U.PORTO

MESTRADO INTEGRADO EM MEDICINA

New and emerging treatments for Generalized Pustular Psoriasis

João Pedro Pinheiro Vilaça

M

2024

New and emerging treatments for Generalized Pustular Psoriasis

Artigo de Revisão Narrativa

Dissertação de Mestrado Integrado em Medicina

Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Estudante:

João Pedro Pinheiro Vilaça

Mestrado Integrado em Medicina (Número mecanográfico 201807708)

Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Endereço de correio eletrónico: up201807708@edu.icbas.up.pt

Orientador:

Professor Doutor Tiago da Costa Ferreira Torres

Assistente Graduado do Serviço de Dermatologia do Centro Hospitalar Universitário de Santo António

Professor Associado do Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Coorientadora:

Dra. Ana Maria Ferreira Lé

Interna de Formação Específica de Dermatologia do Serviço de Dermatologia do Centro Hospitalar Universitário de Santo António

abril de 2024

Estudante:

_____

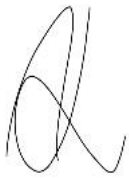
(João Pedro Pinheiro Vilaça)

Orientador:

_____

(Professor Doutor Tiago da Costa Ferreira Torres)

Coorientadora:



_____

(Doutora Ana Maria Ferreira Lé)

Dedication

Aos meus pais, cujo constante apoio durante todos estes anos me permitiu chegar aqui.

Acknowledgments

Ao meu orientador, Prof. Doutor Tiago Torres, por prontamente ter aceitado este desafio e se ter mostrado sempre disponível e interessado. Por toda a ajuda que me deu e por me ter incitado a ir mais longe, durante a realização desta dissertação.

Resumo

Introdução: A Psoríase Pustulosa Generalizada é um subtipo de psoríase raro e grave que afeta pessoas em todo o mundo, tendo um impacto significativo na sua qualidade de vida. Até recentemente, não existiam agentes terapêuticos específicos para o tratamento desta doença, pelo que se utilizavam tratamentos convencionais, que não eram eficazes em todos os casos e apresentavam efeitos secundários. Como tal, alternativas mais eficazes e seguras são necessárias. Os fármacos direcionados para a via da IL-36 já se encontram em ensaios de fase 3 e 4 para o tratamento desta doença e parecem ser uma solução promissora para este problema.

Objetivos: Esta revisão visa explorar e sumarizar a literatura científica atual acerca dos tratamentos mais recentemente desenvolvidos para a Psoríase Pustulosa Generalizada.

Metodologia: Procedeu-se a uma investigação bibliográfica recorrendo a duas bases de dados: PubMed e ClinicalTrials.gov. Foram incluídos artigos escritos em inglês, publicados entre janeiro de 2018 e janeiro de 2024, tendo sido posteriormente selecionados com base nos seus títulos, resumos e restante conteúdo do texto.

Discussão: A patofisiologia da Psoríase Pustulosa Generalizada é complexa e não se encontra totalmente compreendida, mostrando alguma sobreposição com a patogénese da psoríase em placas. No entanto, na PPG o sistema imune inato parece ter um papel mais significativo, com a via da IL-36 a ser fundamental. O tratamento atual da PPG ainda segue as guidelines para o tratamento da psoríase em placas, consistindo no uso de retinoides, metotrexato e até biológicos, que, embora eficazes em alguns casos, não são adequados para a PPG. O spesolimab e o imsidolimab, dois agentes terapêuticos recentemente desenvolvidos, têm como alvo a via inflamatória da IL-36, ligando-se ao IL-36R. Ambos já foram submetidos a ensaios de fase 1 e 2, nos quais a sua segurança e eficácia no tratamento desta doença foram avaliadas, apresentando resultados bastante promissores.

Conclusões: Os inibidores da IL-36 demonstraram uma grande eficácia e um bom perfil de segurança no tratamento de doentes com PPG, mostrando o seu potencial para se tornarem a primeira escolha para o tratamento desta condição. Mais estudos são necessários para aferir o seu papel em grupos específicos de pacientes e avaliar a sua segurança a longo prazo.

Palavras-chave: “Generalized Pustular Psoriasis”, “Spesolimab”, “Imsidolimab”, “IL36 Inhibitors”, “Treatment”

Abstract

Introduction: Generalized Pustular Psoriasis is a rare and severe subtype of psoriasis that affects people worldwide, having a significant impact on their quality of life. Until recently, no specific therapeutic agents for the management of this disease were available, so conventional treatments were used, which weren't effective in all cases and bear side effects. As so, more effective and safe options are required. Agents targeting the IL-36 pathway are already in phase 3 and 4 trials for the treatment of GPP and seem to be a promising solution for this matter.

Objectives: This review aims to explore and summarize the current scientific literature on the most recently developed treatments for Generalized Pustular Psoriasis.

Methods: A bibliographic search was conducted using two databases: PubMed and ClinicalTrial.gov. Articles in English dating from January 2018 to January 2024 were included and then selected based on their titles, abstracts, and full-text articles.

Discussion: The pathophysiology of Generalized Pustular Psoriasis is complex and not fully understood, showing some overlap with the pathogenesis of Plaque Psoriasis. However, in GPP the innate immune system seems to have a more significant role, with the IL-36 pathway being fundamental. The current treatment for GPP still follows the guidelines for the treatment of plaque psoriasis, consisting of retinoids, methotrexate and even biologics, which, although effective in some cases, aren't properly suited for GPP. Spesolimab and imsidolimab, two recently developed therapeutic agents, target the IL-36 inflammatory pathway, by binding to the IL-36R. Both have already undergone phase 1 and 2 trials, where their safety and efficacy were evaluated for the management of this disease, showing very promising results.

Conclusion: IL-36 inhibitors demonstrated great efficacy and a good safety profile in the management of patients with GPP, showing their potential to become the top choice for the treatment of this condition. Further studies are needed to assess their role in specific patient groups and to evaluate their long-term safety.

Keywords: "Generalized Pustular Psoriasis", "Spesolimab", "Imsidolimab", "IL36 Inhibitors", "Treatment"

List of Abbreviations

AEs – Adverse Effects

CGI – Clinical Global Impression

ERASPEN – European Rare and Severe Psoriasis Expert Network

GPP – Generalized Pustular Psoriasis

GPPGA – Generalized Pustular Psoriasis Global Assessment

IL-1 – Interleukin-1

IL-1R – Interleukin-1 Receptor

IL-17 – Interleukin-17

IL-17RA – Interleukin-17 Receptor A

IL-23 – Interleukin-23

IL-36 – Interleukin-36

IL-36Ra – Interleukin-36 Receptor Antagonist

IL-36R – Interleukin-36 Receptor

INF-β – Interferon beta

IV - Intravenous

MPO – Myeloperoxidase

NF-κB – Nuclear Factor kappa-light-chain-enhancer of activated B cells

TNF – Tumour Necrosis Factor

Index

Acknowledgments i
Resumo ii
Abstract iii
List of Abbreviations iv
Index v
List of Tables vi
List of Figures vii
Introduction 1
Objectives 3
Methods 3
Discussion 4
1. Pathophysiology of GPP 4
2. Current treatment of GPP 5
3. New treatments for GPP 7
3.1 Spesolimab 7
3.2 Imsidolimab 9
3.3 Other therapeutic agents 10
Conclusion 11
Attachments 12
References 17

List of Tables

Table I – Current treatments available for GPP ……12

Table II – Efficacy and safety data regarding the IL-36 inhibitors ……13

Table III – Ongoing/Planned Clinical Trials for GPP's treatments ……15

List of Figures

Figure 1 – The IL-36 signalling pathway ……16

Introduction

Generalized pustular psoriasis is a rare and severe auto-inflammatory skin disease characterized by the sudden and diffuse appearance of superficial sterile pustules with erythema. It has a life-threatening potential due to its multisystemic nature and it may or not be associated with a past history of plaque psoriasis.[1,2] This disease affects both men and women and it is more common in adults than in children. Its prevalence varies with ethnicity, being more frequent in Asia and less in the Caucasian population.[1,3]

Regarding its clinical features, GPP exhibits a broad spectrum of variability, as it can present as a relapsing condition marked by recurrent flares without pustulation between them, or, alternatively, as a chronic disease featuring persistent pustular eruptions with exacerbations.[4] It is usually characterized by the bursting of sterile pustules through painful, erythematous skin, spreading and recruiting previously unaffected skin. In some cases, it might lead to erythroderma. Patients are visibly ill presenting high-grade fever, malaise, and arthralgia.[5,6] Acute infections, menstruation, and rapid withdrawal of systemic corticosteroids have been proved to trigger acute flares.[4]

Extracutaneous manifestations, such as cholangitis and acute renal failure, are a result of its multisystemic nature and can bear serious complications.[5,6] In fact, this condition presents a heavy burden of morbidity, and potentially mortality, having a significant impact in the patients' quality of life.[7]

Since it was described for the first time in 1910 by von Zumbusch, finding the adequate treatment for this disease has been a real challenge.[1,5] Its rarity, making clinical trials very scarce and difficult to manage, and the necessity of treatment for both flare control and prevention, are the main obstacles.[8] Until very recently, no specific therapeutic agents nor guidelines where available for the treatment of GPP, commonly following the standard treatment of plaque psoriasis.[1] So it consisted in conventional options such as retinoids and methotrexate, and while they might be effective in favourable courses of GPP, they bear significant side effects and seem to be insufficient in more severe cases.[3,5,9]

With the discovery of new biologic therapies, particularly those approved for the treatment of psoriasis, new therapeutic agents started to be considered for the treatment of GPP, providing new and more adequate options.[9] These new agents targeted cytokines involved in the immune pathways of psoriasis (such as TNF, IL-17 or IL-23), which at some points overlaps the GPP pathway, and showed good effectiveness in people with this disease. However, they must be used carefully, as, paradoxically, they have been reported to induce pustular disease in patients being treated for other conditions.[8,9]

The discovering of the importance of the IL-36 pathway in the pathogenesis of GPP led to the development of the first specific therapeutic agent for GPP, spesolimab, an IL-36 receptor antagonist, that was recently approved in Japan, the US, and the EU, after demonstrating very positive results. Other similar therapeutic agents are also being evaluated as this pathway seems to be the main focus regarding the development of GPP therapies.[7,8,10]

Objectives

This review aims to explore and summarize the current scientific literature on the most recently developed treatments for Generalized Pustular Psoriasis.

Methods

To produce this review, a bibliographic search was performed using the database PubMed. It included original and review articles dating from January 2018 to January 2024, written only in English.

The following terms were searched in association: “Generalized Pustular Psoriasis”, “Spesolimab”, “Imsidolimab”, “IL36 inhibitors” and “Treatment”.

The articles were selected based on a careful analysis of their abstract and, afterwards, of their full text.

A total of 38 articles were consulted, and all of them are referenced at the end of this review (see References). Additional data regarding the clinical trials was obtained by consulting the website clinicaltrials.gov.

Discussion

1. Pathophysiology of GPP

Currently, the understanding of the pathophysiological mechanisms of GPP remains incomplete. According to the ERASPEN definition, although it shares substantial cytokine pathway overlap with plaque psoriasis, its genetics and pathophysiology diverge significantly.[9–11]

Plaque psoriasis is an autoimmune condition, having both innate and adaptive immunopathogenic responses. GPP, in turn, is an autoinflammatory condition, resulting essentially from an innate immune inflammation.[11] Some experts even consider it an example of an autoinflammatory keratinization disease.[12] Its histopathology is characterized by the epidermal infiltration of neutrophils and mononuclear cells, leading to the emergence of clinically evident, sterile pustules.[13]

The current scientific evidence supports that the IL-36 axis plays a fundamental role in the innate immune system hyperactivation, verified in GPP.[14]

IL-36 cytokines are part of the IL-1 superfamily and consist of three pro-inflammatory agonists (IL-36α, IL-36β, IL-36γ) and the IL-36 receptor antagonist. These are expressed by different types of cells, such as keratinocytes, epithelial cells and immune cells, also acting upon them in an autocrine and paracrine way.[11,14] They are released as precursors and, to become bioactive, they need to be proteolytically cleaved by specific proteases, especially by neutrophil-derived proteases.[14,15] The three proinflammatory agonists activate nuclear factor-κB and mitogen activated protein kinase, by binding to the IL-36 receptor. Consequently, downstream pathways are triggered, leading to the development of pro-inflammatory cytokines, chemokines, and costimulatory molecules. This is usually regulated by IL-36Ra, a cytokine that competes with IL-36 agonists for binding to the IL-36R, and so preventing the activation of those pathways (Fig. 1).[14]

When IL-36 agonists are excessively expressed or when the function of IL-36Ra is impaired, it triggers a positive feedback loop, leading to uncontrolled signalling and surplus production of inflammatory cytokines. Consequently, chemokines such as CXCL1 and CXCL8, known for their pro-inflammatory properties, are induced, resulting in the formation of a chemokine gradient. This gradient attracts numerous neutrophils to the epidermis, culminating in the development of spongiform pustules of Kogoj and the accumulation of neutrophils within the epidermal layer. This manifestation, characterized by the presence of “lakes of pus”, is a hallmark feature frequently observed in patients affected by GPP.[11]

Further data demonstrated that skin biopsy samples of individuals with GPP had higher levels of TNF, IL-1, IL-17, and IL-36 than healthy controls. When compared to individuals with

plaque psoriasis, the levels of IL-1 and IL-36 where higher, but the ones of IL-17A and interferon-γ were lower.[11]

In a significant amount of GPP cases, mutations of the *IL36RN* gene have been identified, indicating a correlation with this condition. This gene is responsible for encoding the anti-inflammatory cytokine IL-36Ra.[12]

Other five genes that play a role in the innate immune and autoinflammatory response have been associated to the development of GPP (*CARD14*, *AP1S3*, *SERPINA3*, *MPO*, *TNIP1*). *CARD14* mediates NF-κB transduction, contributing to inflammatory signalling. *AP1S3* loss of function results in autoinflammation by decreasing INF-β expression and elevating IL-1 levels. *SERPINA3* is responsible for inhibiting a neutrophil protease, so its loss of function stimulates IL-36 pro-inflammatory activity and neutrophil activation. *MPO* loss of function leads to MPO deficiency, fostering the activation of IL-36 signalling by controlling the activity of serine proteases, which, in turn, causes the accumulation and activation of neutrophils. *TNIP1* plays a role in restraining NF-κB signalling, yet its gene locus exhibits only a limited association with GPP.[15]

2. Current treatment of GPP

At the moment, there are no well-established guidelines for the treatment of GPP, due to the lack of evidence, the rarity of the disease and the spontaneously remitting pattern of its flares.[13] In fact, for years, the management of this condition has followed the recommendations established for the treatment of plaque psoriasis.[15]

The most used therapeutic agents for the management of GPP are still the non-biological ones, especially retinoids, cyclosporine, and methotrexate. These are considered first line treatments.[16]

Retinoids, such as acitretin, are one of the oldest systemic agents used to treat GPP. Even though many experts consider them a successful treatment modality, the evidence supporting its use is limited and they must be used cautiously, given their teratogenicity and their predisposition to hepatotoxicity, as well as other major side effects.[16–18]

Cyclosporine is a calcineurin inhibitor also used in patients with GPP. Although it is effective and useful, its evidence is limited to case reports and studies with few subjects. Since its chronic use has been associated with the development of hypertension and renal dysfunction, it is not recommended as a long-term agent, being more adequate for the control of acute flares.[16–18]

Methotrexate is a dihydrofolate reductase inhibitor of frequent use in inflammatory conditions that is recommended for the treatment of GPP with some efficacy. Nevertheless,

regarding its flares, there aren't clinical studies available that can prove its usefulness. Moreover, methotrexate has an unfavourable slow onset of action, as well as a safety profile that may not be indicated in some patients, due to its liver toxicity.[16,17]

There are multiple other non-biologic agents, such as mycophenolate mofetil, hydroxyurea, apremilast, colchicine, and corticosteroids that have to some extent been used in patients with GPP, with very limited evidence.[10,16]

Granulocyte and monocyte adsorption apheresis has shown promising results in skin diseases associated to activated neutrophils, being also an option for GPP. However, its evidence consists of a few case reports.[16,19]

Over the last years, because of a better understanding of the pathophysiology of GPP, there has been noticed a shift in its treatment towards a greater use of biologics. These have shown a high treatment efficacy, in some cases even having less side effects, given their specificity of action.[7,16,17]

TNF is an important cytokine in the control and amplification of inflammatory pathways, already in use as a molecular target for the treatment of plaque psoriasis.[16,17] Infliximab, etanercept, adalimumab, and certolizumab are known anti-TNF agents, which have been shown to be effective and safe on the management of GPP by case reports and clinical trials conducted with a small sample of patients. Even so, in a few cases paradoxical GPP developed during treatment with adalimumab, infliximab, and certolizumab.[18,20,21]

IL-17, a cytokine produced by T-helper 17 cells, contributes to the onset of psoriasis, by triggering the activation of keratinocytes, attracting neutrophils, and promoting neovascularization. IL-17A is the most prominent member of this cytokine family.[16,22] Brodalumab, secukinumab and ixekizumab target the IL-17 pathway, the first by binding to the IL-17RA and the last two by inhibiting IL-17A. Small clinical trials have been conducted with these therapeutic agents, showing good effectiveness on the treatment of GPP, as well as a rapid onset of action and an excellent safety profile.[22–24]

IL-23 plays a crucial role in the development of plaque psoriasis by stimulating Th17 cells, fostering the progression of the disease, and activating keratinocytes.[17] The biologics used to target this cytokine are guselkumab, risankizumab and ustekinumab (in this case also targeting IL-12). Guselkumab and risankizumab data on their use for GPP is scarce, with a small clinical trial and some case reports proving their clinical efficacy and safety.[16,20,25,26] Ustekinumab has not been assessed in clinical trials for patients with GPP, only being considered effective in a few case reports.[7,16,20]

IL-1 is highly involved in the autoinflammation associated with GPP.[17] Canakinumab, gevokizumab and anakinra are the available therapeutic options for addressing this pathway and

evidence of their use in patients with this condition is limited to a few case reports that demonstrated encouraging results. However clinical trials are needed to confirm its efficacy and safety as a viable therapy.[16,18]

All these treatments are summarized in Table I.

3. New treatments for GPP

As mentioned before, the discovery of the central role of the IL-36 pathway in the pathophysiology of GPP led to the development of therapeutic agents targeting this immune pathway, such as spesolimab and imsidolimab.[10]

3.1 Spesolimab

Spesolimab is the first agent developed to target the IL-36 proinflammatory pathway, consisting of a humanized monoclonal immunoglobulin G1 antibody, that targets the IL-36R. By binding to this receptor, it blocks it, impeding the IL-36 ligands of activating it, and inhibiting the inflammatory response.[27,28] Currently, it has already been approved by the FDA, EMA and Japan for the treatment of GPP flares. Besides GPP, it is also being studied for use in other auto immune conditions, such as ulcerative colitis, Crohn's disease, palmoplantar pustulosis and hidradenitis suppurativa.[28]

It all started with a phase I clinical trial involving 7 patients with an ongoing GPP flare, who were given a single IV dose of spesolimab, aiming to investigate the safety and efficacy of this agent. Initially, they all had a GPPGA score of 3 (moderate disease), and by week 1 five of the patients had already reached a score of 0 or 1 (clear or almost clear skin). By week 4, all of them had achieved the same results, and maintained them until the 20th week. None of the adverse effects were considered serious.[29,30]

Effisayil 1, a phase II, multicentre, randomized, double-blind, placebo-controlled clinical trial, involving 53 patients with a GPP flare was conducted afterwards. The patients were randomly assigned in a 2:1 ratio to the spesolimab group, where they were given a single 900 mg IV dose of spesolimab, or to the placebo group. After week 1, it was possible for patients of both groups to receive a dose of spesolimab on day 8, after that as a rescue medication, or both.[31]

To assess spesolimab's efficacy on the treatment of GPP, the investigators proposed to evaluate the patients' GPPGA pustulation subscore and GPPGA total score, being the primary outcome a GPPGA pustulation subscore of 0 at week 1 and the key secondary outcome a GPPGA total score of 0 or 1 at week 1. Both scores range from 0 to 4, being the higher punctuation associated with the more severe disease.[31]

At the beginning of the trial, all the patients had a GPPGA pustulation subscore of at least 2 and a GPPGA total score of at least 3 (moderate-to-severe intensity). By the end of week 1, 54% of the spesolimab group patients evidenced a GPPGA pustulation subscore of 0 and 43% of the same group had a GPPGA total score of 0 or 1, showing a remarkably higher response than the placebo group, where only 6% and 11% had shown the same results, respectively.[31]

At day 8, 83% of the placebo randomized patients received a rescue dose of spesolimab, while only 34% of the patients who had already been administered spesolimab needed a second dose, making it impossible to compare the effects of spesolimab and of the placebo any further. Regarding the placebo assigned patients who received a spesolimab rescue dose at day 8, 73% had already reached a GPPGA pustulation subscore of 1 by week 2 and 53% had reached a GPPGA total score of 0 or 1.[30,31]

Very recently, Effisayil 2, another multicentre, randomised, placebo-controlled, phase 2b trial following 123 patients, with a history of frequent flares, and a GPPGA score of 0 or 1 at screening, published its results on evaluating the efficacy and safety of this drug for GPP flare prevention. These patients were randomly assigned on a 1:1:1:1 ratio for a subcutaneous placebo group, a subcutaneous low dose spesolimab group (300 mg loading dose followed by 150 mg every 12 weeks), a subcutaneous medium dose spesolimab group (600 mg loading dose followed by 300 mg every 12 weeks), and a subcutaneous high dose spesolimab group (600 mg loading dose followed by 300 mg every 4 weeks), being followed for over 48 weeks.[32]

To assess spesolimab's efficacy on preventing GPP flares, as a maintenance treatment, this clinical trial analysed the patients' time to develop the first flare by week 48, attempting to demonstrate a non-flat dose-response curve. If so was achievable, then the secondary objective would be to evaluate the possible superiority of high-dose or medium-dose spesolimab over placebo, by also analysing the time to develop the first flare by week 48 and the occurrence, or not, of at least one GPP flare by the same time.[32]

By week 48 of the trial, 35 patients of the original 123 had GPP flares: 16 in the placebo group (52%), 7 in the low-dose group (23%), 9 in the medium-dose group (29%) and 3 in the high-dose group (10%). It was then possible to demonstrate a non-flat dose-response relationship with statistical significance, comparing spesolimab to the placebo. It was also statistically proved that, when in comparison to the placebo, high-dose spesolimab improved the time to GPP flare and reduced the risk of its occurrence. However, the same didn't happen with lower doses of spesolimab.[32]

Patients who completed both these trials, were then eligible to participate in Effisayil ON trial, a long-term extension trial, where the long-term safety and efficacy of spesolimab in patients with GPP is being assessed. Up to date, there aren't still any results published.[33]

In Japan and China, phase III trials have already been conducted but no results have been published yet.[34,35]

Regarding safety, GPP patients showed good tolerance to spesolimab. In the Effisayil 1 trial, by week 12, 82% of the patients who received at least one dose of spesolimab had experienced some kind of adverse event, but only 12% had had a serious one. In the Effisayil 2 trial, it was evidenced that a resembling proportion of both patients receiving spesolimab and placebo experienced adverse events, most of which weren't even serious or severe. The incidence of these AEs was also proved not to follow a dose-dependent pattern.[30–32]

3.2 Imsidolimab

More recently, another therapeutic agent has also been designed to treat GPP by targeting the IL-36 pathway. Imsidolimab is, in fact, a humanized IgG4 monoclonal antibody with high affinity to IL-36R, binding to it and inhibiting IL-36 activity.[10,36,37]

To assess imsidolimab's clinical efficacy, tolerability, and safety the GALLOP trial was designed. It consisted in a single-arm, open-label, multiple-dose study, where a total of 8 patients with relevant GPP were enrolled. They received a single 750 mg IV dose of imsidolimab on the first day of the trial, and then three subcutaneous doses of 100 mg of the same drug, on days 29, 57 and 85.[37]

As a primary endpoint it would evaluate the number of patients clinically responding to the treatment at weeks 4 and 16 after the first administration, using the CGI scale, where clinical response was positive when "very much improved", "much improved" or "minimally improved" scores were reached.[37]

By weeks 4 and 16, it was evident that 75% of the patients had achieved clinical response, 50% even achieving the "very much improved" score, and so imsidolimab seemed to act effectively, rapidly improving the patients' GPP status.[37]

As a secondary outcome, it was also noted that the patients quality of life improved.[37]

Regarding its safety and tolerability, 75% of the patients reported at least one adverse effect related to imsidolimab, 2 of them experiencing severe ones. In general, the doses given looked adequate and tolerable.[37]

All data of the prementioned spesolimab's and imsidolimab's clinical trials is outlined in Table II.

3.3 Other therapeutic agents

The search for new and more adequate treatments for this condition is far from over and, currently, a new anti-IL36R drug, HB0034, has already been developed and is being tested for use in patients with GPP.[38]

Information on ongoing clinical trials with this new drug, as well as more extensive ones being conducted with spesolimab and imsidolimab is summarised in Table III.

Conclusion

Although rare, GPP is a very incapacitating condition, potentially life threatening, that can affect people from all over the globe, independently of their age, gender, or ethnicity. For years, its treatment has followed the plaque psoriasis' guidelines, with biological and non-biological approaches, as very few knowledge was available regarding this specific condition. Indeed, it works, but the results are not optimal, especially in more severe cases.

Recently, it was discovered that IL-36 plays a crucial role in the pathogenesis of GPP, being responsible for triggering the inflammatory cascade that leads to this condition. Spesolimab and imsidolimab, IL-36 inhibitors, were then developed to specifically treat this condition and, after undergoing some clinical trials, they have been proven to be serious "game-changers", having already been approved for the treatment of GPP flares.

In summary, these IL-36 inhibitors have shown promising results, changing the paradigm in the treatment of GPP. However, further trials are required, as more data is needed to confirm the efficacy and the safety profile of these drugs, to assess their role in specific subpopulations, and to check if they could be an effective long-term treatment of this disease.

Attachments

Table I – Current treatments available for GPP

Non-biologic	Biologic
Retinoids	Anti – TNF
Cyclosporine	Infliximab
Methotrexate	Etanercept
Granulocyte and monocyte apheresis	Adalimumab
Mycophenolate Mofetil	Certolizumab
Hydroxyurea	Anti – IL17
Apremilast	Brodalumab
Colchicine	Secukinumab
Corticosteroids	Ixekizumab
	Anti – IL23
	Guselkumab
	Risankizumab
	Ustekinumab
	Anti – IL1
	Canakinumab
	Gevokizumab
	Anakinra

Table II – Efficacy and safety data regarding the IL-36 inhibitors

Trial	Study design	Endpoints	Main results	Main AEs
Spesolimab Phase I[29,30]	Single arm, open label - 7 participants - Follow up 20 weeks SD of spesolimab 10 mg/kg IV at baseline	Primary: - Safety and tolerability (% AE) Secondary: - GPPGA 0/1 at week 2	GPPGA 0/1 in 71% of patients by week 1 and in 100% of patients by week 4, sustained up to week 20	Mild to moderate eosinophilia Infections Vomiting Pain Infusion-related reactions No severe AE
Spesolimab Phase II Effisayil 1[30,31]	Randomized, PC, DB - 53 participants - 12 weeks Randomized 2:1 - Spesolimab 900 mg SD - Placebo	Primary: - GPPGA Pustulation Subscore 0 at week 1 Secondary: - GPPGA score of 0 or 1	GPPGA Pustulation subscore of 0 at week 1 in 54% of the spesolimab group and 6% of the placebo group (p<0,001) GPPGA total 0/1 in 43% of the spesolimab group and 11% of the placebo group (p<0,02)	Infections Systemic symptoms Antidrug antibodies
Spesolimab Phase IIb Effisayil 2[30,32]	Randomized, PC, DB - 123 participants - 48 weeks Randomized 1:1:1:1 - Spesolimab LD 600 mg, followed by maintenance 300 mg q4w	Primary: - Time to first GPP flare Secondary: - Occurrence of at least 1 GPP flare - GPPGA score of 0 or 1 up to week 48	Non-flat dose-response relationship for the different spesolimab groups when compared to the placebo Compared to the placebo, high-dose spesolimab showed statistically significant superiority	Infections Injection-site erythema Arthralgias Spesolimab and placebo groups with similar incidence of AEs Spesolimab groups with 10% of serious AEs and 3% in

	- Spesolimab LD 600 mg, followed by maintenance 300 mg q12w - Spesolimab LD 300 mg, followed by maintenance 150 mg q12w - Placebo		on time to GPP (p=0,0005)	placebo group
Imsidolimab Phase II Gallop[37]	Single arm, open label - 8 participants - 24 weeks SD of imsidolimab 750 mg IV at baseline, followed by maintenance 100 mg SC dose monthly	<u>Primary:</u> - Clinical response at weeks 4 and 16, evaluated using the CGI scale <u>Secondary:</u> - Change in DLQI from baseline	75% of the patients achieved clinical response by weeks 4 and 16, as evaluated by the CGI scale DLQI had reduced 4.1 points by week 4 and 6.1 points by week 16	Blood and lymphatic system disorders GI disorders Infections Respiratory disorders Skin and subcutaneous disorders 2 experienced SAEs, resolved without sequelae

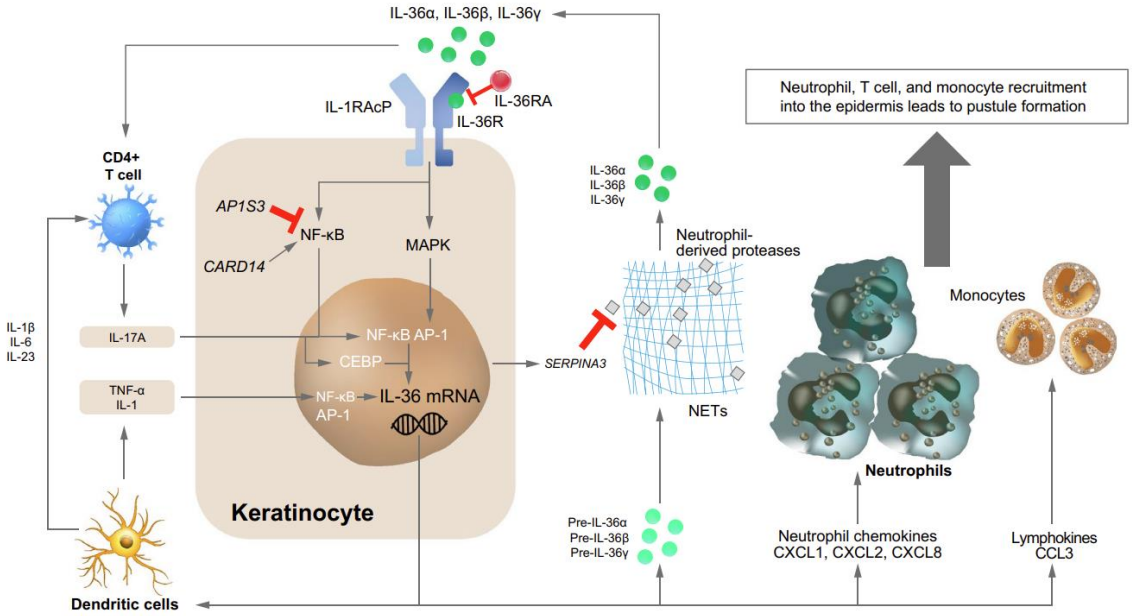
AE – Adverse Event; DB – Double Blind; DLQI – Dermatology Quality of life Index; GI – Gastrointestinal; GPP – Generalized Pustular Psoriasis; GPPGA – Generalized Pustular Psoriasis Physician Global Assessment; IV – Intravenous; LD – Loading Dose; PC – Placebo Controlled; q4w – every 4 weeks; q12w – every 12 weeks; SAE – Serious Adverse Event; SC – Subcutaneous; SD – Single Dose

Table III – Ongoing/Planned Clinical Trials for GPP's treatments

Drug Name	Clinical Trial	Phase	Status
Spesolimab	NCT03886246	2	Active, non recruiting
	NCT05239039	3	Completed
	NCT05200247	3	Completed
	NCT06013969	4	Recruiting
	NCT05670821	4	Recruiting
Imsidolimab	NCT05366855	3	Active, non recruiting
	NCT05352893	3	Completed
HB0034	NCT05512598	1	Completed
	NCT06231381	2	Not yet recruiting

Figure 1

The IL-36 signalling pathway.



Keratinocytes secrete IL-36 cytokines as precursors. These are cleaved, becoming biologically active and bind to IL-36 on the surface of keratinocytes, inducing an inflammatory cascade that promotes IL-36 expression. IL-36 cytokines also induce the expression of numerous cytokines, neutrophilic chemokines, and lymphokines, further propagating this pro inflammatory cycle. *AP-1* activating protein-1, *CARD* caspase recruitment domain, *CCL* chemokine (C–C motif) ligand, *CXCL* chemokine (C–X–C motif) ligand, *IL* interleukin, *MAPK* mitogen-activated protein kinase, *mRNA* messenger RNA, *NET* neutrophil extracellular trap, *NFκB* nuclear factor kappa-light-chain-enhancer of activated B cells, *R receptor* RA receptor antagonist, *RAcP* receptor accessory protein, *TNF* tumor necrosis factor. Image retrieved from Marrakchi S, Puig L. Pathophysiology of Generalized Pustular Psoriasis. *Am J Clinic Dermatol.* 2022;23(Suppl 1):13-19. Licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

References

1. Gooderham MJ, Van Voorhees AS, Lebwohl MG. An update on generalized pustular psoriasis. *Expert Rev Clin Immunol*. 2019;15(9):907-919. doi:10.1080/1744666X.2019.1648209

2. Zhou J, Luo Q, Cheng Y, Wen X, Liu J. An update on genetic basis of generalized pustular psoriasis (Review). *Int J Mol Med*. 2021;47(6):118. doi:10.3892/ijmm.2021.4951

3. Boehner A, Navarini AA, Eyerich K. Generalized pustular psoriasis - a model disease for specific targeted immunotherapy, systematic review. *Exp Dermatol*. 2018;27(10):1067-1077. doi:10.1111/exd.13699

4. Rivera-Díaz R, Daudén E, Carrascosa JM, Cueva P de la, Puig L. Generalized Pustular Psoriasis: A Review on Clinical Characteristics, Diagnosis, and Treatment. *Dermatol Ther*. 2023;13(3):673-688. doi:10.1007/s13555-022-00881-0

5. Hoegler KM, John AM, Handler MZ, Schwartz RA. Generalized pustular psoriasis: a review and update on treatment. *J Eur Acad Dermatol Venereol JEADV*. 2018;32(10):1645-1651. doi:10.1111/jdv.14949

6. Vasudevan B, Das P, Bhatt S. Pustular psoriasis: A distinct aetiopathogenic and clinical entity. *Indian J Dermatol Venereol Leprol*. Published online May 28, 2023:1-11. doi:10.25259/IJDVL_542_2022

7. Komine M, Morita A. Generalized pustular psoriasis: current management status and unmet medical needs in Japan. *Expert Rev Clin Immunol*. 2021;17(9):1015-1027. doi:10.1080/1744666X.2021.1961580

8. Bachelez H, Barker J, Burden AD, Navarini AA, Krueger JG. Generalized pustular psoriasis is a disease distinct from psoriasis vulgaris: evidence and expert opinion. *Expert Rev Clin Immunol*. 2022;18(10):1033-1047. doi:10.1080/1744666X.2022.2116003

9. Reynolds KA, Pithadia DJ, Lee EB, Clarey D, Liao W, Wu JJ. Generalized Pustular Psoriasis: A Review of the Pathophysiology, Clinical Manifestations, Diagnosis, and Treatment. *Cutis*. 2022;110(2 Suppl):19-25. doi:10.12788/cutis.0579

10. Kodali N, Blanchard I, Kunamneni S, Lebwohl MG. Current management of generalized pustular psoriasis. *Exp Dermatol*. 2023;32(8):1204-1218. doi:10.1111/exd.14765

11. Marrakchi S, Puig L. Pathophysiology of Generalized Pustular Psoriasis. *Am J Clin Dermatol*. 2022;23(Suppl 1):13-19. doi:10.1007/s40257-021-00655-y

12. Akiyama M. Pustular psoriasis as an autoinflammatory keratinization disease (AiKD): Genetic predisposing factors and promising therapeutic targets. *J Dermatol Sci*. 2022;105(1):11-17. doi:10.1016/j.jdermsci.2021.11.009

13. Menter A, Van Voorhees AS, Hsu S. Pustular Psoriasis: A Narrative Review of Recent Developments in Pathophysiology and Therapeutic Options. *Dermatol Ther*. 2021;11(6):1917-1929. doi:10.1007/s13555-021-00612-x

14. Genovese G, Moltrasio C, Cassano N, Maronese CA, Vena GA, Marzano AV. Pustular Psoriasis: From Pathophysiology to Treatment. *Biomedicines*. 2021;9(12):1746. doi:10.3390/biomedicines9121746

15. Reich K, Augustin M, Gerdes S, et al. Generalized pustular psoriasis: overview of the status quo and results of a panel discussion. *J Dtsch Dermatol Ges J Ger Soc Dermatol JDDG*. 2022;20(6):753-771. doi:10.1111/ddg.14764

16. Krueger J, Puig L, Thaçi D. Treatment Options and Goals for Patients with Generalized Pustular Psoriasis. *Am J Clin Dermatol*. 2022;23(Suppl 1):51-64. doi:10.1007/s40257-021-00658-9

17. Kearns DG, Chat VS, Zang PD, Han G, Wu JJ. Review of treatments for generalized pustular psoriasis. *J Dermatol Treat*. 2021;32(5):492-494. doi:10.1080/09546634.2019.1682502

18. Zhou LL, Georgakopoulos JR, Ighani A, Yeung J. Systemic Monotherapy Treatments for Generalized Pustular Psoriasis: A Systematic Review. *J Cutan Med Surg*. 2018;22(6):591-601. doi:10.1177/1203475418773358

19. Gnesotto L, Mioso G, Alaibac M. Use of granulocyte and monocyte adsorption apheresis in dermatology (Review). *Exp Ther Med*. 2022;24(2):536. doi:10.3892/etm.2022.11463

20. Megna M, Camela E, Ruggiero A, et al. Use of Biological Therapies for the Management of Pustular Psoriasis: A New Era? *Clin Cosmet Investig Dermatol*. 2023;16:1677-1690. doi:10.2147/CCID.S407812

21. Morita A, Yamazaki F, Matsuyama T, et al. Adalimumab treatment in Japanese patients with generalized pustular psoriasis: Results of an open-label phase 3 study. *J Dermatol*. 2018;45(12):1371-1380. doi:10.1111/1346-8138.14664

22. Plachouri KM, Chourdakis V, Georgiou S. The role of IL-17 and IL-17 receptor inhibitors in the management of generalized pustular psoriasis. *Drugs Today Barc Spain 1998*. 2019;55(9):587-593. doi:10.1358/dot.2019.55.9.3020159

23. Okubo Y, Mabuchi T, Iwatsuki K, et al. Long-term efficacy and safety of ixekizumab in Japanese patients with erythrodermic or generalized pustular psoriasis: subgroup analyses of an open-label, phase 3 study (UNCOVER-J). *J Eur Acad Dermatol Venereol JEADV*. 2019;33(2):325-332. doi:10.1111/jdv.15287

24. Rosi E, Fastame MT, Di Cesare A, Prignano F. Targeting IL-17A for the treatment of pustular psoriasis: a comprehensive review. *Expert Opin Biol Ther*. 2022;22(12):1475-1487. doi:10.1080/14712598.2022.2116978

25. McKeage K, Duggan S. Risankizumab: First Global Approval. *Drugs*. 2019;79(8):893-900. doi:10.1007/s40265-019-01136-7

26. Yamanaka K, Okubo Y, Yasuda I, Saito N, Messina I, Morita A. Efficacy and safety of risankizumab in Japanese patients with generalized pustular psoriasis or erythrodermic psoriasis: Primary analysis and 180-week follow-up results from the phase 3, multicenter IMMspire study. *J Dermatol*. 2023;50(2):195-202. doi:10.1111/1346-8138.16667

27. Navarini AA, Prinz JC, Morita A, et al. Spesolimab improves patient-reported outcomes in patients with generalized pustular psoriasis: Results from the Effisayil 1 study. *J Eur Acad Dermatol Venereol JEADV*. 2023;37(4):730-736. doi:10.1111/jdv.18820

28. Blair HA. Spesolimab: First Approval. *Drugs*. 2022;82(17):1681-1686. doi:10.1007/s40265-022-01801-4

29. Bachelez H, Choon SE, Marrakchi S, et al. Inhibition of the Interleukin-36 Pathway for the Treatment of Generalized Pustular Psoriasis. *N Engl J Med*. 2019;380(10):981-983. doi:10.1056/NEJMc1811317

30. Bernardo D, Thaçi D, Torres T. Spesolimab for the Treatment of Generalized Pustular Psoriasis. *Drugs*. 2024;84(1):45-58. doi:10.1007/s40265-023-01988-0

31. Bachelez H, Choon SE, Marrakchi S, et al. Trial of Spesolimab for Generalized Pustular Psoriasis. *N Engl J Med*. 2021;385(26):2431-2440. doi:10.1056/NEJMoa2111563

32. Morita A, Strober B, Burden AD, et al. Efficacy and safety of subcutaneous spesolimab for the prevention of generalised pustular psoriasis flares (Effisayil 2): an international, multicentre, randomised, placebo-controlled trial. *Lancet Lond Engl*. 2023;402(10412):1541-1551. doi:10.1016/S0140-6736(23)01378-8

33. Boehringer Ingelheim. *Effisayil™ ON: An Open-Label, Long Term Extension Study to Assess the Safety and Efficacy of Spesolimab Treatment in Patients With Generalized Pustular Psoriasis (GPP)*. clinicaltrials.gov; 2023. Accessed January 1, 2023. https://clinicaltrials.gov/study/NCT03886246

34. Boehringer Ingelheim. *Multi-Centre, Open-Label, Expanded Access Trial of Spesolimab i.v. in Patients With Generalized Pustular Psoriasis (GPP) Presenting With a Flare*. clinicaltrials.gov; 2024. Accessed January 1, 2024. https://clinicaltrials.gov/study/NCT05200247

35. Boehringer Ingelheim. *Multi-Centre, Open-Label, Expanded Access Program of 900mg Intravenous (i.v.) Spesolimab in Patients With Generalized Pustular Psoriasis (GPP) Presenting With a Flare*. clinicaltrials.gov; 2024. Accessed January 1, 2024. https://clinicaltrials.gov/study/NCT05239039

36. Hwang J, Rick J, Hsiao J, Shi VY. A review of IL-36: an emerging therapeutic target for inflammatory dermatoses. *J Dermatol Treat*. 2022;33(6):2711-2722. doi:10.1080/09546634.2022.2067819

37. Warren RB, Reich A, Kaszuba A, et al. Imsidolimab, an anti-interleukin-36 receptor monoclonal antibody, for the treatment of generalized pustular psoriasis: results from the phase II GALLOP trial. *Br J Dermatol*. 2023;189(2):161-169. doi:10.1093/bjd/ljad083

38. Shanghai Huaota Biopharmaceutical Co., Ltd. *Multi-Centre, Open-Label, Single-Arm, Phase Ib Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of a Single Dose of HB0034 in Patients Acute Generalized Pustular Psoriasis (GPP) Flare*. clinicaltrials.gov; 2024. Accessed January 1, 2024. https://clinicaltrials.gov/study/NCT05512598

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**