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DRUG SAFETY EVALUATION

Efficacy and safety of spesolimab for the management of generalized pustular psoriasis: a drug safety evaluation

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ABSTRACT

Introduction: Generalized pustular psoriasis (GPP) is a rare form of psoriasis (less of 1% of cases). Currently, GPP is recognized as a clinical entity, distinguished from plaque psoriasis. However, there are not guidelines for GPP management and treatments are often derived from plaque psoriasis. Therefore, conventional systemic drugs are usually used as first-line treatment options, and biologics are still used off label. Recently, spesolimab, an anti-IL36 receptor humanized IgG1 monoclonal antibody, has been specifically approved for GPP disease, revolutionizing treatment scenario.

Areas covered: The aim of this review is to investigate current literature on the use of spesolimab for GPP management to underline its potential role in GPP and offer a current clinical perspective. Literature research using the Google Scholar, Pubmed, Embase, Cochrane Skin, and clinicaltrials.gov databases was performed, selecting the most relevant manuscripts.

Expert opinion: Spesolimab is efficacious and has a consistent and favorable safety profile in patients presenting with a GPP flare. However, despite excellent results in terms of safety and efficacy have been reported by both clinical trials and very limited real-life experiences, long-term data, especially in flare-up prevention, are scant. Thus, while the available data are encouraging, further research is warranted to understand the efficacy, safety, and long-term outcomes associated with spesolimab treatment in GPP.

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Spesolimab; pustular psoriasis; biologic drug; treatment; IL-36

1. Introduction

Psoriasis is chronic inflammatory cutaneous disorder affecting up to 3% of the worldwide population and strongly impacting patients' quality of life [1]. Clinically it is usually characterized by the presence of thick, red patches of skin covered with silvery scales, which are often accompanied by itching, inflammation, and discomfort [2]. Moreover, psoriasis should be considered a systemic disorder as several comorbidities may be associated with psoriatic disease such as psoriatic arthritis, inflammatory bowel diseases, cardiovascular disease, diabetes, depression, etc [3,4].

Even if plaque psoriasis is the commonest clinical presentation (about 90% of cases), several clinical phenotypes can be distinguished: guttate psoriasis, erythrodermic psoriasis and pustular psoriasis [5]. Pustular psoriasis can be classified in localized disease (palmoplantar pustular psoriasis and acrodermatitis continua of Hallopeau) or generalized disease [generalized pustular psoriasis (GPP), pustular psoriasis of pregnancy (or impetigo herpetiformis), annular and circinate, and infantile/juvenile pustular psoriasis] [6,7]. Among these, GPP is a rare form of the disease (less of 1% of cases), presenting with an acute onset in which small, monomorphic sterile pustules develop in painful inflamed skin, often associated with systemic symptoms, particularly leukocytosis, fever and fatigue, being a potential life-threatening condition [8]. Even if often idiopathic, GPP may be triggered by internal and external factors, such as pregnancy, infections, and corticosteroid withdrawal [9,10]. Of interest, also COVID-19 vaccination has been associated with GPP exacerbation [11]. However, it should be discussed that several cutaneous reactions have been described following COVID-19 vaccination [12–14], and the safety of biologics treatment has been widely reported [15,16]. Clinically, GPP clinical course may be heterogenous, varying from relapsing disease with recurrent flares developing years after the initial diagnosis to a persistent disease continuously flaring over time [9,10]. Histopathological examination of GPP lesions shows parakeratosis, substantial mononuclear and neutrophilic infiltration into the epidermis, and epidermal edema and hyperplasia. However, typical histologic finding of plaque psoriasis (hyperplasia of the suprapapillary capillaries, Spongiform pustules of Kogoj, and Munro's microabscesses) are also present [17]. Indeed, GPP may occur in parallel with plaque psoriasis, which can complicate clinical picture [5]. However, recent knowledge on GPP pathogenesis has led to recognize GPP as a clinical entity, clearly distinguished from plaque psoriasis [5]. Clinical and pathogenetic differences reflect the need for specific treatment for GPP [18–20]. However,

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there are not guidelines for GPP management [21,22], and treatments are often derived from plaque psoriasis [23–25]. Conventional systemic drugs used for psoriasis (methotrexate, oral retinoids and cyclosporin) are usually used as first-line treatment options but their use is often limited by contraindication or lack of efficacy [23–25]. The management of plaque psoriasis has been revolutionized by the introduction of biologic treatments which are agents specifically targeting interleukins (IL)s involved in psoriasis pathogenesis [26–29]. However, data on the effectiveness of 12 biologic drugs approved for plaque psoriasis in GPP are scant, and their use for GPP is still off label [30–33]. Moreover, clinical trials investigating efficacy and safety in GPP are often limited to the Japanese population with small number of patients, and the dosage of the drug differs from that approved by the EMA or FDA for psoriasis, making generalization of results difficult [19]. Recently, spesolimab, an anti-IL36 receptor humanized IgG1 monoclonal antibody, has been specifically approved for GPP disease, revolutionizing treatment algorithm [30]. In this scenario, we performed a review article with the aim of investigating current literature on the use of spesolimab for the management of GPP in order to point out its potential therapeutic role in GPP and to offer a wide current clinical perspective.

1.1. GPP pathogenesis

GPP is mainly characterized by innate immune inflammation and considered as an autoinflammatory pustular neutrophilic disease while plaque psoriasis is considered an autoimmune condition where both innate and adaptive immunopathogenic responses are involved [34]. On consequence, while IL23/17 play a key role in plaque psoriasis, IL36 has the central role in GPP [35,36]. IL36 is a cytokine of the IL1 family, expressed by and acting on several cell types (epithelial cells, bronchial and intestinal epithelium, immune cells, and keratinocytes, in an autocrine or paracrine manner) [37]. Globally, four isoforms can be distinguished: IL-36α, IL-36β, IL-36γ (pro-inflammatory cytokines) and IL-36 receptor antagonist (IL-36 Ra) (anti-inflammatory cytokines) [38]. In particular, 36γ has been identified as a specific biomarker in psoriasis [38]. IL36 plays a regulatory role in the innate immune system and its uncontrolled expression led to the perpetuation of inflammatory cascades [39,40]. The signaling of IL36 involves IL36 receptor (IL36R) and IL1R accessory protein, increasing epithelial inflammatory response [39,40]. This signaling cascade seems to have the central role in GPP [39,40]. Indeed, overexpression of IL36 agonists or expression of a dysfunctional IL36R antagonist, can cause uncontrolled positive feedback, leading to a dysregulated production of inflammatory cytokines which induce chemokines that attracts neutrophils into the epidermis, forming spongiform pustules of Kogoj and 'lakes of pus' (sub-corneal accumulation of neutrophils), typical of GPP [39,40].

These data were confirmed by gene expression analyses which showed increased levels of tumor necrosis factor-α, IL1, IL17A, and IL36 in skin biopsy samples from patients with plaque psoriasis or GPP [36]. Of note, higher levels of IL1 and IL36, higher expression of neutrophilic chemokines and neutrophil and monocyte transcripts as well as lower levels of IL17A and interferon-γ were found in GPP lesions as compared with plaque psoriasis [36].

Moreover, interlinked immunologic pathways underline the pathogenesis of both forms of psoriasis. Indeed, IL36 and IL23 pathways may crosstalk extensively, and the dysregulation of either pathway is capable of perpetuating an inflammatory response [41].

The role of IL36 has been confirmed by genetic analysis which showed IL36RN mutations in patients with GPP [42,43]. This mutation causes a response pathway whereby IL36R-activating ligands are not regulated by IL36RA, leading to self-amplifying IL36 production [42,43]. Of interest, the occurrence of IL36RN mutations may differ by ethnicity, suggesting the likelihood of genetic diversity in the pathophysiology of GPP [42,43]. An earlier age of onset and more severe GPP is associated with IL36RN mutations, with a different onset time between biallelic (earlier) compared with monoallelic (delayed) mutations furthermore [42,43]. However, the presence of IL36RN mutation is not present in all GPP patients [44]. Alternative genetic mutations associated with the IL36-mediated inflammatory cascade such as gain-of-function mutations in CARD14 and loss-of-function mutations in AP1S3 which facilitate activation of nuclear factor-κB (NF-κB), leading to IL36 overexpression [45–47].

Finally, also mutations in SERPINA3, a protease secreted by neutrophils that cleaves IL36 precursors, and other proteases (cathepsin G, elastase, proteinase 3) have been found in GPP patients [45–47].

2. Material and methods

Literature research using the Google Scholar, Pubmed, Embase, Cochrane Skin, and clinicaltrials.gov databases (until 30 June 2023) was carried out using the following terms: 'psoriasis'', 'general pustular psoriasis', ''biologic drugs'', 'efficacy', ''safety', 'spesolimab'. Relevant data from the screened and analyzed manuscripts were pointed out following the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines [48]. Metanalyses, reviews, clinical trials, case reports and series, and real-life experiences were investigated in our review, selecting the most relevant manuscripts. Only English language articles were collected. The texts and the abstracts of designated manuscripts were reviewed to refine the research. Bibliography was also examined in order to avoid that some manuscripts could be missed. This manuscript is based on previously performed studies and does not contain any studies with animals or human participants carried out by any of the authors.

3. Introduction to spesolimab

Spesolimab is a humanized antagonistic monoclonal IgG1 antibody acting on human IL36R signaling by the bind to IL36R which causes the blockage of the activation of IL36R with the downstream activation of pro-inflammatory pathways [49–51]. The recommended dosage is a single dose of 900 mg (2 vials of 450 mg) administered as an intravenous infusion, followed by an additional 900 mg dose 1 week after the initial dose if flare symptoms persist (Box 1).

Box1. Drug Summary Box.

Drug name: spesolimab
Phase: approved (FDA, EMA)
Indication: treatment of flaresin adult patients with generalized pustular psoriasis as monotherapy
Pharmacology: humanisedantagonistic monoclonal immunoglobulin G1 antibody blocking
human IL36R signaling
Route of administration:intravenous use
Chemical structure: $C_{6480}H_{9988}N_{1736}O_{2012}S_{46}$
Pivotal trials: Effisayil 1 trial

3.1. Pharmacokinetic properties

Data collected from healthy subjects, GPP patients and subjects with other diseases led to the development of population pharmacokinetic model [51,52]. The typical volume of distribution at steady state was 6.4 liters [51,52]. Following a single intravenous dose of spesolimab 900 mg, the population pharmacokinetic model-estimated Area Under the Curve (AUC)0-∞ (95% CI) and maximum (or peak) serum concentration (Cmax) (95% CI) in a typical anti-drug antibodies (ADA)-negative patient with GPP were 4750 (4510, 4970) µg·day/mL and 238 (218, 256) µg/mL, respectively [51,52]. In some cases, if patients had ADA titer values >4000, spesolimab concentrations in plasma were reduced, without and apparent impact on pharmacokinetics at ADA titers below 4000 [51,52]. The metabolism of spesolimab is not fully understood characterized. As a humanized IgG1 monoclonal antibody, it is expected to be degraded into small peptides and amino acids via catabolic pathways, similar to endogenous IgG [51,52].

As regards spesolimab elimination, in the linear dose range (0.3–20 mg/kg), spesolimab clearance (95% CI) in an ADA-negative GPP patient, weighing 70 kg, was 0.184 L/day, with a terminal-half-life of 25.5 days. Of note, spesolimab clearance was increased in some patients with ADA titer values >4000. Finally, spesolimab concentrations were lower in patients with higher body weight [51,52].

3.2. Pharmacodynamic properties

During treatment with spesolimab in GPP patients, reduced levels of IL6, T helper cell (Th1/Th17) mediated cytokines, C-reactive protein (CRP), neutrophilic mediators, keratinocyte-mediated inflammation, and proinflammatory cytokines were reported in both skin and serum at week 1 as compared with baseline and was associated with a reduction in clinical severity [49–51]. These biomarkers reductions became more evident at the last measurement at week 8 in Effisayil 1 clinical trial [49–51].

3.3. Drug to drug interactions

Despite limited experience on the use of spesolimab, its use is not expected to cause cytokine mediated CYP interaction. However, no interaction studies have been carried out. Globally, live vaccines should not be administered concurrently with spesolimab [49–51].

3.4. Special population

The use of spesolimab has not been investigated in pediatric population [51]. On the contrary, dose adjustment is not required in elderly patients as well as in patients with renal or hepatic impairment since these conditions are not expected to impact on the pharmacokinetics of this monoclonal antibodies [51]. As regards pregnancy, there are no data on the use of spesolimab in pregnant women [51]. Globally, it is preferable to avoid spesolimab administration during pregnancy as human immunoglobulin (IgG) is known to cross the placental barrier. Similarly, there are no data on the excretion of spesolimab in human milk and it is well known that the excretion of IgG antibodies in milk occurs during the first few days after birth [51]. On consequence, the risk of spesolimab transmission to the breastfed child cannot be ruled out and spesolimab may be used during breastfeeding only if clinically needed. Finally, there are no study on human fertility [51]. However, studies in mice do not indicate a harmful effects with respect to fertility from antagonism of IL36R [51].

3.5. Clinical applications and key efficacy and safety data

Spesolimab has been approved as monotherapy for the management of GPP flares in adult patients (age ≥18 years). It is scheduled as a single dose of 900 mg (2 vials of 450 mg) administered as an intravenous infusion followed by an additional 900 mg dose 1 week after the initial dose if flare symptoms persist [51].

4. Efficacy and safety of spesolimab

The effectiveness and safety of spesolimab has been reported in both clinical trials (Table 1) and real-world experiences.

4.1. Clinical trials

4.1.1. Phase I trial

The first trial investigating the efficacy and safety as well as pharmacokinetics (PK) and pharmacogenomics of spesolimab for the treatment of active GPP was a phase I proof-of-concept study that enrolled 7 patients from 5 countries (France, Malaysia, Republic of Korea, Taiwan and Tunisia) [50,53]. Patients received a single open-label intravenous infusion of spesolimab 10 mg/Kg body weight, and then monitored for 20 weeks: 5 of 7 (71.4%) patients achieved Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) 0 or 1 within 1 week, and 100% by week 4. The fastest response was observed in 2 days in 3 patients. No severe AEs were reported [50,53].

4.1.2. Phase II trials

Effisayil 1 (NCT03782792) was a multicentre, randomized, double-blind, placebo-controlled study that aimed at assessing the efficacy and safety of spesolimab versus placebo in treating GPP flares. Fifty-three patients were enrolled and 2:1 randomized to receive either a single dose of spesolimab 900 mg ($n = 35$) or placebo ($n = 18$) intravenously [54].

Table 1. Clinical trials on the efficacy and safety of spesolimab for GPP.

Type of study	No. of patients	Duration	Efficacy	Safety	State of the study
Phase I	7	20 days	Week 1 GPPGA 0 or 1: 5 of 7 (71.4%) patients achieved, and 100% by week 4. The fastest response was observed in 2 days in 3 patients.	No serious AD reported	Concluded
Effisayil 1 Phase II	53	12 weeks	Week 1 -GPPGA pustulation subscore of 0: 54.3% ($n = 19/35$) versus 5.6% ($n = 1/18$) for patients receiving the active treatment and the inert product ($p < 0.001$). - GPPGA total score of 0 and 1 (42.9% [$n = 15/35$] for spesolimab versus 11.1% [$n = 2/18$] for placebo).	Week-1 AEs were reported in 65.7% ($n = 23/35$) and 55.6% ($n = 10/18$) of patients under spesolimab and placebo respectively. They were mainly mild in severity and included pyrexia and dizziness. Also serious AEs were collected such as drug reaction with eosinophilia and systemic symptoms, urinary tract infections and drug-induced hepatic injury.	Concluded
Effisayil 2 Phase II	123	48 weeks	n/a	n/a	Concluded
Effisayil ON Phase II	n/a	5 years	n/a	n/a	Ongoing

n/a, not available.

At week 1, the proportion of patients reaching a GPPGA pustulation subscore of 0 was 54.3% ($n = 19/35$) versus 5.6% ($n = 1/18$) for patients receiving the active treatment and the inert product, respectively ($p < 0.001$) [54]. A similar trend was observed for the GPPGA total score of 0 and 1 (42.9% [$n = 15/35$] versus 11.1% [$n = 2/18$]) [54]. After 1 week, 15 out of 18 placebo-treated patients received spesolimab at day 8 [54]. Also, at day 8, 12 patients (34%) in the spesolimab group and 15 patients (83%) in the placebo group received an open-label dose of spesolimab. Afterwards, 32 patients (91%) randomly assigned to spesolimab and 17 patients (94%) randomly assigned to placebo completed the 12-week follow-up period [54]. By week 12, 39 patients were enrolled in the open-label extension trial [54]. Concerning safety, week-1 AEs were reported in 65.7% ($n = 23/35$) and 55.6% ($n = 10/18$) of patients under spesolimab and placebo respectively. They were mainly mild in severity and included pyrexia and dizziness. Serious AEs were registered in 3 out of 35 (11.4%) patients and included drug reaction with eosinophilia and systemic symptoms ($n = 1$), urinary tract infections ($n = 1$), arthritis ($n = 1$) and drug-induced hepatic injury ($n = 1$) [54]. Overall, no deaths or treatment withdrawal for AEs were recorded over the study period [54]. At week 12, the percentage of patients under at least one dose of spesolimab that experienced AEs was 82% ($n = 42/51$) and included the already mentioned ones and arthritis, influenza, worsening of chronic plaque psoriasis and cutaneous squamous cell carcinoma. The entity of AEs was severe in 6 cases (12%) [55].

A further sub-analysis was performed in order to define the performance of spesolimab in terms of efficacy and safety in prespecified populations, identified according to the following variables: sex (female versus male), Body Mass Index (BMI), GPPGA total score, GPPGA pustulation subscore, GPPASI total score, JDA GPP severity index, presence of plaque psoriasis at baseline, background medication before randomization and IL36RN mutation status. Overall, the efficacy of spesolimab was consistent across all the patient subgroups, as was safety, except for the severity that differed according the variable probably due to the small sample size of some sub-groups [56].

The Effisayil 2 is a phase 2, multicenter, randomized, parallel-group, double-blind, placebo-controlled, dose-finding study that aims at evaluating the performance of spesolimab in preventing GPP flares in patients with a history of GPP [57]. A total of 123 patients have been enrolled but results are not available yet [57]. The study protocol displays the 1:1:1:1 randomization of GPP patients to 4 groups receiving: i) a 600-mg subcutaneous loading dose of spesolimab followed by a 300-mg maintenance dose administered every 4 weeks; ii) a 600-mg subcutaneous loading dose of spesolimab followed by a 300-mg maintenance dose administered every 12 weeks; iii) a 300-mg loading dose followed by a 150-mg maintenance dose administered every 12 weeks; iv) placebo for 48 weeks. The primary endpoint is represented by time to first GPP flare up to 48 weeks [57]. In case of flares during the randomized maintenance treatment period, an open-label intravenous dose of 900-mg spesolimab may be administered, with a -possible second dose the week after. Data have not been published yet [57].

Patients who complete the treatment period and comply with the eligibility criteria, may enter the ongoing open-label extension study to assess the long-term safety and efficacy of spesolimab treatment in patients with GPP (NCT03886246).

A 5-year extension study, the Effisayil ON, has been recently initiated to assess the long-term efficacy and safety of spesolimab for GPP [58]. The study sample includes those patients who completed previous spesolimab trials and are qualified to enter the trial. Spesolimab will be administered every 4, 6 or 12 weeks [58]. The primary endpoint is the occurrence of treatment emergent adverse events (TEAEs) up to week 252 of maintenance treatment [58]. Secondary endpoints include any GPP flare, time to achieve GPPGA score of 0 or 1, a GPPGA pustulation sub-score of 0 and change from baseline in Psoriasis Symptom Scale (PSS) score up to 252 weeks [58].

4.2. Real-life

Ran et al. described the performance of spesolimab in treating GPP flare in 5 Chinese adult patients [59]. They observed a fast

onset of action since one patient experienced an almost complete resolution of pustules within 12 hours, two in 24 hours, one in 48 and the last in 96 hours [59]. A GPPGA score of 1 was achieved in 2/5 patients (40%) and the other three achieved a GPPGA score of 2 at week 1 [59]. Also, 3 patients achieved a score of 0 and 2 patients achieved a score of 1 at week 16 [59]. Moreover, at week 1, the mean percentage improvement of GPPASI score for the whole group was 62.9% at week 1, 92.5% at week 4 and 98% at week 16 [59]. Concerning safety, 4 out of 5 subjects (80%) experienced mild AEs (mild anemia, URTI, elevated uric acid level or liver enzymes, UTI, elevated platelet count and hypoproteinaemia) [59]. All of the mentioned AEs resolved after symptomatic treatment and mainly occurred within the 1 week after spesolimab administration [59].

Müller et al. reported the case of a 63-year-old man with a GPP recalcitrant to topical and systemic corticosteroids, MTX, infliximab and Risankizumab that completely cleared with spesolimab [60]. The drug was administered intravenously at the dosage of 900 mg at day 1 and 8 [60]. AEs were not recorded [60].

4.3. Post marketing study

A post-marketing surveillance study to evaluate the incidence of adverse drug reactions to spesolimab in real-world practice is about to start. Inclusion criteria include acute GPP that received intravenous spesolimab in Japan; naïve patients that have never received spesolimab. About 40 patients are expected to be enrolled [61].

5. Expert opinion

GPP is a rare and severe clinical phenotype of psoriasis characterized by flares of cutaneous pustulation often associated with systemic inflammation [62]. Despite GPP may occur in parallel with plaque psoriasis, GPP has been recognized as a clinical entity, clearly distinguished from plaque psoriasis for immunological, histological and pathogenetic factors [62]. On consequence, GPP should not be longer considered as a phenotype of psoriasis but as a distinct clinical entity. However, for a long-time treatment for GPP were borrowed from those for psoriasis [19]. Conventional systemic drugs were often used as first-line treatment, were replaced by the advent of biologics [63–66]. However, the excellent results showed by these drugs in plaque psoriasis, are not supported for GPP due to the lack of clinical trials [19]. Indeed, clinical trials are limited to Japanese population with limited number of patients, not allowing the formulation of consistent data applicable to the general population [19]. Thus, effective and targeted treatment were needed [19].

In this scenario, recent advantages on GPP pathogenesis, particularly the role of IL36, led to development of new drugs [62]. In particular, spesolimab, an IL36 receptor antibody, has been recently approved for the management of GPP. Of note, it is the first biologic drug licensed for this use as well as the unique on label biologic available for GPP management [62]. Its effectiveness and safety were suggested in both clinical trials and real-life experiences. In particular, the promising results of the phase I study were confirmed by Effasyil I, which showed a statistically significant improvement of GPPGA pustulation after 1 week of treatment as compared with placebo (GPPGA pustulation subscore of 0 (54.3% vs 5.6%, $p < 0.001$)) [54]. In addition, AEs were collected in 65.7% and 55.6% of patients under spesolimab and placebo, respectively, mainly mild in severity [54]. Of note, clinical results were obtained after only one week of treatment, suggesting a promising speed of action of the drug.

Moreover, a 48-week phase II trial and a 5-year extension study were ongoing to confirm these results in long term. As regards real-life, even if limited to few cases, data are promising. Indeed, 6 cases of GPP successfully treated with spesolimab have been already reported. Of interest, spesolimab showed not only clinical safety (only mild AEs reported) but also a fast onset of action with patients experiencing an almost complete resolution of pustules between 12 hours and 7 days of treatment.

Despite the encouraging results, it is important to acknowledge the limitations of the current evidence. The number of clinical trials evaluating spesolimab in GPP is limited, and larger studies are needed to confirm the efficacy and safety findings. Additionally, the long-term outcomes and durability of response to spesolimab require further investigation since the use of spesolimab has been reported only during acute phase of GPP and data on long-term results or long-term use are still absent. Indeed, GPP treatment should be focalized on both immediate/short-term period with the aim of improving skin manifestations and reducing the burden of systemic symptoms as well as on long-term management with the purpose of minimizing or preventing new flare-ups and disease progression [67,68]. Thus, several questions remain as to how and when to continue treatment with spesolimab.

Finally, as several patients affected by GPP also present plaque psoriasis, it is essential to investigate if spesolimab could be used to treat both forms of the disease or if biologics approved for plaques psoriasis are more adequate. In this scenario, updated guidelines and new drugs are required to offer patients the right treatment at the right moment as there are not GPP-specific therapeutic agents licensed in Europe except for spesolimab, as well as the use of biologic drugs available in Japan (Tumor Necrosis Factor inhibitors, IL-17/IL-17 R inhibitors, and IL-23 inhibitors) is still off-label due to the limited evidence on their safety and effectiveness [17,69,70].

To sum up, great expectations are linked to spesolimab even if few gaps on its use may remain. On one hand, promising results in terms of safety and efficacy have been reported by both clinical trials and very limited real-life experiences; on the other hand, long-term data, especially in flare-up prevention, are scant and real-life experiences are limited. Moreover, the new guidelines/treatment algorithm for GPP suggesting the correct indications for the use of spesolimab are required.

In conclusion, spesolimab is efficacious and has a consistent and favorable safety profile in patients presenting with a GPP flare, regardless of baseline sex, race, BMI, GPPGA total score, GPPGA pustulation subscore, GPPASI total score, JDA GPP severity index, presence of plaque psoriasis at baseline, background medication before randomization and IL36RN mutation status.

Certainly, spesolimab represents a significant advancement in the treatment options for patients suffering from GPP. While the available data are encouraging, further research is warranted to fully understand the efficacy, safety, and long-term outcomes associated with spesolimab treatment in GPP. These studies should be extended to other inflammatory diseases involving both the skin (hidradenitis suppurativa, neutrophilic dermatoses, acne, atopic dermatitis, …) and other organs (rheumatoid arthritis, inflammatory bowel disease, …), where IL36 signaling seems to contribute to inflammation [71–73].

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Author contribution statement

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