualização sobre Psoríase Pustulosa Generalizada

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ABSTRACT

Generalized pustular psoriasis (GPP) is a rare but severe inflammatory skin disease characterized by the eruption of widespread sterile pustules, often accompanied by systemic inflammation. Although GPP can coexist with plaque psoriasis, it is increasingly recognized as a distinct entity with unique clinicopathological, immunologic, and genetic features. The dysregulated IL-36 pathway, including mutations in the *IL36RN* gene, is implicated in GPP pathogenesis, providing a molecular basis for targeted therapies. Diagnosing GPP requires a comprehensive evaluation, including clinical presentation, potential triggers, patient history, histopathologic findings, and laboratory results. Disease severity must be assessed through both cutaneous symptoms and systemic involvement, as GPP flares can lead to life-threatening complications such as sepsis and multi-organ failure. Historically, GPP treatment primarily relied on therapies approved for plaque psoriasis, despite their limited specificity for this condition. Recent advances in understanding the molecular mechanisms of GPP, particularly the central role of interleukin-36 pathway, have led to the development of targeted therapies for this rare condition. Currently, spesolimab is the only therapy specifically approved for treating GPP flares in adolescents and adults, in both Europe and the United States of America. However, the management of GPP remains complex and challenging. This narrative review provides an overview of the epidemiology, pathophysiology, clinical features, comorbidities, and evolving therapeutic strategies for GPP.
Keywords: Antibodies, Monoclonal, Humanized/therapeutic use; Interleukin /therapeutic use; Psoriasis/drug therapy

RESUMO

A psoríase pustulosa generalizada (PPG) é uma doença inflamatória da pele, rara embora potencialmente grave, caracterizada pelo aparecimento de pústulas estéreis generalizadas, frequentemente acompanhadas por inflamação sistémica. Embora possa coexistir com psoríase em placas, a PPG é cada vez mais reconhecida como uma entidade distinta, com características clinicopatológicas, imunológicas e genéticas únicas. A desregulação da via da interleucina-36, incluindo mutações no gene *IL36RN*, está implicada na patogénese da PPG, proporcionando uma base molecular para terapêutica dirigidas. O diagnóstico de PPG requer uma avaliação abrangente, incluindo as características clínicas, possíveis fatores desencadeantes, antecedentes do doente, achados histopatológicos e resultados laboratoriais. A gravidade da doença deve ser avaliada através do atingimento cutâneo e do envolvimento sistémico, uma vez que as exacerbações da PPG podem levar a complicações com potencial risco de vida, incluindo sépsis e falência multiorgânica. Historicamente, o tratamento da PPG era baseado em terapêuticas aprovadas para a psoríase em placas, apesar da sua limitada especificidade para esta condição. Os avanços recentes na compreensão dos mecanismos moleculares da PPG, particularmente o papel central da via de interleucina-36, levaram ao desenvolvimento de moléculas direcionadas para esta doença rara. Atualmente, o spesolimab é a única terapêutica especificamente aprovada para o tratamento de exacerbações da PPG em adolescentes e adultos, tanto na Europa como nos Estados Unidos da América. No entanto, a gestão da PPG continua a ser complexa e desafiante. Esta revisão narrativa oferece uma visão geral da epidemiologia, fisiopatologia, características clínicas, comorbilidades e estratégias terapêuticas em evolução para a PPG.
Palavras-chave: Anticorpos Monoclonais Humanizados/uso terapêutico; Interleucinas/ Psoríase/tratamento farmacológico

INTRODUCTION

Pustular psoriasis is an uncommon variant of psoriasis distinguished by the presence of sterile neutrophilic pustules, with a variety of distribution patterns and a broad severity spectrum.[1,2] It can be categorized into three main phenotypes: palmoplantar pustulosis (PPP) and acrodermatitis continua of Hallopeau (ACH), both of which are localized acral forms; and generalized pustular psoriasis (GPP).[2–4]

Generalized pustular psoriasis is the rarest yet most severe form, characterized by the eruption of widespread sterile pustules, often accompanied by systemic inflammation.[2] It is an immune-mediated disease with a heterogeneous clinical course that can manifest as an acute flare, known as the von Zumbusch type, but can also be a chronic or relapsing disease in which flares of greater severity may

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overlap. The most commonly reported case is the development of GPP in patients with plaque psoriasis treated with corticosteroids, but it can more rarely occur after corticosteroid withdrawal for other conditions. Infections, particularly bacterial and viral, have been reported as triggers for GPP flares. Commonly implicated infections include upper respiratory tract infections but any infection can potentially be associated with a GPP flare. The exact incidence of infection-triggered GPP flares is not well established due to limited epidemiological data. Several medicines have been associated with GPP exacerbations, including tumor necrosis factor (TNF)-alpha inhibitors, hydroxychloroquine, lithium, nonsteroidal anti-inflammatory drugs (NSAIDs), and certain systemic antifungals. The incidence of medication-induced GPP remains difficult to quantify due to limited data.[2,5] The differential diagnosis of GPP requires careful interpretation of the clinical picture, medical history, laboratory tests and histopathologic features to exclude other inflammatory skin conditions.[6]

Generalized pustular psoriasis flares have the potential to develop into life-threatening complications, such as sepsis and multisystem organ failure.[3,7] Therefore, GPP requires prompt accurate diagnosis and effective treatment, with most of the cases requiring inpatient management.[4] Established international guidelines are currently lacking and management guidance of GPP often follows that for plaque psoriasis. However, while about half of patients diagnosed with GPP have a prior diagnosis of plaque psoriasis, there is currently a consensus on GPP being phenotypically, genetically and immunologically distinct from plaque psoriasis.[1,8] Over the past decade, advances in the knowledge of the molecular basis behind GPP immunopathogenesis, namely the central role of the interleukin(IL)-36 pathway, have led to the development of targeted therapies for this rare disease.[9] Optimal treatment for GPP should ensure a rapid onset of therapeutic action, including skin clearance and prevention of systemic involvement, as well as the capacity to prevent the recurrence of flares, while providing a favorable safety profile both in the short- and long-term.[10] Spesolimab is currently the only therapy approved in both Europe and the United States of America (USA) for the treatment of GPP flares in adults, also with the indication of flare prevention in the USA.[11]

A literature review (up until October 2024) was performed to provide a comprehensive overview of the epidemiology, pathophysiology, clinical features, associated complications, and management of GPP.

Epidemiology

Generalized pustular psoriasis is a rare disease with a paucity of epidemiological data available. Its exact prevalence is unknown, but it was estimated to range between 1.8 and 124 per million people in the general population, with significant ethnic and geographical variability. It is predominantly reported in East Asia, while its prevalence in European individuals seems to be considerably lower.[5,12,13] Estimates of GPP prevalence among patients with psoriasis range between 0.6% and 2.4%.[5]

It primarily affects adults, with a median reported age at diagnosis of around 50 years.[7,12] However, it can also occur in children, where it is more likely to be associated with an *IL36RN* mutation.[1,14] There does not seem to be a strong sex predilection, although some studies suggest a slight predominance among women.[7,12] In a recent Portuguese multicentric study, it was found that two-thirds of patients with GPP were women, with a mean age at presentation of 55 (± 21) years.[15]

Etiology and pathophysiology

Generalized pustular psoriasis may arise with pre-existing plaque psoriasis in about half of the patients, thus suggesting an overlap and interconnection between the immunologic pathways of both conditions. However, GPP has also been shown to present independently of plaque psoriasis and research conducted from the past two decades recognized it as distinct clinical entity, with its own genetic and immunologic determinants, and response to treatment. While plaque psoriasis is primarily driven by an adaptive immune response involving the IL-23/IL-17 axis, histopathological, molecular, and genetic data indicate that GPP is mainly driven by the hyperactivation of innate immunity, with a central role of the IL-36 pathway.[1,5,16,17] This has led some authors to classify GPP within the spectrum of autoinflammatory keratinization diseases.[18]

IL-36 cytokines belong to the IL-1 superfamily, and include the proinflammatory agonists IL-36α, IL-36β and IL-36γ, and the IL-36 receptor antagonist (IL-36Ra).[19] The role of the IL-36 pathway was first identified through the discovery of loss-of-function mutations in the IL-36 receptor antagonist (*IL-36Ra*), encoded by the *IL36RN* gene, that was found to be associated with GPP.[20] Mutations in *IL36RN* leading to unrestrained IL-36 activity are associated with a severe form of GPP characterized by early onset, more systemic inflammation and the absence of plaque psoriasis.[21,22] More recently, mutations and allelic variations in other genes functionally connected with the IL-36 pathway led to an enhanced inflammatory cascade and the recruitment of neutrophils and macrophages (e.g., loss-of-function of AP1S3, SERPINA3 and MPO; gain-of-function of CARD14) have also been found to be associated with GPP.[8,14]

IL-36 cytokines are produced by and target various skin cell types, including keratinocytes and immune cells, when stimulated by TNF, IL-17A, IL-22, and IL-1β. After proteolytic activation, IL-36 agonists bind to heterodimeric receptor

complexes [IL-36R and IL-1 receptor accessory protein (IL-1RAcP)], triggering downstream pathways involving protein myeloid differentiated protein 88 (MyD88), mitogen-activated protein kinase (MAPK), and nuclear factor-kappa B (NF-κB). This leads to the release of proinflammatory mediators such as neutrophil-attracting chemokines (CXCL1, CXCL2, and CXCL8), additional IL-36 precursors, TNF, IL-1β and IL-17 cytokines, which recruit and activate neutrophils, T cells, and dendritic cells (Fig. 1). This creates a self-amplifying cycle of unchecked signaling and overproduction of chemokines, which promote epidermal neutrophil infiltration, clinically manifesting as pustules and associated systemic symptoms.[1,8,16,17,23,24] IL-36Ra regulates this process by competing with IL-36 agonists for IL-36R binding, balancing the inflammatory response.[19] The imbalance seen in GPP arises from either an overproduction of IL-36 agonists or a loss-of-function in the IL-36Ra antagonist.[9]

IL-36 cytokines contribute to link innate and adaptive immunity, including the T-helper (Th) 1 and Th17 pathways.[22] Thus, while GPP pathogenesis shares some mediators with plaque psoriasis, it is now known to be primarily driven by a distinct pathway centered on IL-36 signaling.[13] Additional evidence comes from gene expression studies of lesional skin biopsies, which show an overexpression of IL-36 agonists (IL-36α, β, and γ) in keratinocytes surrounding neutrophilic pustules compared to healthy controls. The involvement of TNF, IL-17A, IL-23, IL-1, and interferons (IFNs) in the pathogenesis of GPP was also documented, although GPP lesions exhibited higher levels of IL-1 and IL-36 and lower levels of IL-17A and IFN-ɣ compared to plaque psoriasis. Additionally, a significantly stronger expression of neutrophil chemokines (CXCL1, CXCL2, and CXCL8), as well as IL-1- and IL-36-related transcripts, was observed in GPP lesions, exceeding that seen in plaque psoriasis.[9,21]

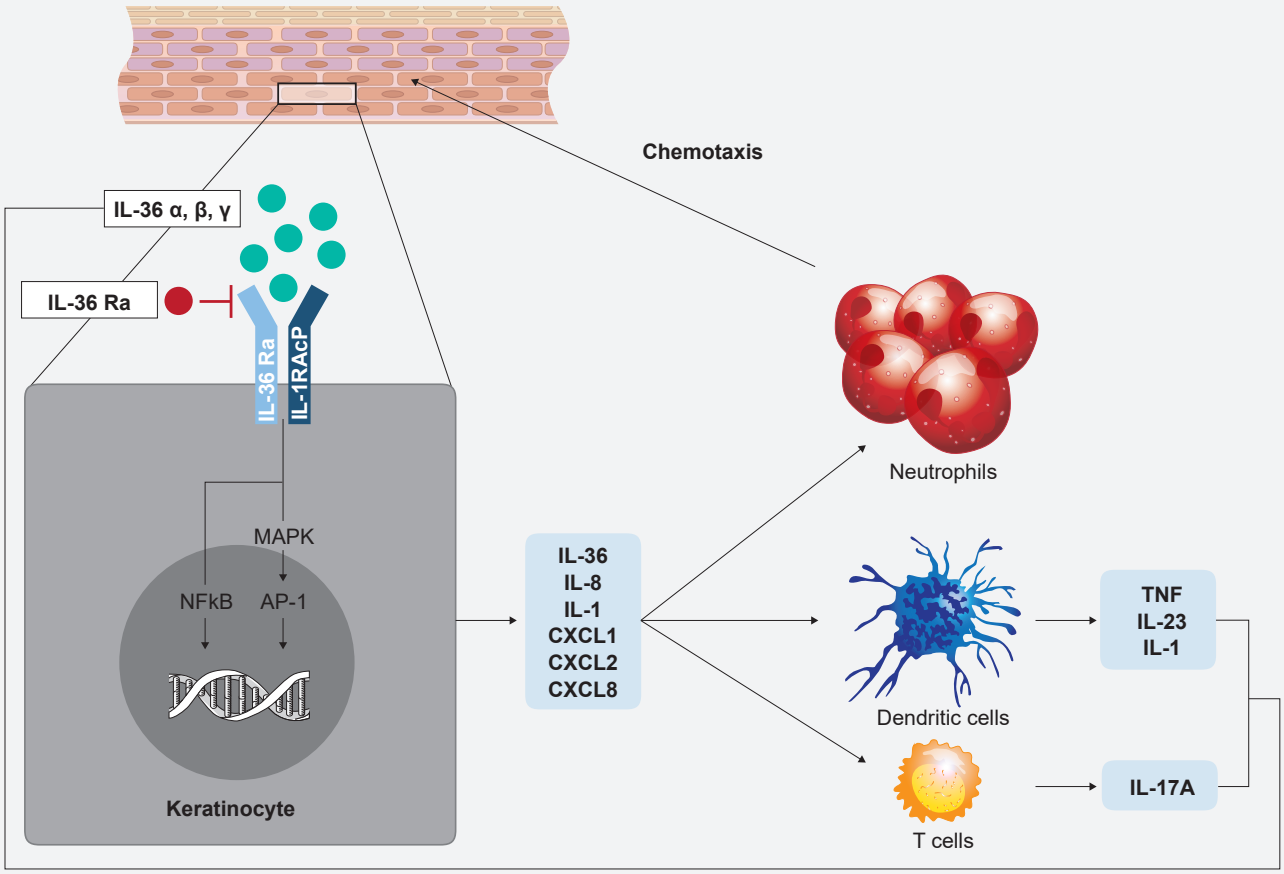

Figure 1 – Overview of IL-36 signaling. After processing by neutrophil-derived proteases, mature IL-36 agonists (α, β and γ) bind to IL-36R on the surface of keratinocytes, inducing an inflammatory cascade that promotes expression of more IL-36 precursors, neutrophilic chemokines (CXCL1, CXCL2, CXCL8) and various cytokines (IL-1β, IL-17A, IL-23, TNF), thus promoting recruitment and activation of neutrophils, T cells and dendritic cells through a self-amplifying loop. Hyperactivation of IL-36 pathways plays a key role in the pathogenesis of GPP. Adapted from Marrakchi *et al.*[1]

AP-1: activating protein-1; CXCL: chemokine (C–X–C motif) ligand; IL: interleukin; MAPK: mitogen-activated protein kinase; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; R: receptor; Ra: receptor antagonist; RAcP: receptor accessory protein; TNF: tumor necrosis factor.

Clinical features and diagnosis

Psoriasis includes both erythrosquamous and pustular lesions, which are distinct in their clinical and histological features but can occur together. In some cases, pustules may develop within psoriasis plaques as a pronounced inflammatory manifestation, as these plaques always contain some granulocytes detectable histologically. Intense inflammation in plaque psoriasis can lead to collections of neutrophils, like Munro's microabscesses and Kogoj's pustules. However, primary visible pustules do not usually form part of the spectrum of plaque psoriasis, except when occasionally arise exclusively within or at the edge of psoriasis plaques, often only detectable with dermoscopy. In these cases, the term to be used is 'psoriasis with pustules' and should not be considered a form of pustular psoriasis.[2]

Distinct phenotypes of pustular psoriasis have been described, universally characterized by persistent or recurrent primary, sterile, macroscopically visible pustules. Palmoplantar pustulosis and ACH are both localized acral forms, with PPP involving the palms and/or soles, while ACH primarily affects, though is not limited to, the nail apparatus.[2] In turn, GPP is characterized by widespread pustules on non-acral skin that are not confined to psoriasis plaques. Mixed forms, other terminologies and variants exist, including pustular psoriasis of pregnancy (previously referred to as 'impetigo herpetiformis'), annular pustular psoriasis and infantile/juvenile pustular psoriasis.[2,6]

Generalized pustular psoriasis is usually relapsing and remitting in nature, with a highly heterogeneous clinical course. The frequency, severity, and duration of the flares can vary both between different patients and between episodes in the same patient, but they have the potential of being life-threatening.[7] Generalized pustular psoriasis of the von Zumbusch type, the most severe form, is marked by the sudden appearance of numerous small, 2 to 3 mm sterile pustules that can merge to form large areas ('lakes') of pus. The underlying skin is red and swollen, and is typically accompanied by pain, pruritus, and burning sensation.

Table 1 – Characteristics of generalized pustular psoriasis

Characteristics of generalized pustular psoriasis	
Clinical presentation	• Sterile pustules on an erythematous background; often coalesce to form 'lakes of pus' • Widespread erythema typically affecting large areas of the body, often involving flexural areas • Extensive peeling of the skin follows, resulting in marked desquamation • Lesions are often painful and can be associated with burning or pruritus • Fever, chills, malaise, fatigue and arthralgias are common • Can present as recurrent flares with intervals of partial or complete remission, punctuated by acute episodes of pustulation • Erythroderma may occur
Triggers	• Withdrawal of systemic corticosteroids • Infections • Medications (e.g., lithium, antimalarials, vaccination) • Pregnancy • Hypocalcemia • Stress
Laboratory findings	• Leukocytosis • Elevated C-reactive protein and erythrocyte sedimentation rate • Hypoalbuminemia • Anemia • Hypocalcemia
Histopathology	• Overall epidermal architecture similar to plaque psoriasis: parakeratosis, elongated rete ridges, thinning of the suprapapillary epidermis. • Superficial dermal infiltrate composed of mononuclear cells, with neutrophils migrating from the papillary capillaries into the epidermis and forming subcorneal macropustules • Spongiform pustules of Kogoj (the Hallmark feature of GPP)
Main complications	• Secondary infections and sepsis • Electrolyte imbalances • Acute kidney injury • Liver dysfunction • Cardiovascular failure • Malnutrition • Neutrophilic cholangitis • Acute respiratory distress syndrome • Arthritis

Erythroderma may occur. Over the next few days days to weeks, the pustules dry out and leave behind residual redness and peeling skin. GPP is often associated with systemic involvement, as denoted by fever, fatigue, malaise and high systemic inflammatory markers. Other extracutaneous manifestations may include arthralgia, peripheral edema and mucosal involvement (e.g. conjunctivitis, uveitis, cheilitis, glossitis).[2–4,6,8]

The diagnosis of GPP is mainly clinical (Table 1).[4] A thorough medical history should be taken for all patients, inquiring about the clinical picture, pre-existing psoriasis history, previous infections and medication history. Although spontaneous in many cases, GPP flares may be caused by internal and external triggers. Systemic corticosteroid withdrawal, infections, medications, stress, pregnancy, vaccination and hypocalcemia have been reported as the main precipitating factors.[3,4,6] Laboratory blood tests are helpful for the assessment of the level of systemic inflammation (leukocytosis with neutrophilia, elevated C-reactive protein levels, increase of the erythrocyte sedimentation rate) and possible complications, such as kidney failure, abnormal liver function tests, and hypoalbuminemia. An arterial blood gas analysis should be carried out to investigate hypocalcemia and other hydroelectrolyte imbalances, and respiratory dysfunction. Blood cultures are mandatory in the presence of systemic inflammation.[3,4,6]

A skin biopsy should be performed to complement the differential diagnosis with other pustular dermatoses (Table 2). However, since histologic features may be nonspecific and often indistinguishable from acute generalized exanthematous pustulosis (AGEP), treatments should not be delayed while waiting for histology if the clinical suspicion is high and AGEP seems unlikely considering the clinical context of the patient. A key distinct histopathologic feature of GPP is the presence of spongiform pustules of Kogoj's, which form due to the subcorneal accumulation of neutrophils. Generalized pustular psoriasis pustules feature more apoptotic keratinocytes, usually do not have eosinophils, and are located at a higher level in the epidermis compared to those in AGEP. Also, the overall epidermal structure in GPP has matches with plaque psoriasis, exhibiting parakeratosis, acanthosis, hyperkeratosis, elongated rete ridges, diminished stratum granulosum, and capillary dilation of the papillary dermis. Munro's microabscesses and superficial perivascular mononuclear cell infiltrations can also be observed.[3,4,7,8,25]

Nonetheless, the classification and definitive diagnosis of GPP can be challenging owing to the lack of standardized global guidelines. The European Rare and Severe Psoriasis Expert Network (ERASPEN) consensus diagnostic criteria (2017) define GPP as primary, macroscopic, sterile pustules not limited to the palms, soles or psoriatic plaques, with or without systemic inflammation, and manifesting with a relapsing or persistent (more than three months) pattern.[2] Japanese diagnostic criteria (2018) state that the definitive diagnosis of GPP can be made if the following four criteria are met: (1) presence of systemic symptoms; (2) widespread erythematous skin with numerous sterile pustules; (3) histopathological evidence of neutrophilic subcorneal pustules (Kogoj's spongiform pustules); and (4) recurrence of these clinical and histological criteria. Generalized pustular psoriasis should also be considered if only criteria 2 and 3 are present.[25]

There is a need to develop standardized international guidelines to improve the diagnosis and treatment of patients with GPP and rapidly exclude other skin conditions that require different treatment strategies. While genetic tests are not currently standard practice for confirming a GPP diagnosis, the future use of genetic strategies could eventually provide new opportunities to improve diagnosis.[6]

Table 2 – Differential diagnoses for generalized pustular psoriasis

Differential diagnoses for generalized pustular psoriasis
Acute generalized exanthematous pustulosis
Other drug-induced pustular eruptions
Subcorneal pustular dermatosis
Widespread suppurative folliculitis
Cutaneous candidiasis
Bullous Impetigo
Staphylococcal scalded skin syndrome
Disseminated gonococcal infection
Autoimune blistering disorders (e.g., dermatitis herpetiformis, IgA pemphigus, pemphigus foliaceus)
Miliaria pustulosa
Erythroderma withsecondary pustulization

Complications

Generalized pustular psoriasis flares can be life-threatening if not diagnosed accurately and treated promptly (Table 1).[6] It can cause a hypermetabolic state with cardiorespiratory dysfunction, extensive catabolism and malnutrition, acute kidney and liver injury, as well as serious electrolyte imbalances. Secondary infections and sepsis are among the most common complications. Rare complications include uveitis and neutrophilic cholangitis. In extreme cases, GPP can escalate to critical multiorgan failure.[3,5,7,13,26,27] Also, most flares typically last between two to five weeks and often require hospitalization, placing a heavy burden on both patients and healthcare providers, and increasing the risk of complications related with the inpatient setting.[15] Mortality data of patients experiencing an acute GPP episode are limited, but rates of 2% to 16% have been reported.[3]

More recently, GPP was recognized as a notable risk factor for various systemic diseases. Generalized pustular psoriasis was associated with an increased incidence of cardiovascular events, such as ischemic heart disease and stroke. It was also linked to a higher occurrence of kidney dysfunction, liver disturbances, interstitial lung disease, anemia, depression, anxiety, osteoporosis and arthritis.[26]

Disease severity measures

The rarity of GPP and its heterogeneous cutaneous and extracutaneous manifestations pose a challenge for implementing comprehensive and precise disease measures in routine clinical assessment and follow-up of the patients.[7] Modified psoriasis disease measures, such as the GPP Physician Global Assessment (GPPGA) and GPP Area and Severity Index (GPPASI), have been developed and validated.[28,29]

The GPPGA was designed to evaluate the overall disease activity in the skin, corresponding to the average of the extent and intensity of the three subscores, namely pustulation, erythema and scaling/ crusting. It typically ranges from 0 to 4, with higher scores indicating more severe disease, respectively clear (0), almost clear (1), mild (2), moderate (3) and severe (4). For GPPASI, the score for each body region is determined by calculating the product of the GPPGA and its corresponding body surface area (BSA) score. This product is then multiplied by a weighting factor specific to each body region. The total GPPASI score is obtained by summing the individual scores from all body regions. However, these scores only assess the severity of skin manifestations and do not consider systemic involvement or overall disease burden. Also, its use in routine clinical practice will depend on its inclusion into hospital protocols or future guidelines. Establishing consensus on scoring systems for assessing disease burden, as well as on objective outcome measures and clinical endpoints, is essential for uniform application in clinical trials, enabling better comparisons between therapies.[28,29]

Establishing treatment goals in generalized pustular psoriasis

Treatment goals in GPP are not well defined primarily due to the rarity of the condition, its heterogeneous clinical manifestations, and the lack of uniform treatment protocols and therapeutic monitoring approaches. Proposed treatment objectives can be broadly categorized into immediate and long-term goals.[10]

Generalized pustular psoriasis is a potentially life-threatening condition that requires prompt diagnosis and intervention.[30] During a flare, the primary short-term goals are to rapidly control the cutaneous manifestations by halting and preventing pustule formation, reducing the burden of systemic signs and symptoms, and preventing the development of complications. In particular, timely management of GPP flares during pregnancy is crucial to avoid complications that could negatively affect both mother and fetus. Recently, rapid control of skin symptoms within one week of treatment has become a feasible goal with the use of IL-36 receptor inhibitors.[7,10,24,31]

Long-term management of GPP should focus on preventing flare-ups and managing associated comorbidities. Although specific long-term goals are not well defined in clinical trials, data from a survey of Corona Registry dermatologists suggested that over 80% of GPP patients experience persistent symptoms between flares, and many treatments fail to prevent recurrence. This highlights the need for comprehensive real-world studies to evaluate existing and emerging therapies, with the aim of establishing clear long-term goals for improving patient outcomes. Proposed long-term objectives include maintaining a low and stable GPPGA score between 0 and 1, ensuring the absence of systemic inflammation, and employing effective clinical monitoring approaches to identify and reduce the recurrence of flares.[7,10]

Disease management

Managing GPP can be complex and typically requires a multidisciplinary approach. Treatment for acute GPP flares depends on the severity of skin and systemic involvement but overall includes a combination of topical therapies, systemic medications, and supportive care, often provided in a tertiary hospital inpatient setting. For severe cases, this may include hospitalization for fluid balance, electrolyte management, and systemic antibiotics if bacterial infection is suspected. Topical therapies, such as corticosteroids, vitamin D analogs, calcineurin inhibitors and emollients, are used as adjuncts to systemic treatments to provide

symptomatic relief and improve skin barrier function. Analgesics, antipyretics and antihistamines may be administered to control the respective signs and symptoms.[7,10,24,31]

Conventional systemic therapies and phototherapy

Acitretin, cyclosporine, and methotrexate are commonly used non-targeted systemic therapies for GPP, although the evidence supporting their efficacy is limited, primarily relying on case reports and small retrospective studies. Acitretin plays a role in chronic GPP management, particularly when immunosuppressive therapies are unsuitable. Despite its effectiveness, it has a slower onset of action and is associated with significant side effects, including hyperlipidemia and liver toxicity. Cyclosporine offers rapid immunosuppressive effects but is limited by serious long-term side effects, such as nephrotoxicity and hypertension. It is typically reserved for short-term management, with patients transitioning to safer long-term therapies once their condition is stabilized. Methotrexate may be cost-effective for long-term management, but its effects may take weeks to manifest, making it unsuitable for acute flares. While these therapies have been historically utilized off-label as first-line systemic treatments for GPP, they are constrained by limited effectiveness and potential toxicities. Also, none of these treatments specifically target the underlying pathophysiology of GPP.[7,10,24,31]

Psoralen ultraviolet A phototherapy can be considered a second-line treatment for adults, but it is not recommended for acute forms of pustular psoriasis.[13] None of the previously mentioned therapies are safe during pregnancy, with the exception of cyclosporine. Systemic corticosteroids are generally avoided due to the risk of rebound flares, except for specific cases of impetigo herpetiformis.[7,10,24,31] Reports have also been published on the treatment of GPP with other agents, including the antineutrophil agent dapsone[32] and the small molecule phosphodiesterase-4 inhibitor apremilast.[33]

Biologic therapy

Various biologic agents approved for moderate to severe plaque psoriasis, such as TNF inhibitors (infliximab, adalimumab, certolizumab), IL-12/23 inhibitors (ustekinumab), IL-23 inhibitors (guselkumab and risankizumab) and IL-17 inhibitors (brodalumab, secukinumab, ixekizumab) have emerged as potential options for the treatment of GPP, with several being licensed in Japan (Table 3).[34–36] These agents have also been frequently used off-label to treat GPP flares in other countries, although evidence supporting their efficacy is mainly derived from case series and small open-label, single-arm trials.[24,31,35–37] In a recent systematic review on the use of these biologics for GPP, secukinumab and ixekizumab had the highest rates of complete resolution (57.7% and 57.6%, respectively).[38] There are also case reports of GPP exhibiting a positive response to IL-1 inhibition with anakinra, canakinumab and gevokizumab.[13,39,40]

Over the last decade, advancements in understanding the molecular mechanisms underlying GPP pathogenesis, especially the key role of the IL-36 pathway, have driven the development of targeted therapies specifically for this condition. Spesolimab is a humanized monoclonal IgG1 antibody that binds strongly to IL-36R, inhibiting the ligands IL-36α, β, and γ from activating the receptor and consequently blocking the subsequent activation of IL-36-mediated proinflammatory and profibrotic pathways. Spesolimab became the first treatment to receive approval from the US Food and Drug Administration (FDA) in September 2022 and from the European Medicines Agency (EMA) in December 2022 for managing GPP in patients aged 12 and older.[11,34] The first evidence emerged from a phase I proof-of-concept study involving 7 patients experiencing a GPP flare. A single intravenous infusion of 10 mg/kg of spesolimab led to rapid, effective, and sustained clearance of skin symptoms, with no significant AE reported.[41] The Effisayil clinical trial program has been investigating the largest population of patients with GPP. The Effisayil 1 phase II trial, which included a multicentric cohort of 53 participants, further demonstrated the efficacy of spesolimab compared to placebo in clearing GPP lesions within one week and enhancing patient-reported pain, fatigue, quality of life, skin symptoms and systemic markers of inflammation.[42] For patients (aged 12 and older and weighing 40 kg or more) experiencing a flare, spesolimab should be administered as soon as possible as a single 900 mg intravenous infusion over 90 minutes. If flare symptoms persist, an additional dose may be administered one week after the initial infusion.[43]

The Effisayil 2 clinical trial assessed the use of spesolimab maintenance treatment to prevent GPP flares. In this multinational study involving 123 adolescents and adults with a history of GPP, high-dose spesolimab demonstrated a significant advantage over placebo in preventing GPP flare-ups over a 48-week period and in reducing the risk of a decline in quality of life, indicating its potential as an effective long-term treatment option for GPP.[44] The recommended dose of spesolimab for maintenance treatment is a subcutaneous loading dose of 600 mg, followed by 300 mg administered subcutaneously 4 weeks later and every 4 weeks thereafter. A subcutaneous loading dose is not required following treatment of a GPP flare with intravenous spesolimab.[43] The efficacy of spesolimab does not seem to be affected by the *IL36RN* mutational status.[41,42,44] Spesolimab was shown to be safe and well-tolerated by GPP patients, with most adverse events being non-serious, non-severe, and not leading to treatment discontinuation.[41,42,44] In the one-week placebo-controlled period of Study Effisayil

Table 3 – Overview of the main treatments for generalized pustular psoriasis[7,8,13,24,25,31,34]

Treatment	Mechanism of action	Efficacy in GPP	Potential safety issues	Indication for GPP
Cyclosporine	Calcineurin inhibitor	Effective in rapid control of acute GPP flares, but typically for short-term use.	Nephrotoxicity, hypertension, gengival hyperplasia, increased risk of infections and malignancies.	Off-label
Methotrexate	Antimetabolite that inhibits folate-dependent enzymes	Moderate efficacy, especially in chronic cases or when combined with other treatments.	Hepatotoxicity, bone marrow suppression, lung toxicity, gastrointestinal toxicity, increased risk of infections.	Off-label
Acitretin	Retinoid (oral)	Effective in chronic management of GPP; slower onset of action.	Teratogenicity, mucocutaneous dryness, hypertriglyceridemia, hepatotoxicity	Off-label
Corticosteroids	Broad immunosuppressive effects	Effective in short-term control of acute GPP flares, but not recommended for long-term use.	Adrenal suppression, weight gain, hypertension, hyperglycemia, osteoporosis, risk of rebound flares.	Off-label
Adalimumab	TNFinhibitor	Clinical efficacy demonstrated in case reports of GPP	Increased risk of infections, malignancies, injection site reactions, cardiovascular risks.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Infliximab	TNFinhibitor	Rapid onset of action (pustule clearance 1–3 days)	Infusion reactions, infections (e.g., tuberculosis), heart failure, hepatotoxicity.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Secukinumab	IL-17A inhibitor	Sustained clinical efficacy demonstrated in case reports and several small open-label phase 3 trials in GPP	Nasopharyngitis, upper respiratory infections, candidiasis, exacerbation of inflammatory bowel disease.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Ixekizumab	IL-17A inhibitor	Clinical efficacy demonstrated in case reports of GPP	Infections, hypersensitivity, exacerbation of inflammatory bowel disease, injection site reactions.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Brodalumab	IL-17 receptor antagonist	Clinical efficacy demonstrated in case reports of GPP	Risk of suicidal ideation and behavior, infections, neutropenia, hypersensitivity reactions.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Ustekinumab	IL-12/IL-23 inhibitor	Variable efficacy; less effective in controlling GPP compared to IL-17 inhibitors.	Increased risk of infections, malignancies, hypersensitivity reactions, reversible posterior leukoencephalopathy.	Off-label
Risankizumab	IL-23 inhibitor (p19 subunit)	Clinical efficacy demonstrated in case reports of GPP	Upper respiratory infections, headache, fatigue, injection site reactions, arthralgia.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Guselkumab	IL-23 inhibitor (p19 subunit)	Clinical efficacy demonstrated in case reports of GPP	Infections, upper respiratory tract infections, headaches, injection site reactions, gastrointestinal symptoms.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Spesolimab	IL-36 receptor antagonist	Sustained efficacy in treating GPP flares and controlling the disease relapses in the long-term	Infections, hypersensitivity reactions.	On-label for GPP flares. Approved by FDA for the treatment of GPP and EMA for prevention of flares.

EMA: European Medicines Agency; FDA: Food and Drug Administration; GPP: generalized pustular psoriasis; IL: interleukin.

1, 14% of subjects receiving spesolimab experienced infections, compared to 6% of those on placebo. Among these, a serious infection, specifically a urinary tract infection, occurred in one subject (3%) treated with spesolimab, while no such infections were reported in the placebo group.[42] Since it is not possible to exclude that IL-36 inhibition may confer higher vulnerability of the host to infections, spesolimab is not recommended for those with active significant infections, and screening for tuberculosis is advised before treatment.[34,43] The safety and effectiveness of spesolimab in pediatric patients younger than 12 years of age or weighing less than 40 kg have not been established.[43]

Imsidolimab is another monoclonal antibody that targets IL-36 signaling. It demonstrated efficacy in an open-label study involving eight patients experiencing a GPP flare and is currently advancing to a phase III clinical trials.[45]

While significant progress has been made in developing targeted therapies for GPP, challenges remain in establishing clear guidelines for treatment success and failure and optimizing treatment for specific populations. There is a critical unmet need for effective and safe treatments for GPP in pregnant women and children, conditions that are even rarer. For impetigo herpetiformis, certolizumab may be a reasonable and safer option, as it exhibits minimal placental transfer. Currently, the dosages of biologics used for juvenile GPP, including etanercept, adalimumab, ustekinumab, ixekizumab, and secukinumab, are based on those approved for pediatric plaque-type psoriasis.[35,46] Ongoing research into biologic therapies for GPP will continue to improve patient outcomes and expand treatment options.

CONCLUSION

Generalized pustular psoriasis is a serious and potentially life-threatening condition that requires accurate diagnosis and prompt treatment. Understanding the IL-36 pathway's role as a critical inflammatory axis in GPP pathogenesis has paved the way for novel therapeutic strategies. Spesolimab has been shown to be effective in the management of GPP, both in the rapid control of the flares and in preventing their recurrence in the long-term, while maintaining a favorable safety profile. By addressing key unmet needs in GPP treatment, spesolimab is antecipated to become the standard of care for this rare orphan disease. Ongoing research and clinical implementation will be fundamental in refining treatment approaches and enhancing patient outcomes in GPP.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

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