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Spesolimab for the treatment of Generalized Pustular Psoriasis

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2023

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Artigo de Revisão Bibliográfica

Dissertação de Mestrado Integrado em Medicina
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Dedication

I dedicate this thesis to the memory of my beloved grandparents, Fernando and Rosa. Their humble beginnings never deterred them from instilling in me a passion for learning and a deep appreciation for education. They worked tirelessly to create a family of educators and academics, and their unwavering support and encouragement have continued to inspire me every day. Their perseverance in the face of adversity is a constant reminder of the importance of hard work and determination. I am forever grateful for their love and guidance throughout my life, and I know that their legacy will live on through my academic pursuits.

To my parents, whose unwavering love, understanding, and belief in me have been a source of strength and encouragement throughout this journey. Your presence and support have provided me with the fortitude to overcome obstacles and pursue my dreams.

To my sister, Filipa, mere words will never suffice to fully express the depth of my gratitude. You are the embodiment of the purest form of love in my life. I wholeheartedly wish for you to continue forging your unique path toward happiness and embracing the remarkable individual that you are.

Acknowledgments

To, Professor Doutor Tiago Torres, for igniting my interest in this field and for consistently providing me with his valuable guidance throughout the process of completing this dissertation.

Resumo

Introdução: A psoríase pustulosa generalizada (PPG) é uma variante grave e potencialmente fatal da psoríase pustulosa, caracterizada por episódios recorrentes de pústulas neutrofílicas extensas em pele eritematosa. A sua evolução clínica é imprevisível e pode ser desencadeada por vários fatores, nomeadamente, infeções e descontinuação de corticoides. Apesar de incerto, o papel do gene IL36RN e da via de sinalização da IL-36 na GPP foi correlacionado com a GPP, tendo sido identificada uma mutação de perda de função no IL36RN, que induz a desregulação do eixo IL-36. Este desequilíbrio resulta num excesso de agonistas pró-inflamatórios que se ligam à IL-36R, contribuindo para um estado pró-inflamatório e para as características clínicas observadas. O tratamento da PPG apresenta desafios significativos e, atualmente, não existem *guidelines* específicas aprovadas na Europa. Não obstante, fármacos como os retinoides, a ciclosporina, o metotrexato e terapêuticas biológicas aprovadas para a psoríase vulgar, são frequentemente usados. Os inibidores dos recetores da IL-36, como o spesolimab, atualmente investigado relativamente à sua segurança e eficácia, são promissores como potenciais opções de tratamento da PPG.

Objetivos: Esta revisão avalia a evidência disponível sobre a eficácia e segurança do spesolimab para o tratamento da PPG.

Métodos: Foi efetuada uma pesquisa bibliográfica utilizando as seguintes bases de dados: PubMed, Google Scholar, Science Direct, Cochrane Library e ClinicalTrial.gov. Foram selecionados artigos originais e de revisão escritos em inglês. Foi também efetuada a recuperação de artigos relevantes a partir da lista de referências bibliográficas dos artigos originais.

Conclusões: O spesolimab tem demonstrado resultados promissores na PPG. Um estudo de prova de conceito e um ensaio clínico de fase II subsequente mostraram que uma única administração intravenosa de spesolimab induziu respostas rápidas e positivas, eliminando as lesões da PPG no espaço de uma semana. Estes estudos indicaram ainda que o spesolimab trata eficazmente a PPG, independentemente das mutações IL36RN. Foram observados efeitos adversos ligeiros a moderados, contudo estes não exigiram a interrupção do tratamento. Com base nestes resultados, o spesolimab foi aprovado pelas autoridades reguladoras, incluindo a *FDA* e a Agência Europeia de Medicamentos, para o tratamento de crises de PPG em adultos. Estes desenvolvimentos vão ao encontro das necessidades dos doentes e constituem uma opção terapêutica promissora para aqueles que não responderam a outros tratamentos.

Palavras-chave: *Generalized pustular psoriasis, interleukin-36, spesolimab, treatment.*

Abstract

Introduction: Generalized Pustular Psoriasis (GPP) is a severe and potentially life-threatening variant of pustular psoriasis characterized by recurrent episodes of extensive neutrophilic pustules on erythematous skin. Its clinical course is unpredictable and can be triggered by various factors, including infections and corticosteroid withdrawal. Despite limited understanding, the role of the IL36RN gene and the IL-36 signaling pathway in GPP has been elucidated. A loss-of-function mutation in IL36RN has been identified, leading to dysregulation of the IL-36 axis. This imbalance results in an excess of proinflammatory agonists binding to the IL-36R, while the antagonists are less prevalent, contributing to a proinflammatory state and the characteristic clinical features observed in GPP. The treatment of GPP presents significant challenges, and currently, there are no approved GPP-specific therapies in Europe. However, retinoids, cyclosporine, methotrexate, and biological therapies approved for Psoriasis Vulgaris are usually used for GPP. Interleukin-36 receptor inhibitors, including spesolimab, currently under investigation for its safety and efficacy, hold promise as potential treatment options for GPP management.

Objectives: This review critically evaluates the available evidence on the efficacy and safety of Spesolimab for the treatment of GPP.

Methods: A bibliographic search was performed using the following databases: PubMed, Google Scholar, Science Direct, Cochrane Library, and ClinicalTrial.gov. Original and review articles written in English were selected. The retrieval of relevant articles from the list of bibliographic references of original articles was also performed.

Conclusions: Spesolimab has demonstrated promising results in GPP. An open-label, proof-of-concept, study and subsequent phase II trial showed that a single intravenous infusion of spesolimab led to rapid and positive responses, clearing GPP lesions within a week. The studies indicated that spesolimab effectively treats GPP, regardless of IL36RN mutations. Mild to moderate adverse effects were observed but did not require treatment discontinuation. Based on these findings, spesolimab has been approved by regulatory authorities, including the FDA and the European Medicines Agency, for the treatment of GPP flares in adults. These developments address the unmet needs of GPP patients and provide a promising therapeutic option for those who have not responded to other treatments.

Keywords: Generalized pustular psoriasis, interleukin-36, spesolimab, treatment

List of Abbreviations

AP-1	Activation Protein 1
CARD14	Caspase recruitment domain family member 14
CTSG	Cathepsin G
c-Jun	Transcription factor c-Jun
CXCL1	C-X-C motif chemokine ligand 1
CXCL8	C-X-C motif chemokine ligand 8
EMA	European Medicines Agency
ERASPEN	European Rare and Severe Psoriasis Expert Network
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
GPP	Generalized Pustular Psorasis
GPPGA	Generalized Pustular Psoriasis Physician Global Assessment
GPPASI-75	75% or greater reduction from baseline in GPPASI score
IL	Interleukin
IL-1RAcP	Interleukin-1 receptor accessory protein
IL-1RL2	Interleukin-1 receptor-like 2
IL-36R	Interleukin-36 receptor
IL-36Ra	IL-36 receptor antagonist
IL36RN	IL-36 receptor antagonist gene
IFN-α	Interferon alpha
IRAK1	Interleukin-1 receptor-associated kinase 1
IRAK2	Interleukin-1 receptor-associated kinase 2
MAPKs	Mitogen-activated protein kinases
MPO	Myeloperoxidase
MyD88	Myeloid differentiation primary response 88
NE	Neutrophil Elastase
NF-kB	Nuclear factor- kappa B
P40	Protein subunits of IL-12 and IL-23
Pain VAS	Pain Visual Analogue Scale
PR3	Proteinase 3
PSS	Psoriasis Symptom Scale
STAT3	Signal transducer and activation of transcription 3
TNF- α	Tumor Necrosis Factor-alpha

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Introduction

Generalized Pustular Psoriasis (GPP) is a severe and potentially life-threatening variant of pustular psoriasis, characterized by recurrent episodes of extensive sterile neutrophilic pustules on erythematous skin.[1] This disease frequently presents with fever and systemic inflammation, which can potentially affect extracutaneous organs.[2] GPP is clinically heterogeneous in presentation and progression and lacks consistent classification. Different subtypes of GPP have been identified, which include acute von Zumbusch type, the most common presentation, impetigo herpetiformis, annular pustular psoriasis, and juvenile pustular psoriasis.[3]

Accurately determining the epidemiology of GPP poses a significant challenge, primarily due to inadequate clinical recognition and inaccurate diagnoses, which ultimately lead to imprecise estimates of disease prevalence.[1] Prevalence rates for GPP exhibit significant variability across different regions, with France reporting a rate of 1.76 cases per million, Japan reporting 7.46 cases per million, and the Republic of Korea reporting a range of 88-124 cases per million. Notably, GPP does not exhibit a strong sex predilection.[1,4] Although existing literature indicates a slightly higher prevalence among females.[5,6]

Without appropriate treatment, GPP typically presents an unpredictable and prolonged clinical course characterized by intermittent flares. Various factors, such as stress, corticosteroid withdrawal, pregnancy, and infections, may trigger these flares.[7,8]

The pathogenesis of GPP is still insufficiently comprehended. Nevertheless, in 2011, the identification that a loss-of-function mutation in the IL36RN gene was associated with GPP underscored the critical role of this signaling pathway in the development of GPP.[9] Since then, the dysregulation of the interleukin (IL)-36 axis in GPP has been extensively documented with a predominance of proinflammatory agonists, such as IL-36α, IL-36β, and IL-36γ, binding to the IL-36 receptor protein (IL-36R) over its antagonists, IL-36Ra and IL-38. This imbalance triggers a proinflammatory state in the skin, which leads to the clinical features observed in the patients.[10]

Currently, no approved GPP-specific therapies are available in Europe for the management and treatment of GPP flares. Treatment goals include rapid resolution of pustules, prevention of new outbreaks, relief of discomfort, and regulation of extracutaneous reactions.[7] Retinoids, cyclosporine, and methotrexate are often recommended for GPP patients.[7,11,12] Biological therapies that focus on crucial cytokines implicated in the initiation of inflammatory pathways of plaque psoriasis, such as tumor necrosis factor-α (TNF- α) inhibitors, IL-17 and IL-23 inhibitors, are also usually used.[7]

Recently, IL-36 receptor inhibitors have surfaced as promising treatment options. Early-phase clinical trials have demonstrated their effectiveness and safety.[13] Spesolimab, a novel humanized selective antibody, blocks the activation of the IL-36 receptor, specifically targeting GPP flares. As the IL-36 pathway plays a critical role in the inflammatory response, targeting this cytokine holds excellent potential for improving GPP treatment.[14]

Although new therapies offer hope, further research is needed to fully understand the complex interplay of genetic, environmental, and immunological factors involved in GPP pathogenesis and to develop more effective and targeted therapies for this debilitating disease.

Objective

This review aims to critically evaluate and synthesize the available evidence on the use of Spesolimab for the treatment of generalized pustular psoriasis, focusing on its efficacy and safety profile.

Methods

The search was conducted in multiple databases, including MEDLINE, Google Scholar, Cochrane Library, Scopus Database, and ClinicalTrial.gov, to ensure comprehensive coverage of the available literature. The time frame was limited to articles published from 2010 to the present. Only articles written in English were included in this review.

The search used a combination of MeSH terms and keywords, including "Generalized Pustular Psoriasis," "Spesolimab," "Interleukin-36", "Anti-IL 36", "Treatment", and "Clinical Trials". These terms were searched alone or in combination. Additional data concerning the clinical trials were acquired from the website clinicaltrials.gov.

The search results were screened by reviewing the titles and abstracts of the articles, and only articles deemed relevant were included in this review. In addition, the bibliographic references from selected articles were also considered.

This review included both original research articles and review articles that focused on the use of Spesolimab for the treatment of generalized pustular psoriasis.

Clinical Features and Diagnosis of Generalized Pustular Psoriasis

Pustular psoriasis can manifest as acute systemic or chronic localized forms, such as palmoplantar pustulosis and acrodermatitis continua of Hallopeau.[15]

The course of GPP can be categorized into acute and chronic stages. During the acute phase, patients experience flares that vary in frequency, duration, and time to resolution.[16] Acute GPP presents with recurrent episodes of systemic inflammation characterized by the emergence of new crops of pustules that often merge to form larger purulent collections, commonly referred to as "lakes of pus". Patients often experience accompanying systemic symptoms, such as pyrexia and malaise, due to the involvement of several autoinflammatory and T-cell-mediated mechanisms.[10] Additionally, extracutaneous symptoms can be present during acute episodes of GPP. These symptoms may include arthralgias, lower extremity edema, jaundice, and ocular abnormalities such as conjunctivitis, iritis, or uveitis. Mucosal involvement may also arise.[1] It is essential to note that acute GPP multisystemic effect can lead to severe and potentially life-threatening complications, such as sepsis, as well as severe renal, hepatic (neutrophilic cholangitis), or respiratory (neutrophilic pneumonitis, acute respiratory distress syndrome) abnormalities, and ultimately lead to death.[5,17] A variable range of clinical presentations, such as plaque-type, pustular, and erythematous lesions, characterizes the chronic phase of GPP.[10]

Stress, corticosteroid withdrawals, pregnancy, or infections typically trigger recurrent acute flares of GPP. [17]

Despite being initially described by von Zumbusch in 1910, the clinical features of GPP have remained poorly defined, leading to difficulties in diagnosis due to a lack of knowledge and clinical similarities with other forms of psoriasis.[15] Recently, the European Rare and Severe Psoriasis Expert Network (ERASPEN) specialists established a consensus to improve the understanding and management of GPP. The diagnosis of GPP is based on the clinical features defined by primary, sterile-appearing pustules on non-apical skin (unless pustulation is limited to psoriatic plaques). A diagnosis can only be made if the condition has recurred on more than one occasion or persists for a minimum of three months.[15,18].

In addition to the diagnosis proposed by ERASPEN, there are guidelines available in Japan, where the incidence of GPP is higher. These guidelines state that the diagnosis of GPP can be confirmed if four specific criteria are met, which include the (1) presence of systemic symptoms, (2) extensive erythematous skin with numerous sterile pustules, (3) histopathological confirmation - neutrophilic subcorneal pustules histopathologically characterized by Kogoj's spongiform

pustules, and (4) recurrence of both clinical and histological criteria. Even if only criteria 2 and 3 are present, GPP should still be considered a possible diagnosis.[19]

Pathogenesis of Generalized Pustular Psoriasis

GPP is a multifactorial disease with contributions from both genetic and environmental factors.[2] The proper functioning of the IL-36 signaling pathway is crucial in regulating the innate immune system, and any imbalance in this pathway seems to be a key factor in the development of GPP.[9,10]

The IL-36 cytokine family comprises three proinflammatory agonists (IL-36α, IL-36β, and IL-36γ) and two antagonists (IL-36Ra and IL-38). These cytokines are expressed in epithelial and immune cells and share the same receptor complex, IL-36R.[20] IL-36 cytokines lack a signal peptide, and their release mechanisms are not fully understood. Nonetheless, it is well established that post-translational processing is necessary to achieve complete agonist and antagonist activity for all IL-36 members.[21]

Structurally, the IL-36R complex consists of two distinct subunits, namely IL-1 receptor-like 2 (IL-1RL2) and IL-1 receptor accessory protein (IL-1RAcP). Upon binding of IL-36 agonists to IL-1RL2, IL-1RAcP is recruited, thereby triggering the activation of the MyD88/IRAK1/IRAK2/TRAF6 signaling complex and its corresponding intracellular signaling pathways, including MAPKs, c-Jun, NF-kB, and STAT3. These signaling pathways subsequently lead to the activation of AP-1 and NF-KB transcription factors within the cell, ultimately promoting the transcription and expression of proinflammatory genes and corresponding intracellular signals that cause inflammation.[20,22,23] Consequently, IL-36 releases inflammatory mediators and chemotaxis, activating neutrophils, macrophages, dendritic cells, and T cells, ultimately amplifying inflammatory responses.[9,20] This cascade of events stimulates the production of chemokines such as CXL1 and CXL8, creating a chemokine gradient that attracts numerous neutrophils into the epidermis. This, in turn, causes the development of spongiform pustules of Kogoj and sub-corneal accumulation of neutrophils, resulting in the recognizable "lakes of pus" characteristic of GPP patients.[10]

Upon activation, IL-36 initiates a cycle of inflammation. However, the presence of IL-36Ra and IL-38 counteract this response by binding to the same receptor protein as IL-36 and blocking its signaling.[10] The IL-36 receptor antagonist (IL-36Ra), a member of the IL-1 family of anti-inflammatory cytokines, is critical in inhibiting proinflammatory signaling pathways and controlling the inflammatory response triggered by IL-36 cytokines. Hence, loss-of-function mutations in the

IL-36RN gene result in the inability of IL-36Ra to antagonize and limit the proinflammatory cytokines, leading to a vicious cycle of enhanced and unopposed inflammation.[8]

By promoting the IL-36 signaling pathway in a self-regulating manner, the IL-36R agonists can exacerbate skin diseases, as they stimulate T-helper 17 cells and enhance the IL-17 signaling pathway.[24] This results in the hyperproliferation and dysplasia of keratinocytes, characteristic features of psoriatic skin.[10] The presence of IL-36 in skin tissues and its regulation by epidermal growth factor underlines its role in maintaining skin barrier function and homeostasis through the proliferation of keratinocytes.[8,25] Therefore, an imbalance in this pathway can affect inflammatory conditions. Additionally, IL-36 enhances neutrophilic responses through various indirect mechanisms, such as robustly inducing the expression of neutrophil-attracting chemokines in keratinocytes and promoting IFN-α responses in blood neutrophils systemically.[26] Patients with dysfunctional antagonistic mechanisms experience distinctive disease flares.[21]

Patients harboring IL36RN mutations exhibit upregulation of IL-1 in response to IL-36 stimulation, highlighting the critical role of the IL1/IL-36 inflammatory axis in driving disease pathology.[23] IL36RN mutations have been identified in individuals who experience an earlier onset of symptoms and have more severe manifestations of the disease, associated with a markedly increased risk of systemic inflammation.[27] It is worth emphasizing that IL36RN mutations are not linked to plaque psoriasis and are less prevalent in GPP patients with co-existing plaque psoriasis.[28] However, not all patients diagnosed with GPP possess mutations in the IL36RN gene. Recent studies have identified genetic variants in other pathogenic genes, such as CARD14, AP1S3, and MPO, associated with GPP in affected individuals.[14] The four genes responsible for causing the disease share common pathogenic molecular pathways. Mutations in IL36RN, CARD14, and AP1S3 genes can trigger proinflammatory signaling pathways through NF-κB, leading to heightened expression of proinflammatory cytokines. Moreover, the deficiency of the MPO gene facilitates the activation of IL-36 signals by regulating the activity of NE, CTSG, and PR3 serine proteases.[9]

Understanding the molecular mechanisms underlying GPP associated with IL36RN mutations is crucial in identifying appropriate treatment options.[20,27]

Current treatment options for Generalized Pustular Psoriasis

GPP lacks established European treatment guidelines due to limited high-quality data on treatment efficacy.[7,14,29] The treatment approach for GPP varies depending on the severity of the condition and may involve a combination of topical treatments, systemic medications, and

supportive therapies.[19,30] Topical treatments, including emollients and corticosteroids, may provide symptomatic relief but are typically reserved for adjunctive therapy.[7] Systemic drugs such as methotrexate, calcineurin inhibitors, and retinol are also used but are associated with long-term multiple organ toxicity and do not target GPP's pathophysiology specifically.[7,31]

Biologic therapies are a promising treatment option for GPP and are specifically designed to target its underlying pathophysiology.[12,31] Although not approved by the FDA or EMA for GPP treatment, biologic therapies that have been approved for the treatment of plaque psoriasis, such as TNF-α inhibitors (Infliximab and Adalimumab), IL-12/IL-23 inhibitors (Ustekinumab), IL-17 inhibitors (Secukinumab, Ixekizumab, and Brodalumab) and IL-23 inhibitors (Guselkumab and Risankizumab), are often used to treat GPP.[19]

Among these agents, TNF-α inhibitors, particularly infliximab, have demonstrated strong evidence of efficacy, safety, and rapid response. However, limitations associated with infliximab include infusion reactions and biological fatigue.[12]

Emerging data suggest that IL-17 inhibitors, such as Brodalumab, Ixekizumab, and Secukinumab, may be effective first-line agents for the treatment of pustular psoriasis. These inhibitors have shown positive clinical outcomes and safety profiles in open-label trials and case reports.[8,32] GPP is characterized by elevated IL-17 levels, and studies have shown that Secukinumab, approved for plaque psoriasis, is also effective and safe for GPP patients. Ixekizumab and Brodalumab have been evaluated in open-label trials, and their efficacy and safety have been reported with positive results.[29,32,33]

Ustekinumab, an antibody that targets IL-12/23 p40, is approved for treating psoriasis vulgaris and psoriatic arthritis, having limited evidence supporting its efficacy for treating GPP, and it should be used when other treatments have failed.[19,34] Guselkumab, a monoclonal antibody targeting the p19 subunit of IL-23, appeared beneficial for treating GPP in a 52-week open-label study.[35]

Canakinumab and anakinra are monoclonal antibodies that target IL-1β, with canakinumab directly targeting it and anakinra blocking its effects by binding to its receptor.[7] Anakinra is particularly effective in rapidly reducing skin symptoms in pustular conditions, including GPP. However, anakinra has been associated with hypersensitivity reactions despite being the safest option initially due to its short half-life.[36]

In conclusion, prospective controlled and comparative trials are needed to further explore the relative efficacy and safety of biological agents and establish objective recommendations for managing this complex condition.[31]

Spesolimab

Spesolimab (BI 655130) is a humanized monoclonal antibody that selectively targets the IL-36R. Its unique mechanism of action involves acting as a high-affinity antagonist to the IL-36R. This enables it to effectively inhibit the IL-36R signaling pathway and suppress the recruitment of IL-1RAcP, which is responsible for the autoinflammatory response and physiological effects of IL-36 cytokines.[37] Spesolimab is currently undergoing investigation and has recently been approved by the FDA and EMA in September and December of 2022, respectively, for the treatment of GPP flares.

In addition, spesolimab is currently being studied for the treatment of neutrophilic skin diseases like palmoplantar pustulosis and hidradenitis suppurativa, as well as Netherton syndrome, Crohn's disease, and ulcerative colitis.[38-46]

Clinical Trials

During the proof-of-concept Phase I, open-label, proof-of-concept clinical trial (NCT 02978690), seven patients experiencing a GGP flare were administered a single intravenous dose of 10 mg/kg of spesolimab. Within one week of treatment, five patients (71.4%) achieved a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1. By week 4, all the patients achieved a GPPGA score of 0 or 1, sustained up to Week 20. However, 57.1% of patients displayed drug-related adverse effects during the trial, reported as mild or moderate in severity, and no serious adverse events were reported.[47] Notably, out of the seven patients, only three had a homozygous IL36RN mutation. This suggests that spesolimab effectively treats GPP, regardless of IL36RN mutations.[47] This study served as the foundation for the ongoing clinical advancement of spesolimab.

In a phase II, 12-week, double-blind clinical trial[48], 53 patients with a moderate to severe GPP flare were randomly assigned in a 2:1 ratio to receive a single 900 mg intravenous dose of spesolimab or placebo on day 1 (NCT03782792). Of these patients, 35 received open-label spesolimab, while 18 were given the placebo. Both groups were monitored for 12 weeks, with options for open-label spesolimab on day 8 based upon response (GPPGA score $\geq$ 2 and GPPGA pustulation subscore $\geq$ 2) and subsequent open-label spesolimab as a rescue treatment.

The study's primary endpoint was a GPPGA pustulation subscore of 0 at the end of week 1. GPPGA pustulation subscore ranges from clear to severe (0 - no visible pustules; 1- almost clear; 2- mild; 3- moderate; and 4- severe pustulation). Initially, 46% and 37% of individuals in the spesolimab group displayed a GGPGA pustulation subscore of 3 and subscore of 4, correspondingly, while 39% and 33% of participants in the placebo group exhibited identical scores. The results showed that, at the end of week 1, 54% of patients in the spesolimab group had a pustulation subscore of 0, compared to 6% in the placebo group ($p < 0.001$). The key secondary endpoint was a GPPGA total score of 0 or 1 at the end of week 1, which was achieved by 43% of patients in the spesolimab group, compared to 11% in the placebo group ($p = 0.02$).[14] Concerning the administration of Spesolimab at week 1, it is notable that out of the initially randomized cohort of 35 patients receiving spesolimab, a second infusion was administered to 34% of the participants. Among the 18 patients assigned to the placebo group, 83% required a second infusion. Consequently, the absence of a statistically significant placebo effect beyond the initial week of the trial becomes apparent, as the substantial requirement for additional infusion among the placebo recipients indicates insufficient symptom management by the placebo treatment alone, warranting the need for supplementary interventions.[14] Table I outlines the efficacy results mentioned above.

The patients initially assigned to spesolimab demonstrated promising results in achieving a GPPASI 75 by week 4, regardless of whether they received additional infusions of spesolimab. Among the patients who initially received placebo but later received an open-label dose of spesolimab, 40% achieved GPPASI 75 by week 4, indicating a significant improvement in symptoms compared to the baseline. Additionally, patients treated with spesolimab experienced positive outcomes in assessments such as the pain Visual Analog Scale (VAS), Psoriasis Symptom Score (PSS), and FACIT-Fatigue scores. These results suggest that spesolimab not only effectively reduced cutaneous manifestations but also led to a notable decrease in pain levels, improved psoriasis-related stress, and reduced self-reported fatigue compared to the baseline measurements.[14] These findings are summarized in Table II.

Pertaining to the mutation status, seven participants were identified to have IL36RN mutations, with five in the spesolimab group and two in the placebo group. Most patients did not exhibit CARD14 mutations, as 38 patients did not have this mutation, and AP1S3 mutations were absent in 42 patients. Spesolimab demonstrated a positive response in both groups, regardless of the presence or absence of mutations.[14]

Regarding safety, during the first week of treatment, adverse events were reported in 66% of patients in the spesolimab group and 56% in the placebo group. Among these adverse events,

pyrexia occurred in 6% of patients in the spesolimab group and 22% in the placebo group. While no serious adverse events were reported in the placebo group, 6% of patients in the spesolimab group had severe adverse events in the first week. Two patients who received spesolimab also experienced drug reactions with eosinophilia and systemic symptoms (DRESS), with one case being concurrent with drug-induced hepatic injury.[14] These symptoms were closely temporally associated with the reported GPP flares, occurring within two days of initiating spesolimab treatment in one case. Notably, both patients were simultaneously taking multiple medications, including cefuroxime, cefepime, spiramycin, and paracetamol, during the onset of DRESS. Considering the rapid manifestation of symptoms following spesolimab administration in one case, establishing a causal relationship between spesolimab and DRESS appears unlikely. Conversely, in the other case, the recurrence of similar cutaneous symptoms upon subsequent administration of spiramycin suggests spiramycin as a plausible alternative explanation. However, it is essential to acknowledge that systemic hypersensitivity reactions, including DRESS, are regarded as significant potential risks associated with spesolimab. Therefore, the potential impact of these reactions on individual health and the overall benefit-risk balance cannot be excluded.[14] Over the course of 12 weeks, 82% of patients who received spesolimab had an adverse event, and serious adverse events occurred in 12% of patients who received at least one dose of spesolimab, including two patients with DRESS. Antidrug antibodies were detected in 46% of patients who received spesolimab. Though adverse effects were more common in the spesolimab group, none required treatment discontinuation.

Infections were reported in 17% of the patients in the spesolimab group and 6% in the placebo group during the first week. Moreover, 47% reported infections in patients who received spesolimab at any time in the trial at week 12, including urinary tract infections, influenza, folliculitis, and otitis externa.[14] Table III provides an overview of reported adverse events.

Patients who demonstrated clinical improvement and did not experience any flares were deemed eligible to participate in the Effisayil ON, a 5-year open-label extension trial (NCT03886246).[49] The primary outcome of this study is to assess the incidence of newly arising adverse events during maintenance treatment with spesolimab up to week 252. The secondary key endpoints include the reoccurrence of a flare by GPPGA, and the duration required to achieve a GPPGA score of 0 or 1. Additionally, the trial will measure the change from baseline in PSS score by visit. Finally, the trial will also track the achievement of a GPPGA pustulation sub-score of 0, indicating no visible pustules, throughout the 252 weeks.[49]

A Phase II clinical trial is currently being conducted to evaluate the safety and efficacy of spesolimab (Effisayil 2) at three different doses compared to a placebo in preventing flares among

individuals with GPP (NCT04399837).[50] The study is designed to evaluate the potential benefit of spesolimab treatment in adolescents and adults with a history of GPP flare-ups but currently presenting with clear or nearly clear skin. Participants are randomized into one of four groups, with three groups receiving different doses of spesolimab and the fourth group receiving a placebo. The medication is administered via subcutaneous injections, and participants are monitored for 16 months with 15 visits to the study site. The primary endpoint is the time to the first GPP flare, measured up to 48 weeks. Secondary endpoints include evaluating the time until the first worsening of PSS and DLQI up to 48 weeks, persistent remission, the occurrence of at least one GPP flare-up up to 48 weeks, and treatment-emergent adverse events up to 64 weeks. [50]

A Phase III Expanded Access trial (NCT05200247) is underway in Japan to provide access to spesolimab for individuals diagnosed with GPP without other treatment options.[51] Similarly, an Expanded Access Program Phase III clinical trial (NCT05239039) is available in China for individuals diagnosed with GPP and no other treatment options.[52]

Conclusion

GPP is a rare and potentially life-threatening condition that requires prompt and effective treatment. Given the complexity of the disease, personalized care is of utmost importance when devising a treatment plan. However, currently, there are no established guidelines for managing GPP, and the available evidence for both non-biologic and biologic therapies remains limited, primarily relying on case studies and small, open-label, single-arm studies. This scarcity of evidence highlights the pressing need for novel therapeutic interventions.

Until recently, GPP treatment heavily relied on off-label utilization of drugs approved solely for plaque psoriasis. Research has established that GPP exhibits distinct characteristics compared to plaque psoriasis. This suggests that therapeutic demands differ. Nonetheless, the recent discovery of IL36RN mutations in a considerable proportion of individuals affected by GPP has unveiled a new therapeutic target. Unlike in plaque psoriasis, these mutations manifest as a distinctive occurrence in GPP, paving the way for innovative avenues in GPP treatment that target the IL-36 signaling pathway.[2] One such treatment is spesolimab, a biologic therapy that has shown promise in recent clinical trials.[7]

In an open-label proof-of-concept study involving seven individuals with GPP, a single intravenous infusion of spesolimab demonstrated promising early results, with all participants

experiencing rapid and positive responses and clearance of skin manifestations.[47] Additionally, a subsequent phase II study further demonstrated the efficacy of spesolimab in clearing GPP lesions within a week. Notably, this study encompassed a larger patient cohort of 53 individuals, providing a more robust analysis of spesolimab efficacy and safety. Moreover, mild to moderate adverse effects were more common in the spesolimab group, although none required treatment discontinuation.[14] The findings provide compelling evidence that individuals, regardless of IL36RN mutations, respond positively to spesolimab, indicating its effectiveness in treating GPP. The results of the spesolimab trials confirmed its potential as a promising therapeutic option for GPP, with early findings showcasing its ability to elicit rapid and positive responses, achieve clearance of skin manifestations, and address the unmet needs of patients with this challenging condition. Furthermore, spesolimab has received regulatory approvals for treating GPP flares in adults, making it a viable treatment option for patients who have not responded to other treatments. It was approved by the FDA in the United States of America in September 2022 and received conditional authorization by EMA in October 2022.

Further extensive investigations are necessary to establish evidence-based treatment guidelines for GPP. This includes a comprehensive evaluation of potential side effects, efficacy in sustaining remission, and comparative analysis against existing biological treatments. Moreover, due to safety concerns, the exclusion of specific special populations from clinical trials, including children, individuals over 75 years, pregnant women, and those with chronic illnesses, introduces uncertainties about using Spesolimab in these groups. Without specific trial data, it becomes difficult to establish the safety and efficacy in these populations. In this regard, real-world data will be crucial in offering further insights into the drug's performance and safety profile across diverse populations.

The heterogeneity of GPP also poses a challenge, as there is limited information available regarding its natural history and disease progression in published literature. This lack of comprehensive understanding raises concerns about potential misclassifications, which can delay treatment initiation and hinder the inclusion of appropriate patients in clinical trials. Therefore, further research and documentation of the disease course are needed to enhance accurate diagnosis and ensure timely intervention.

While spesolimab holds promise as a viable treatment option for GPP, more investigation is needed to assess its long-term safety and efficacy. In addition, developing targeted and effective treatments requires a thorough understanding of the disease and precise diagnosis. Therefore,

continued research is necessary to establish evidence-based treatment guidelines and enhance patient outcomes and quality of life.

Attachments

Table I

Phase 2 Clinical Trial: Efficacy at Week 1

Endpoint	Spesolimab (N= 35)	Placebo (N=18)
Primary endpoint: GPPGA pustulation subscore of 0 at week 1	54%	6%
Key secondary endpoint: GPPGA total score of 0 or 1 at week 1	43%	11%

Note. GPPGA- Generalized pustular psoriasis physician global assessment.

Table II

Phase 2 Clinical Trial: Efficacy at week 4- Secondary Endpoints

Treatment Group	GPPASI 75	Pain VAS	PSS	FACIT-Fatigue
Spesolimab (All) (N=35)	51%	-53.4 (-77.8, -20.2)	-7 (-10.0, -3.0	22.0 (1.0, 31.0)
Spesolimab randomized 900 mg single dose only (N=23)	70%	-63.1 (-79.8, -22.5)	-7 (-11.0, -2.0)	22.0 (3.0, 35.0)
Spesolimab randomized 900 mg single dose + open label day 8 spesolimab (N=12)	17%	-44.6 (-71.2, -17.3)	-6 (-7.0, -3.5)	15.0 (5.5, 28.5)
Placebo randomized + open-label day 8 spesolimab (N=15)	40%	-54.3 (-79.0, 33.3)	-5 (-9.0, -2.0)	16.0

Note. GPPASI 75- 75% or greater improvement in GPPASI total score. Pain VAS- Change from baseline in pain VAS score. PSS- Change from baseline in PSS score. FACIT-Fatigue- Change from baseline in FACIT-Fatigue score. All these secondary endpoints were evaluated at week 4.

Table III

Phase 2 Clinical Trial Safety: Adverse Events at Week 1 and Week 12

	Spesolimab (N=35)	Placebo (N=18)	Spesolimab (N=51)
	Week 1		**Week 12**
Any adverse event	66%	56%	82%
Severe adverse event: RCTC grade 3 or 4	2%	6%	10%
Serious adverse events	6%	0%	12%
DRESS	3%	0%	4%
Drug-induced hepatic injury	3%	0%	2%
Worsening of chronic plaque psoriasis	0%	0%	2%
Infections	17%	6%	47%
Adverse event leading to discontinuation	0%	0%	0%
Common adverse events			
Pyrexia*	6%	22%	10%
Dizziness	0%	11%	0%
Mortality	0%	0%	0%

Note. The week 12 Spesolimab group comprises 51 patients from the spesolimab group, who received up to three doses of spesolimab, and the placebo group, who received open-label spesolimab on or after day 8. All adverse events occurring from the initial administration of spesolimab to the residual-effect period following the last dose of spesolimab are included in the analysis.

*All Pyrexia events occurred in the context of the underlying GPP flare, but pyrexia cannot be ruled out

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