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Clinical Characteristics and Outcomes of Generalized Pustular Psoriasis Flares

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Keywords
Generalized pustular psoriasis · Psoriasis · Clinical research · Clinical trial

Abstract

Background: Generalized pustular psoriasis (GPP) is a rare, neutrophilic skin disease that can become life-threatening if flares are untreated. There are limited data describing the characteristics and clinical course of GPP disease flares with current treatment options. ***Objective:*** The aim of the study was to describe the characteristics and outcomes of GPP flares using historical medical information from patients enrolled in the Effisayil™ 1 trial. ***Methods:*** Investigators collected retrospective medical data characterizing patients' GPP flares prior to clinical trial enrollment. Data on overall historical flares were collected, as well as information on patients' typical, most severe, and longest past flares. This included data on systemic symptoms, flare duration, treatment, hospitalization, and time to clearance of skin lesions. ***Results:*** In this cohort (N = 53), patients with GPP experienced a mean of 3.4 flares per year. Flares were painful, associated with systemic symptoms, and often triggered by stress, infections, or treatment withdrawal. Resolution of flares was longer than 3 weeks in 57.1%, 71.0%, and 85.7% of documented (or identified) typical, most severe, and longest flares, respectively. GPP flares led to patient hospitalization in 35.1%, 74.2%, and 64.3% of patients for their typical, most severe, and longest flares, respectively. For the majority of patients, pustules took up to 2 weeks to clear for a typical flare and 3–8 weeks to clear for the most severe and longest flares. ***Conclusion:*** Our findings highlight that current treatment options are slow to control GPP flares and provide context for assessing the efficacy of new therapeutic strategies in patients with a GPP flare.

Trial registration details: ClinicalTrials.gov identifier, NCT03782792.

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Introduction

Generalized pustular psoriasis (GPP) is a rare autoinflammatory skin disease characterized by the widespread eruption of sterile, neutrophilic pustules [1]. GPP is a heterogeneous disease, and patients exhibit a wide spectrum of disease severity and a highly variable clinical course. Whereas some patients experience relapsing disease with recurrent GPP flares, others have persistent disease with perpetual mild pustulation and intermittent flares of increased severity. Flares may or may not be associated with clinical symptoms or biological markers of systemic inflammation, such as fever and/or fatigue, elevated serum levels of C-reactive protein (CRP), and peripheral blood neutrophilia [2]. Inciting factors that can trigger GPP flares include withdrawal from medications (including corticosteroids), bacterial or viral infections, stress, pregnancy, and menstruation [3–5].

GPP flares may be accompanied by extracutaneous involvement of neutrophilic inflammation, such as lesions of the oral mucosa, onychodystrophy, arthritis, epigastric pain, and cholangitis [6–9]. If untreated, systemic inflammation in GPP flares may progress into life-threatening complications, such as congestive heart failure, shock, renal failure, or sepsis [6, 10, 11]. Indeed, a recent study found that sepsis, heart disease, and liver disease were the leading causes of death in patients with GPP [12]. Moreover, patients with GPP often experience anxiety and depression, which further impact their quality of life [13, 14]. It was proposed at recent roundtable meetings between GPP clinical experts and patient advocacy groups that the term "skin failure" be used to capture the disastrous impact of the overwhelming skin and systemic inflammation seen in GPP [15]. Although in recent years, European and Japanese definitions of GPP have been published, there is a lack of international consensus on its diagnosis and treatment [1, 2]. In line with this, the patient roundtable meetings also highlighted the need for an improved definition of GPP and emphasized the importance of distinguishing the disease from other forms of psoriasis [15].

Current treatment options for GPP, which include cyclosporine, retinoids, and methotrexate, are based on trials in patients with plaque psoriasis. However, there is limited, very weak evidence for their clinical efficacy in patients with GPP [2]. Some biologic therapies have been approved for use in patients with GPP in Japan, based on small open-label studies; these include tumor necrosis factor α inhibitors, interleukin (IL)-17/IL-17 receptor inhibitors, and IL-23 inhibitors [2, 16, 17]. Current therapeutic strategies are slow to control GPP flares and do not always completely resolve GPP disease manifestations [15, 18].

Data characterizing the clinical course of GPP flares, including their frequency, duration, and clinical features, are currently limited. Greater understanding of the clinical features and natural course of GPP flares, and how they respond to current treatment options, is therefore needed. These data will provide insights into how to improve care for patients with GPP flares and to support physicians in making informed treatment and management decisions. Effisayil™ 1 (NCT03782792) was a randomized, placebo-controlled study that investigated the efficacy and safety of spesolimab, an anti-IL-36R monoclonal antibody, in patients presenting with a GPP flare [19]. To date, this is the largest randomized, placebo-controlled clinical trial conducted in patients with GPP. Here, we use historical medical data collated from patients enrolled in the trial to describe the clinical characteristics and outcomes of GPP flares.

Materials and Methods

Patient Population

Full details on the study design and results of Effisayil™ 1 have been previously published [19, 20]. Patients were eligible for inclusion if they were between 18 and 75 years old and had a history of GPP as defined by the European Rare and Severe Psoriasis Expert Network diagnostic criteria, as well as previous evidence of systemic inflammation, such as fever, asthenia, myalgia, elevated CRP, or leukocytosis. Patients were excluded if they presented with plaque psoriasis without pustules or with pustules restricted to psoriatic plaques; drug-triggered acute generalized exanthematous pustulosis; or an immediate life-threatening GPP flare.

Data Collection

At screening, information on the characteristics and clinical course of past GPP flares was obtained from each patient and substantiated by retrospective clinical chart review. Investigators collected information on flares prior to consent using a standard study questionnaire. Data collected included (i) the average number of flares per year or whether the patient was constantly flaring with persistent pustules; (ii) the duration of affected and clear skin over the past year; (iii) treatments given for past GPP flares; and (iv) clinical and laboratory characteristics of identified typical, most severe, and longest flares, as well as treatment instituted, duration of hospitalization, and outcome of the three categories of flares identified. There was no standard definition of a typical, most severe, and longest flare: assignment of flares to each category was based on investigator interpretation.

Statistical Analyses

Descriptive statistics are reported for all parameters. Proportions of patients are given as percentages of the total population, including those with missing data, and means, medians, and standard deviations (SDs) are calculated based on all patients with

Table 1. Patient clinical characteristics

Characteristic	Overall population (*N* = 53)
Sex, *n* (%)	
Male	17.0 (32.1)
Female	36.0 (67.9)
Age, years	
Mean (SD)	43.0 (10.9)
Study region, *n* (%)	
USA	3.0 (5.7)
Japan	2.0 (3.8)
Asia	25.0 (47.2)
Europe	16.0 (30.2)
Africa	7.0 (13.2)
Number of flares per year per patient[a]	
Mean (SD)	3.4 (3.5)
Median (range)	2.0 (0.0–14.0)
Time with involved skin over the past year, *n* (%)	
<1 week	4.0 (7.5)
1–2 weeks	11.0 (20.8)
3–4 weeks	8.0 (15.1)
5–8 weeks	5.0 (9.4)
9–12 weeks	2.0 (3.8)
>12 weeks	13.0 (24.5)
Missing	10.0 (18.9)
Time with completely clear skin over the past year, *n* (%)	
<1 week	13.0 (24.5)
1–2 weeks	1.0 (1.9)
3–4 weeks	5.0 (9.4)
5–8 weeks	2.0 (3.8)
9–12 weeks	2.0 (3.8)
>12 weeks	16.0 (30.2)
Missing	14.0 (26.4)
IL36RN mutation (historical data),[b] *n* (%)	
Yes	10.0 (18.9)
No	10.0 (18.9)
Unknown	33.0 (62.3)

SD, standard deviation. [a]Data available for 29 patients; of patients who did not provide the number of flares per year, six had constant flares with persistent pustules; [b]of the 53 enrolled patients, 46 had further genetic testing as part of the Effisayil™ 1 trial; 14 (26.4%) had an *IL36RN* mutation, 5 (9.4%) had a *CARD14* mutation, and 1 (1.9%) had an *AP1S3* mutation.

data available. For variables referring to durations of time, categories are given as <1 week, 1–2 weeks, 3–4 weeks, 5–8 weeks, 9–12 weeks, and >12 weeks.

Results

Patient Clinical Characteristics

From the 53 patients enrolled, 37 typical, 31 most severe, and 14 longest flares were identified. Patients had a mean (SD) age of 43 (10.9) years and were mostly female (67.9%), and mostly from Asia (47.2%) or Europe (30.2%). Whereas 28.3% of patients reported up to 2 weeks spent with involved skin during the previous year, 24.5% spent over 12 weeks of the year with involved skin. Similarly, during the previous year, 30.2% of patients had completely clear skin for over 12 weeks and 24.5% of patients reported less than a week of completely clear skin (Table 1). Where frequency data were available ($n = 29$), the mean (SD) number of flares per patient per year was 3.4 (3.5), with a range of 0–14 flares per patient per year (Table 1). Historical information on *IL36RN* mutation status was available for 20 patients, 10 (18.9%) of whom had a confirmed mutation (Table 1). Targeted DNA re-sequencing was performed as part of the Effisayil™ 1 trial, and data are available for 46 of the 53 enrolled patients; 14 patients (30.4%) were found to carry an *IL36RN* mutation, 5 (10.9%) had a *CARD14* mutation, and 1 (2.2%) had an *AP1S3* mutation.

The majority of patients (86.6%) received treatment for past GPP flares with at least one medication (online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000529274). Overall, treatment with systemic therapies was more common than with topical therapies; the most common systemic treatments included acitretin (45.3%), methotrexate (43.4%), and cyclosporine (30.2%). The most frequently used topical treatments included clobetasol propionate (20.8%) and potassium permanganate (17.0%), and 24.5% of patients were previously treated with biologic therapies, the most frequent being ustekinumab (13.2%) and adalimumab (9.4%) (online suppl. Table S1).

Characteristics of Typical, Most Severe, and Longest Flares

For those GPP flares where a trigger event was identified, the most common inciting factors were stress (19.4–21.4%), infections (19.4–21.4%), and treatment withdrawal (7.1–20.0%; none due to the withdrawal of steroids); for 2 patients, their longest GPP flares were triggered by pregnancy (14.3% of 14 longest flares) (online suppl. Fig. S1). For all three categories of flare, the majority of patients experienced flares of moderate-to-severe intensity according to investigator assessment (73.0% for a typical past flare; 100.0% for the most severe past flare; and 85.7% for the longest past flare) (Table 2). The proportion of patients with ≥30% of skin body surface area affected was similar across the different past flare types, ranging from 64.3% to 67.7% (Table 2).

Typical, most severe, and longest past flares were often associated with systemic symptoms and increases

Table 2. Clinical features of past GPP flares

Clinical feature, *n* (%)	Typical past flare (*n* = 37)	Most severe past flare (*n* = 31)	Longest past flare (*n* = 14)
Flare intensity at baseline			
Mild	5.0 (13.5)	0.0 (0.0)	1.0 (7.1)
Moderate	13.0 (35.1)	8.0 (25.8)	3.0 (21.4)
Severe	14.0 (37.8)	23.0 (74.2)	9.0 (64.3)
Unknown	5.0 (13.5)	0.0 (0.0)	1.0 (7.1)
BSA of skin affected ≥30%	24.0 (64.9)	21.0 (67.7)	9.0 (64.3)
C-reactive protein ≥7 mg/dL	7.0 (25.9)[a]	14.0 (45.2)	4.0 (28.6)
Leukocytosis ≥15,000 WBC/μL	3.0 (11.1)[a]	9.0 (29.0)	3.0 (21.4)
Body temperature >38.5°C	5.0 (18.5)[a]	12.0 (40.0)[b]	6.0 (46.2)[c]
Albumin <3.0 g/dL	3.0 (11.5)[d]	6.0 (20.0)[b]	1.0 (7.1)
Fatigue	20.0 (74.1)[a]	23.0 (74.2)	11.0 (78.6)
Malaise	13.0 (48.1)[a]	12.0 (38.7)	6.0 (42.9)
Asthenia	16.0 (59.3)[a]	19.0 (61.3)	9.0 (64.3)
Myalgia	12.0 (44.4)[a]	13.0 (41.9)	6.0 (42.9)
Edema	10.0 (37.0)[a]	10.0 (32.3)	4.0 (28.6)
Pain	17.0 (63.0)[a]	23.0 (74.2)	13.0 (92.9)
Neutrophilia	7.0 (25.9)[a]	13.0 (41.9)	4.0 (28.6)

BSA, body surface area, WBC, white blood cells. [a]Data available for 27 patients. [b]Data available for 30 patients. [c]Data available for 13 patients.

in markers of inflammation, including elevated CRP levels (25.8–45.2%), body temperature of >38.5°C (18.5–46.2%), fatigue (74.1–78.6%), pain (63.0–92.9%), and neutrophilia (25.9–41.9%) (Table 2). Compared with a typical flare, a higher proportion of patients experienced leukocytosis and a body temperature of >38.5°C during their most severe and longest flares (11.1% vs. 29.0% vs. 21.4% for leukocytosis; 18.5% vs. 40.0% vs. 46.2% for body temperature of >38.5°C). Furthermore, the proportions of patients with elevated CRP and neutrophilia were highest for the most severe flare compared with the other flare categories. Almost all patients (92.9%) experienced pain during their longest flare, compared with 63.0% and 74.2% of patients for the typical and most severe flares, respectively (Table 2).

The majority of patients' most severe and longest past flares were characterized by the worsening of pre-existing pustules, erythema, and scaling. In contrast, for the majority of typical past flares, pustules were mostly new, and erythema and scaling were new or worsened (Table S2). The longest flare prior to enrollment took more than 3 weeks to resolve for most patients (85.7%) and lasted for over 12 weeks in 28.6% of patients (Fig. 1); 64.3% of patients required hospitalization for their longest flare and were hospitalized for 1–4 weeks (Fig. 2). The duration of the most severe flare was more than 3 weeks in 71.0% of patients and lasted for over 12 weeks in 12.9% of patients (Fig. 1); 74.2% of patients required hospitalization for their most severe flare, with a typical stay of 1–2 weeks (Fig. 2). The flare duration of more than 3 weeks in 57.1% of patients with typical flare and the hospitalization rate of 35.1% were lower than documented for most severe and longest flares (Fig. 1, 2).

Treatment and Outcomes of Past GPP Flares

The vast majority of patients received treatment for their GPP flares prior to enrollment (83.8% for a typical flare, 90.3% for the most severe flare, and 92.9% for the longest flare) (Fig. 3). For all categories of flare, the majority of patients received treatment with systemic therapies (64.3–71.0%) (Fig. 3).

Pustules typically resolved in 1–2 weeks, 3–4 weeks, and 5–8 weeks in patients with typical, most severe, and longest flares, respectively (Fig. 4a). For a typical flare, cutaneous symptoms generally cleared in 1–2 weeks; however, some patients took ≥9 weeks to clear erythema (28.6%) and scaling (20.7%). This trend was mirrored for the most severe past flare, where cutaneous symptoms cleared in most patients in 3–8 weeks, but erythema and scaling persisted for ≥9 weeks in 33.3% and 25.9% of patients, respectively. Similarly, for the longest flare, 36.4% of patients had cleared cutaneous symptoms within 5–8 weeks, but high proportions of patients took ≥9 weeks to achieve clearance of erythema (54.5%) and scaling (45.5%) (Fig. 4b, c).

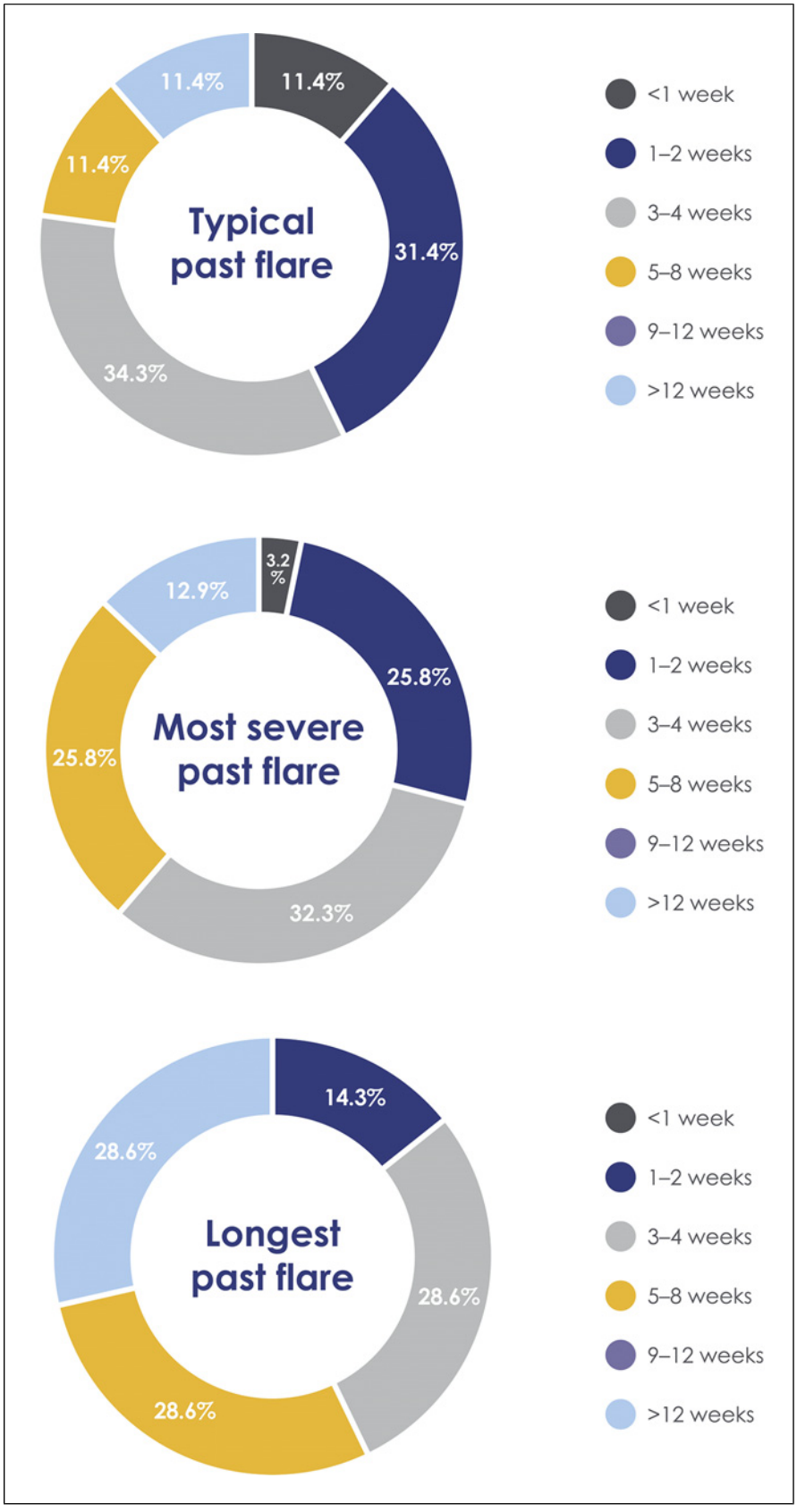

Fig. 1. Duration of past flares. The doughnut plots show for a typical, most severe, and longest past flare the proportion of patients (%) with different flare durations. Flare duration is categorized as <1 week, 1–2 weeks, 3–4 weeks, 5–8 weeks, 9–12 weeks, and >12 weeks. Typical past flare, $n = 35$; most severe past flare, $n = 31$; longest past flare, $n = 14$.

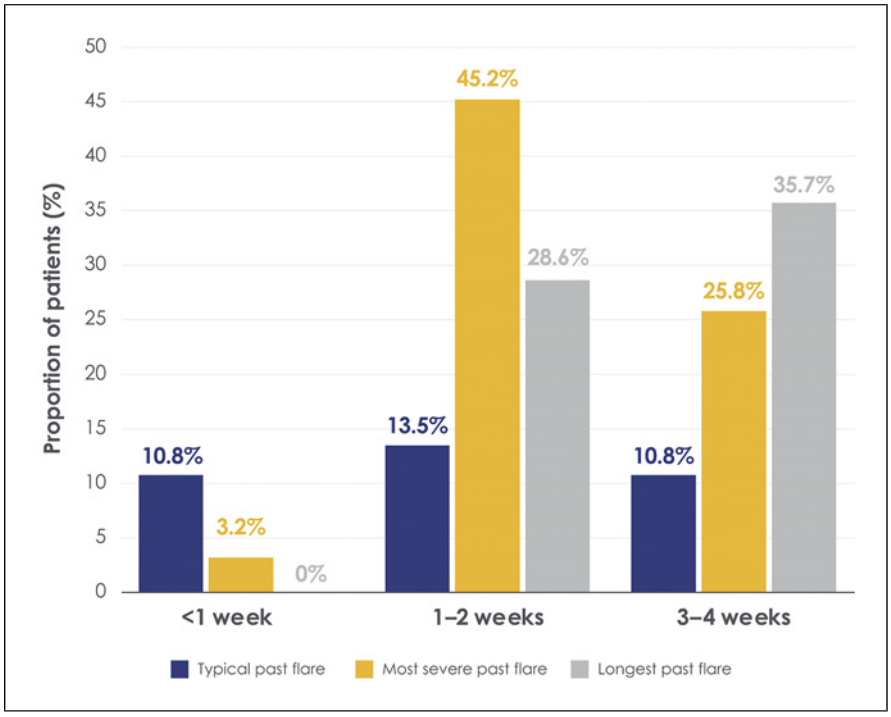

Fig. 2. Duration of hospitalization for past flares. The bar chart shows the proportion of patients (%) with different durations of hospitalization for a typical, most severe, and longest past flare. Duration of hospitalization is categorized as <1 week, 1–2 weeks, and 3–4 weeks. Hospitalization data were unknown in 4 patients (10.8%) for a typical past flare. Typical past flare, $n = 37$; most severe past flare, $n = 31$; longest past flare, $n = 14$.

Discussion

Driven by the lack of literature describing the clinical course of GPP flares with currently available treatments, this study used historical medical data from patients enrolled in the Effisayil™ 1 trial to characterize the clinical features and disease burden of past GPP flares. In this population, patients experienced an average of 3.4 GPP flares per year, with approximately a quarter of patients having involved skin for over 12 weeks in the year prior to enrollment. All types of GPP flares, but in particular patients' longest flares, were painful, and flares were consistently associated with systemic symptoms such as fatigue, asthenia, and myalgia. The clinical course of GPP flares was highly variable, with both the longest and shortest categories for time spent with affected skin each including approximately 20–30% of patients. A high proportion of patients required hospitalization because of severe or long flares, and the duration of hospitalization and the time taken to achieve clear skin were often prolonged despite treatment with systemic agents. The findings presented here suggest that current strategies used for the treatment of GPP are slow to control flares and even question the efficacy of such therapies, given the partially or completely self-remitting course of GPP flares [3]. Altogether, these past and presently reported data demonstrate the urgent need for improved therapeutic approaches.

Our findings are supported by recent publications from the CorEvitas Psoriasis Registry. In a 2021 survey of 29 dermatologists in the CorEvitas Psoriasis Registry, 72% of dermatologists reported that the currently available treatments were too slow to control GPP flares [18]. In our study, lesions associated with GPP flares took between 1 and 8 weeks to clear in the majority of patients, with some patients taking over 12 weeks, depending on the type of flare (9.1–27.3% of patients). An analysis of GPP disease characteristics in patients enrolled in the CorEvitas Registry described the great impact of the disease on patients' quality of life and indicated that current treatment options did not adequately resolve GPP flares [21]. Moreover, recently published data from a retrospective case series of 95 patients with GPP complement the findings reported in our study: 67.4% of patients with GPP were treated with systemic therapies and 35.8% of patients required hospitalization [22]. This is similar to our data for a patient's typical GPP flare (70.3% of patients were treated with systemic therapies, and 35.1% of patients required hospitalization) and highlights the clinical burden of GPP. The average number of GPP flares experienced per patient per year reported in our study is higher than in other datasets, where frequencies of 0–1 GPP flares per year have been observed in the majority of patients [6, 12, 18, 23].

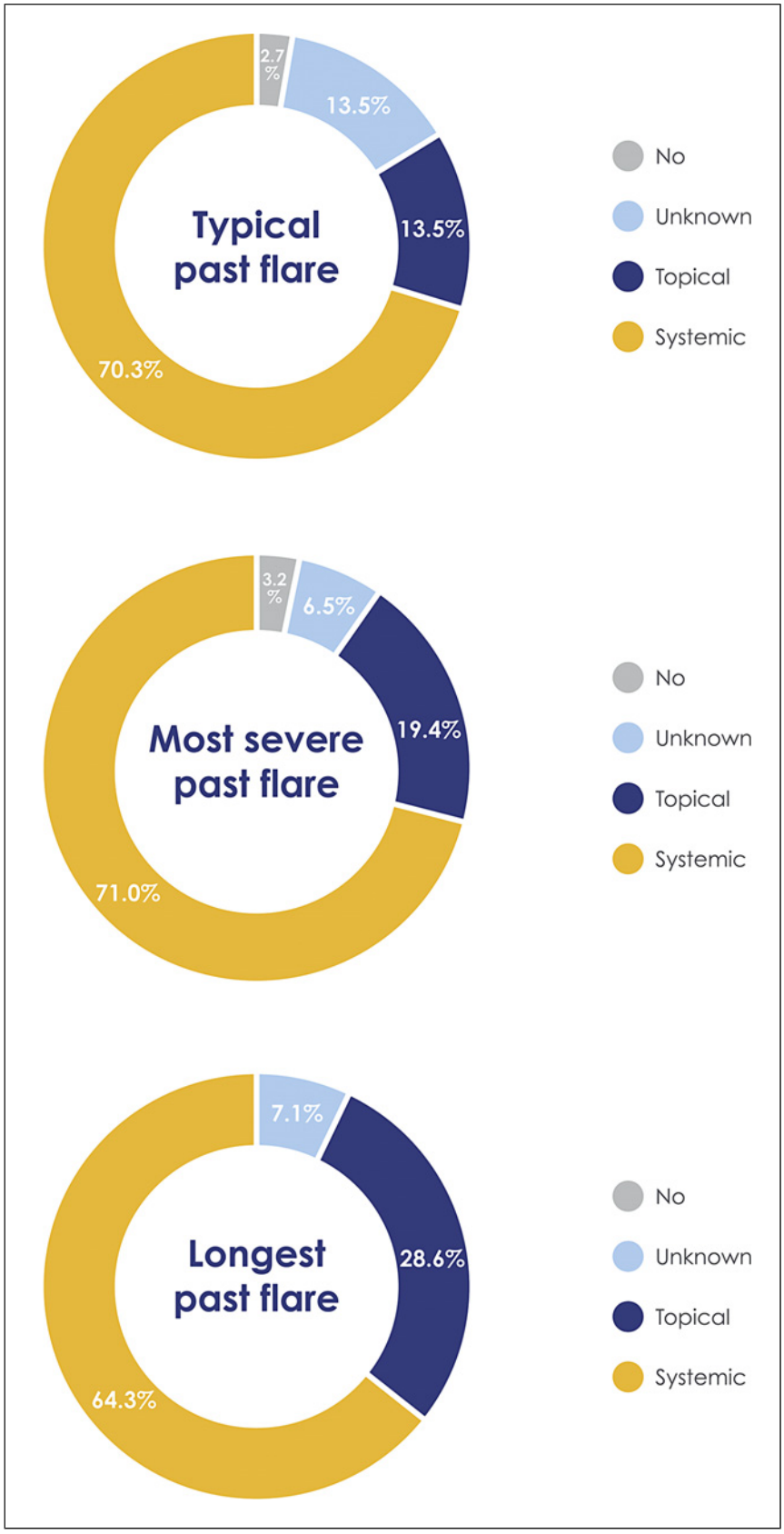

Fig. 3. Treatment of past flares. The doughnut plots show the proportion of patients (%) who have received prior treatment with systemic therapy, topical therapy, no therapy, or unknown, for their typical, most severe, and longest past flares. Typical past flare, n = 37; most severe past flare, n = 31; longest past flare, n = 14.

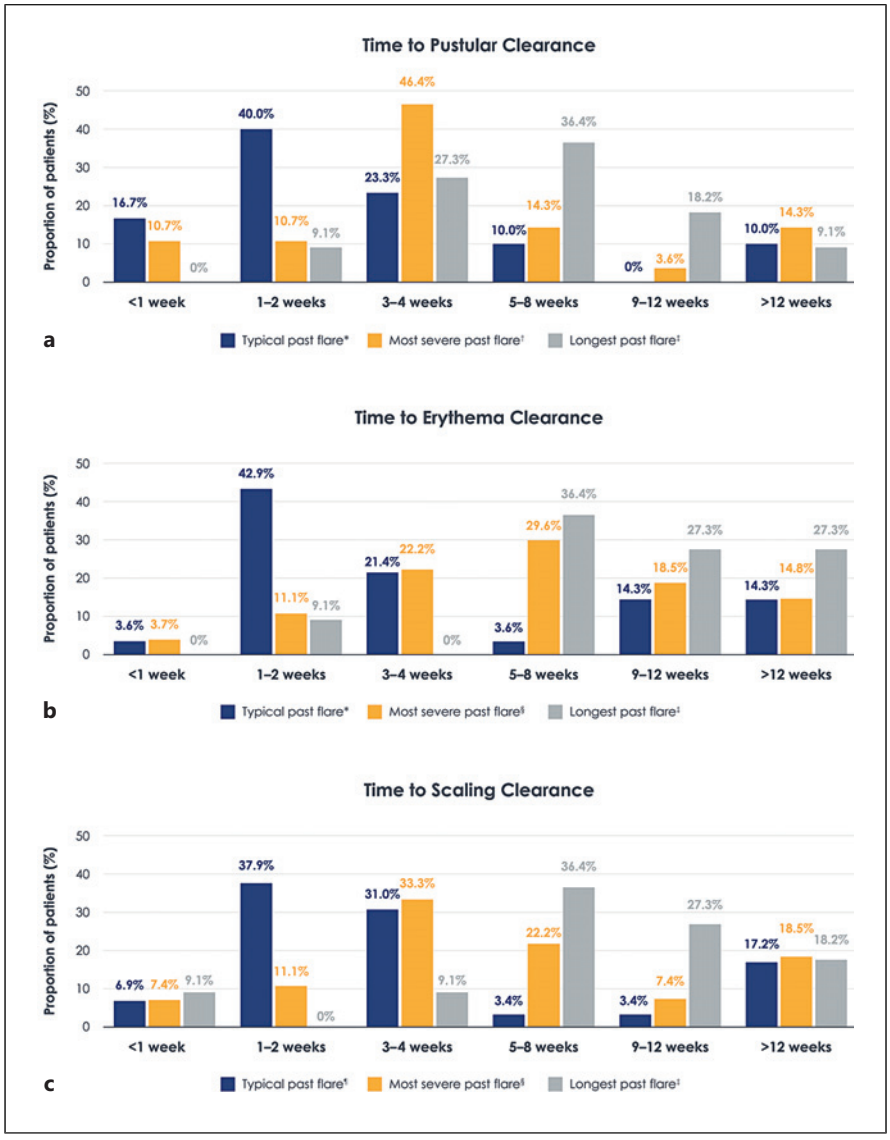

Fig. 4. Time to clearance of pustules, erythema, and scaling. The bar charts show the proportion of patients (%) with different amounts of time taken to achieve clearance of pustules (**a**), erythema (**b**), and scaling (**c**) for their typical, most severe, and longest past flares. Time to clearance is categorized as <1 week, 1–2 weeks, 3–4 weeks, 5–8 weeks, 9–12 weeks, and >12 weeks. *Data available for 28 patients; †data available for 28 patients; ‡data available for 11 patients; §data available for 27 patients; ¶data available for 29 patients.

This study has some limitations inherent to historical data collection. As the process of data collection was retrospective, information on some parameters was not available for all patients. In contrast to the assessments in the Effisayil™ 1 trial itself, historical medical data were subjectively assessed by the investigators and not guided by pre-specified criteria. A definition of a flare was not provided, and investigators determined flare occurrences at their own discretion. Indeed, investigators often found it difficult to determine whether individual manifestations were new or a worsening of pre-existing lesions, and this highlights the need for a standardized tool for assessing disease severity in patients with GPP. Data were collected by patient recall and validated where possible by chart review; it was unclear which data were confirmed. The patient population in this study was limited to those meeting the inclusion criteria of the Effisayil™ 1 trial and is therefore not reflective of all patients attending clinical practices in a real-world setting. For instance, patients with immediately life-threatening flares were excluded from the study. However, as this was an international, multicenter trial, the results presented here are reflective of global treatment options for GPP rather than country-specific approaches that may be biased by healthcare access issues or regional trends. This study has the key advantage of allowing comparison between treatment outcomes for past and current flares in the same patient cohort from the Effisayil™ 1 trial. The findings of this

study therefore provide important context to the observed efficacy of spesolimab in patients with GPP.

Overall, these analyses highlight the heterogeneous and often debilitating nature of GPP flares and demonstrate that current treatment options are associated with slow clearance of disease symptoms, resulting in frequent and prolonged hospital stays. By providing healthcare providers with an improved understanding of the characteristic features of GPP flares and clinical course with current therapeutic options, these findings may enhance informed treatment decisions for patients with GPP. Crucially, these observations provide context for ongoing and future trials assessing the efficacy of new treatments for patients with GPP flares, such as spesolimab.

Key Message

GPP flares are heterogeneous and debilitating, and current treatment options inadequate, resulting in frequent hospitalization.

Statement of Ethics

The Effisayil™ 1 study (NCT03782792) was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was reviewed and approved by Ethics Committees at participating institutions and/or countries; the list of these has been previously published in full [20]. All patients provided written informed consent prior to participation in the study.

Conflict of Interest Statement

The authors did not receive payment related to the development of this manuscript. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations. Siew Eng Choon declares paid activities as an advisor, speaker, or consultant for AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, LEO Pharma, MSD, Novartis, Pfizer, Sanofi, and UCB. Mark G. Lebwohl is an employee of Mount Sinai, has received research funds from AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara Therapeutics, Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development, LLC, Ortho Dermatologics, Regeneron, and UCB, and is a consultant for Aditum Bio, Almirall, AltruBio, AnaptysBio, Arcutis, Arena Pharmaceuticals, Aristea Therapeutics, Arrive Technologies, Avotres Therapeutics, BiomX, Boehringer Ingelheim, Brickell Biotech, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, CorEvitas, Dermavant Sciences, Dr. Reddy's Laboratories, Evelo Biosciences, Evommune, Facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Helsinn Therapeutics, Hexima, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, and Verrica. Hamida Turki declares paid consulting activities for Boehringer Ingelheim. Min Zheng declares receiving grants, consulting fees, and/or speaker's fees from AbbVie, Boehringer Ingelheim, Janssen-Cilag, LEO Pharma China, Novartis, Pfizer, and Xian Janssen. A. David Burden declares paid consulting activities for AbbVie, Almirall, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis, and UCB. Ling Li, Manuel Quaresma, and Christian Thoma are employees of Boehringer Ingelheim. Hervé Bachelez declares paid consulting activities for AbbVie, Almirall, AnaptysBio, Aristea Therapeutics, BIOCAD, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant Sciences, Eli Lilly, Janssen, Kyowa Kirin, LEO Pharma, Novartis, UCB, and Xion Pharmaceuticals; grant support from Boehringer Ingelheim, Bristol Myers Squibb, Janssen, LEO Pharma, Novartis, and Pfizer; and participation in a data safety monitoring board/advisory board for Avillion.

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Author Contributions

The authors met criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). Ling Li conducted data analyses. Ling Li, Manuel Quaresma, and Christian Thoma contributed to the concept and design of this study. Siew Eng Choon, Mark G. Lebwohl, Hamida Turki, Min Zheng, A. David Burden, Ling Li, Manuel Quaresma, Christian Thoma, and Hervé Bachelez were involved in the data acquisition and data interpretation; critically revised the manuscript content; provided their approval of the final manuscript version; and provided their agreement to be accountable for all aspects of the work.

Data Availability Statement

To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data when it becomes available on Vivli – Center for Global Clinical Research Data, and earliest after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Please visit Medical & Clinical Trials | Clinical Research | MyStudyWindow for further information.

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