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A Non-Interventional, Multicenter Study to Characterize the Socio-Demographics, Clinical Characteristics, and Management of Generalized Pustular Psoriasis Patients in Spain: IMPULSE Study

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Keywords
Generalized pustular psoriasis · Biologic treatment · Spesolimab · Disease management

Abstract

Introduction: Generalized pustular psoriasis (GPP) is a chronic, rare, and potentially life-threatening skin condition characterized by flares comprising widespread sterile pustules and systemic inflammation. Both the rarity and heterogeneity of the disease have made GPP classification and standardization of clinical criteria challenging. Before the approval of spesolimab (IL-36R antibody) in 2022, there were no approved treatments in the USA or Europe for GPP flares. Treatment for GPP has amounted to off-label use of medicines approved to treat plaque psoriasis. Our aim was to describe the sociodemographics, clinical characteristics, and treatment patterns of patients with GPP in Spain. ***Methods:*** Non-interventional, descriptive, multi-center, retrospective chart review of patients diagnosed with GPP in Spain. ***Results:*** 56 patients (50% women) were included, with a mean (standard deviation, SD) age at diagnosis of 53.7 (20.5) and a mean (SD) time of follow-up of 3.7 (3.1) years. In 80% of patients, GPP diagnosis was associated with a flare and 67.3% had known risk factors for GPP (such as previous diagnosis or family history of plaque psoriasis, comorbidities, smoking or stress). Hypertension and plaque psoriasis were the most frequent comorbidities (44.6% each). The number of GPP flares per patient-year was 0.55 with (range 0–4) a mean (SD) body surface area involvement of 21.3% (19.1). The most frequent manifestations of GPP flares were pustules (88.5%), erythema (76.9%), and scaling (76.9%). Additionally, 65.4% of patients had plaque psoriasis, 53.8% had

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unspecified skin lesions, and 30.8% experienced pain. The treatments used for GPP flares were off-label conventional systemic drugs (75%), mostly corticosteroids, cyclosporine, and acitretin. In the periods between flares, off-label biologics were used in 56.5% of patients. During the study period, 9 patients (16.1%) had at least one complication and 5 of them required hospitalization. ***Conclusion:*** This is the first multicenter study in Spanish GPP patients. Most patients were in their fifties, with personal or family history of plaque psoriasis, stress, smoking and a wide range of comorbidities and complications. Even though the number of flares per patient/year was 0.55, there was variability between patients. Both off-label conventional systemics and off-label biologics were used for flare management without a clear treatment pattern.

Introduction

Generalized pustular psoriasis (GPP) is a rare, chronic, neutrophilic disease with episodes of systemic inflammation involving the skin and other organs [1]. The disease manifests itself as repeated flares of widespread sterile pustules, fever, pain, arthralgia [2–5], but can also be associated with other conditions including cholestasis and heart, renal, or liver failure [6]. GPP causes significant morbidity and even mortality, especially in patients with underlying comorbidities. Renal failure, liver failure, sepsis, and multisystem organ failure are the most common complications and causes of death [2, 7–11].

Many cases of GPP are idiopathic; however, other cases are due to mutations in genes involved in the IL-36 pathway leading to uncontrolled IL-36 pathway activation. There is an association between GPP and allelic variations and mutations of the *IL36RN*, *CARD14*, *AP1S3*, and *MPO* genes, among others, playing an important role in common signaling pathways, especially in the IL-1/IL-36 axis [12, 13]. Dysregulation of the IL-36 pathway is present even in those individuals without a clear genetic basis for GPP. Other risk factors for GPP include a positive family history of psoriasis, stress, corticosteroid or cyclosporin withdrawal, infections (viral or bacterial), and pregnancy [8, 10, 14–17].

GPP is considered an orphan disease and has a low prevalence worldwide. Prevalence varies by geography and ethnic background, possibly due to genetic factors, and is higher in Asian countries (7.46/million in Japan) compared to European countries (1.76/million in France) [2, 7, 8, 10, 18, 19]. In Spain, according to a recent survey of 33 dermatologists in 28 different hospitals, the estimated prevalence is 13.05 cases/million adults (18 years and above) [20]. According to epidemiological studies, the prevalence may be higher in females (ratio 2:1) and the mean age of disease onset is approximately 40 years [10].

The key diagnostic criteria for acute GPP, according to the European Rare and Severe Psoriasis Expert Network (ERASPEN) consensus, include the presence of primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriasis vulgaris lesions), with or without systemic inflammation, with or without plaque psoriasis, with an either relapsing (>1 episode) or persistent (>3 months) course [1–5]. However, in Japan GPP is designated as an intractable disease with systemic inflammation and is defined as a rare disease in which acute fever, generalized skin rashes and many sterile pustules develop [21].

The lack of consensus on clinical and diagnostic criteria for GPP, the heterogeneous nature of the disease and its rarity, all point to the need to further characterize GPP. Nevertheless, some triggers known to cause flares include: Certain medications (withdrawal of systemic or topical corticosteroids; antibiotics such as amoxicillin; terbinafine; calcipotriol ointment; betamethasone ointment; and tumor necrosis factor [TNF] inhibitors); infections by several pathogens including *Streptococcus sp.*, *Trichophyton rubrum*; cytomegalovirus; Epstein-Barr virus; *Varicella zoster* virus, and environmental factors [1, 10, 11, 22–24]. Additionally, modifiable factors such as psychological stress, obesity, smoking, and alcohol consumption have been associated with exacerbations of the disease [25, 26].

Regarding treatment, before the approval of the humanized anti-IL-36 receptor monoclonal antibody spesolimab [27–30] in 2022, there were no approved targeted GPP treatments in the USA or Europe, where current therapeutic management of GPP is largely based on the treatment guidelines for plaque psoriasis [31]. Treatments include the use of oral retinoids, methotrexate, cyclosporine, topical corticosteroids, and topical therapy. Recently, several biological treatments for plaque psoriasis targeting TNF, interleukin (IL)-17 or its receptor, the p40 subunit of IL-12/23, and the p19 subunit of IL-23 have been reported to be useful in individual patients in small case series or uncontrolled studies, even though the scope and quality of the available evidence are limited [9, 15, 32–35]. The aim of this non-interventional retrospective study was to collect patient chart data to better understand the sociodemographic and clinical characteristics of GPP, including the frequency of flares and their management, as well as the complications, comorbidities, and treatment patterns of patients with GPP in Spain.

Materials and Methods

Study Design

This is a retrospective, noninterventional, descriptive, multicenter study using existing data extracted from the medical charts of patients diagnosed with GPP in Spain from January 2011 through December 2022. Sites were selected based on a feasibility study result. A total of 14 dermatologists from reference Spanish centers of excellence with considerable expertise in psoriasis took part in the study (online supplementary material, available at https://doi.org/10.1159/000540019). Participating dermatologists identified eligible patients within their clinical practice.

Only patients for whom diagnosis and management of GPP occurred during or after 2011 were eligible to participate in the study. Choosing this period made it possible to reflect the current disease management and to ensure an accurate follow-up period. The retrospective eligibility observation period of the study spanned from the index date (when the diagnosis of GPP was made) up to the last data entry available in the medical chart at the time of data collection. If there was a loss of follow-up, data were collected up to the visit closest to that date. Loss of follow-up was defined by patient's death, referral to another center or other reasons as recorded in the patient's source documents. If the patient was included in a clinical trial during the study period that period was excluded from data collection.

For each eligible patient, information about medical history and follow-up visits was collected covering all visits related to GPP disease monitoring and flare management. No study visit was planned for the study. If a patient met all the study selection criteria, all the required information was recorded in an electronic case report form by the investigator or designee during the study recruitment period.

Inclusion and Exclusion Criteria

The clinical diagnosis of GPP was established by dermatologists based on at least one of these criteria: physical examination, laboratory and histopathology studies, mutation analysis and/or published consensus criteria (e.g., ERASPEN, national criteria). Because there are no national guidelines on GPP, national criteria were based on several publications of Spanish Psoriasis Group of the Spanish Academy of Dermatology and Venereology [36, 37]. Patients included were those of any age with a confirmed diagnosis of GPP made during or after 2011 and at least 6 months prior to data collection, and with at least 2 records related to GPP during the study period (including the GPP diagnosis visit). Patients with a confirmed diagnosis of acute generalized exanthematous pustulosis (AGEP) but with no history of GPP were excluded.

Variables and Outcomes

Sociodemographic and clinical characteristics were collected, including potential risk factors related to the development of GPP and its initial diagnosis. Comorbidities and GPP complications were recorded for the purpose of describing the burden of disease. The characteristics, frequency, potential triggers, and assessment (including calculation of body surface area [BSA], Generalized Pustular Psoriasis Physician Global Assessment [GPPGA], and Generalized Pustular Psoriasis Area and Severity Index [GPPASI] scores when recorded) of GPP flares were analyzed. Finally, to describe treatment patterns of GPP, the following variables were collected for both flares and intercurrent periods: pharmacologic treatment type, dose, frequency and duration, non-pharmacologic treatment, and treatment response (as per clinician's judgment). Treatment response was recorded as complete response (total resolution/remission of pustules, namely, complete clearance, and systemic signs recovery), partial response (partial resolution of pustules, namely, incomplete clearance, and incomplete symptoms recovery), or treatment failure (poor resolution of pustules and symptoms or emergence of fresh pustules). Also, the reason for discontinuation of GPP flare or maintenance treatment (i.e., ineffectiveness, adverse events, remission, or a combination thereof) was collected.

Statistical Analysis

A descriptive analysis was conducted for all patients in the study population and by sub-groups of interest. Continuous variables were summarized using mean, standard deviation (SD), median and quartiles, minimum and maximum values, and number of valid, not applicable, and missing cases. Categorical variables were summarized with number of valid cases and percentage of total. Treatment persistence was calculated as the time until discontinuation using Kaplan-Meier survival analysis. The percentage of patients who maintained treatment during the study period was recorded. Patients who remained on treatment throughout the study were censored at the date of last data available in the medical chart. All analyses were conducted using Statistical Analysis System [38] software, Enterprise Guide 7.15 (Cary, NC, USA).

Results

Socio-Demographics and Clinical Characteristics of Patients at Diagnosis of GPP

A total of 56 patients meeting the selection criteria were included (Fig. 1). Results of sociodemographic and global variables at the time of GPP diagnosis are summarized in Table 1. The mean (SD) age at diagnosis was 53.7 years (20.5) with a median [first quartile (Q1) – third quartile (Q3)] of 57.5 (40.5–67.5) years. The most frequent age cohorts were ≥65 years (n = 17; 30.4%) and ≥55–64 years (n = 13; 23.2%). In 44 patients (80.0% of total valid cases), the diagnosis of GPP was associated with a GPP flare. The mean (SD) time since diagnosis of the disease until inclusion in this study was close to 5 years (4.7 [3.1]) with a median (Q1–Q3) of 4.2 (2.0–7.5) years. At the time of their initial GPP diagnosis, 91.1% of patients had received drug treatments.

Thirty-seven patients (67.3%) had potential risk factors for GPP development at diagnosis. The risk factors most frequently observed were as follows: previous diagnosis of psoriasis (n = 22); comorbidities (at least one: n = 15, including plaque psoriasis n = 7; hypertension n = 2, psoriatic arthritis n = 2, neoplastic disease n = 2, and inflammatory bowel disease, n = 2); family history of psoriasis (n = 13); smoking (n = 11); stress (n = 10); alcohol consumption (n = 8); medication or treatment

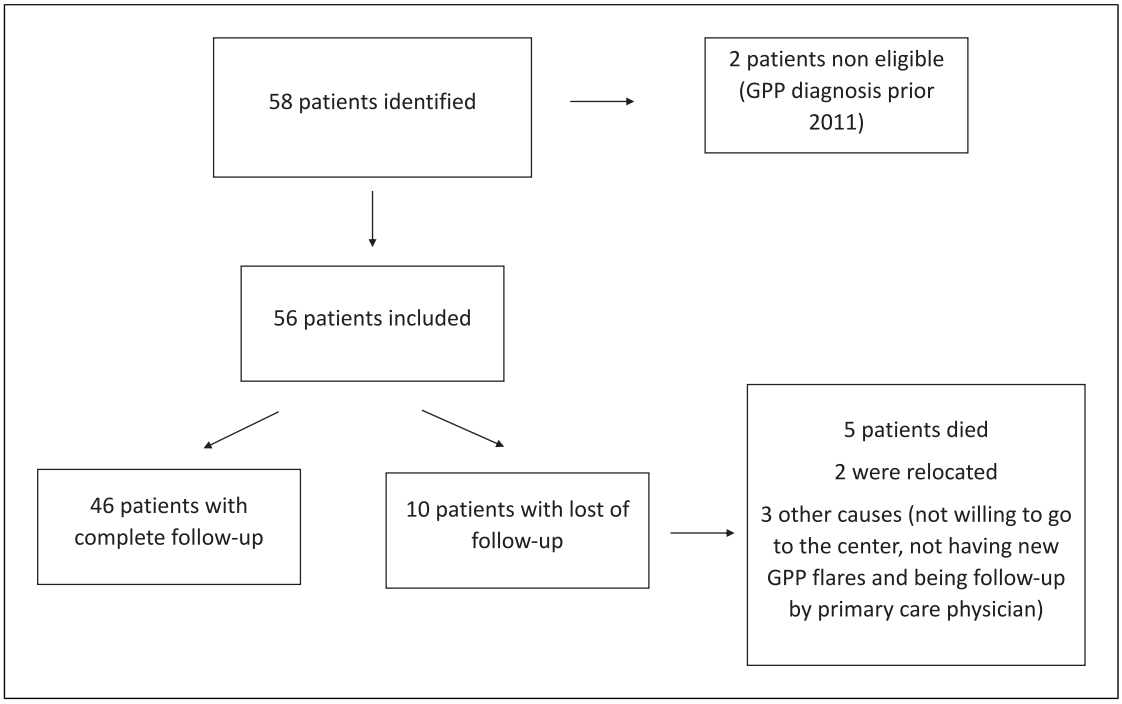

Fig. 1. Flowchart of patients included in the study.

(n = 6; including adalimumab n = 2 and methotrexate n = 2); and family history of psoriatic arthritis (n = 3). The procedures aimed at confirming the diagnosis of GPP are shown in Table 1. The diagnostic criteria (applied in 20 of 56 patients) were based on ERASPEN (n = 7 of 39 patients with data available; 17.9%), national criteria (n = 6 of 39 patients with data available; 15.4%), or institutional guidelines (n = 3 of 39 patients with data available; 7.7%).

In skin biopsy specimens obtained at the time of GPP diagnosis (samples available in 35 patients), the most frequent histopathological findings were neutrophilic and lymphocytic infiltration in the upper dermis (seen in 74.3%, 26 of 35 biopsy specimens), superficial perivascular mononuclear cell infiltrates (65.7%, 23 of 35), Kogoj's spongiform pustules (neutrophilic subcorneal pustules, 62.9%, 22 of 35), acanthosis (54.3%, 19 of 35), or hyperkeratosis (45.7%, 16 of 35), among others.

Eighteen patients (62.3% (18/28) patients with available laboratory results) had abnormal values; the mean (SD) values were 137.4 (154.3) U/L for alanine aminotransferase (n = 5), 167.4 (269.6) U/L for aspartate aminotransferase (n = 5), and 66.9 (103.26) mg/L for C-reactive protein serum levels (n = 10). Genetic testing at diagnosis was performed in 2 patients (out of 56 patients, or 3.6%). IL36RN and CARD14 gene mutations were found in one, and none were detected in the second patient.

BSA was measured in 26.8% (n = 15 of 56) of patients at diagnosis of GPP, with a mean (SD) of 41.3% (21.3). According to BSA categories, 6.7% of patients (n = 1) had BSA involvement between 0 and 10%, 6.7% (n = 1) between 11 and 20%, 26.7% (n = 4) between 21 and 30%, 13.3% (n = 2) between 31 and 40%, 26.7% (n = 4) between 41 and 50%, 6.7% (n = 1) between 51 and 60%, 6.7% (n = 1) between 61 and 70%, and 6.7% (n = 1) between 81 and 90%.

The cutaneous signs at diagnosis of GPP are detailed in Table 1; the most frequent were pustules (n = 52; 94.5%), scaling (n = 39; 70.9%) and erythema (n = 39; 70.9%). Extracutaneous manifestations were quite common (n = 21; 37.5%) and heterogeneous; the most frequently observed are also detailed in Table 1.

Clinical Characteristics, Assessment, and Trigger Factors of GPP Flares

The number of GPP flares per patient/year was 0.55 (range between 0 and 4 flares per patient-year), and the total number of recorded flares was 112, with a mean (SD) BSA involvement of 21.3% (19.1). The mean (SD) time from diagnosis to the first flare of GPP was 49.9 (208.2) days in patients with flares (n = 52; only 4 patients did not have a flare). The mean (SD) duration of GPP flares was 53.4 (61.9) days with a median of 31.5 days (Q1–Q3, 15–74). Among the patients with examinations and/or

Table 1. Sociodemographics and clinical characteristics of patients at diagnosis of GPP

Variable	Total	*N* valid
Age at diagnosis, mean (SD), years Median (Q1–Q3)	53.7 (20.5) 57.5 (40.5–67.5)	56
Follow-up duration, mean (SD), years Median (Q1–Q3)	3.7 (3.1) 3.7 (1.2–5.8)	56
Female sex, n (%)	28 (50.0)	56
Geographical ancestry, *n* (%)		
Central, South, and/or East Asian Descent	2 (3.6)	
Central and/or South American Descent	7 (12.5)	56
Middle Eastern and/or North African Descent	1 (1.8)	
White Caucasian and/or European Descent	46 (82.1)	
BMI, mean (SD), kg/m^2	26.6 (6.5)	38
Pregnancy status, *n* (%)	1 (3.8)	25
Mean % BSA	41.3 (21.3)	15
Examinations and test performed at GPP diagnosis, *n* (%)		
Physical examinations	56 (100)	
Histopathological examination	38 (67.9)	
Laboratory tests	28 (50.0)	56
Vital signs	12 (21.4)	
Genetic analysis	2 (3.6)	
Abdominal echography	1 (1.8)	
Cutaneous symptoms at GPP diagnosis; *n* (% relative to patients who presented cutaneous manifestations, *n* = 55)		
Pustules	52 (94.5)	
Scaling	39 (70.9)	
Erythema	39 (70.9)	
Plaque	34 (61.8)	55
Skin lesions	30 (54.5)	
Itchiness	20 (36.4)	
Pain	17 (30.9)	
Edema	12 (21.4)	
Burning	11 (20.0)	
Nail abnormalities	10 (18.2)	
Extracutaneous manifestations at GPP diagnosis; n (% relative to patients who presented extracutaneous manifestations, *n* = 21)		
Fatigue	9 (42.9)	21
Myalgia	8 (38.1)	
Fever	8 (38.1)	

SD, standard deviation; Q1–Q3, quartile 1–quartile 3; BMI, body mass index; BSA, body surface area; GPP, generalized pustular psoriasis.

tests performed at diagnosis during GPP flares (*n* = 52), 50.0% (*n* = 26) had a physical examination available, a histopathological exam of a biopsy specimen was performed in 9.6% (*n* = 5), laboratory tests were carried out in 15.4% (*n* = 8), vital signs were recorded in 1.9% (*n* = 1), and a teledermatological assessment was performed in 1.9% (*n* = 1). The most frequent symptoms accompanying GPP flares (in patients with physical examination *n* = 26) were pustules (*n* = 23, 88.5%), erythema (*n* = 20, 76.9%), and scaling (*n* = 20, 76.9%). In addition, 65.4% of patients (*n* = 17) had psoriasis plaques, 53.8% (*n* = 14) had unspecified skin lesions, and 30.8% (*n* = 8) experienced pain. Regarding extracutaneous signs and symptoms (in patients with physical examination *n* = 26), 14 (53.8%) patients had none, 4 (15.4%) had fatigue, 4 (15.4%) had fever, 3 (11.5%) had anorexia, 3 (11.5%) had edema, and 3 (11.5%) had acute respiratory symptoms. The most frequently identified histopathological findings

(in patients with histopathological exam of a biopsy specimen, n = 5) were neutrophilic and lymphocytic infiltration in the upper dermis (n = 4; 80.0%), Kogoj's spongiform pustules (neutrophilic subcorneal pustules (n = 4; 80.0%), capillary dilation in the papillary dermis (n = 3; 60.0%), and superficial perivascular mononuclear cell infiltrates (n = 3; 60.0%).

Flare assessment was based on scales or patient questionnaires in only 3 patients (5.8%). The GPP Physician Global Assessment scale (GPPGA) was used in 2 patients to assess disease severity (one of these patients had moderate disease activity and the other severe activity according to this scale), and the GPP area and severity index scale (GPPASI) was used in 1 patient (indicating severe disease activity according to this scale). Additionally, the PGA score was used in 1 patient (with severe activity according to this scale) and in another one, a PASI score of 11.0 was calculated. No scales were used to assess disease symptoms, such as visual analog scale score [39] or quality of life (Dermatology Life Quality Index [DLQI], EQ-5D, work productivity, and activity impairment scores (WPAI]).

Among the 51 patients with flare and potential trigger data available, 21 (41.2%) had potential GPP triggers, including viral, bacterial, or fungal infections (5 cases, 23.8%), stress (5 cases, 23.8%), drug-based treatment of GPP or GPP flare withdrawal (3 cases, 14.3%), or other triggers (6 cases, 28.6%, including fever, amoxycillin treatment [provocation allergy tests], flu vaccination, tapering down of cyclosporine dose, acitretin withdrawal, and dose decrease with concomitant withdrawal of corticosteroids).

Treatment of GPP

Treatment of GPP Flares

The treatments most commonly used for flares were conventional systemics (in 75% of patients, 33 of 44 patients with any treatment, mostly corticosteroids, cyclosporine, and acitretin), followed by topical treatment (40.9%, 18 of 44 patients with any treatment), biological treatment (36.4%, 16 of 44 patients with any treatment), and antibiotics and other treatments (22.7%, 10 of 44 patients with any treatment) (Fig. 2a, b.).

Regarding biological treatments, anti-IL-17 agents were received by 20.5% of patients (n = 9 of 44 patients with any treatment), anti-TNF agents by 13.6% (n = 6 of 44 patients with any treatment), and anti-IL-23 and anti-IL12/23 were used in 1 patient each. The mean (SD) time from diagnosis to treatment initiation was 11.2 (15.3) months for anti-IL-17 agents and 7.82 (13.28) months for TNF-antagonists. The median (Q1-Q3) time from diagnosis to treatment initiation was 5 (1.5–13.9) months for anti-IL-17 agents and 3.2 (0–6.1) months for TNF-antagonists.

Psoralen plus ultraviolet light-A therapy, emollients and narrow-band ultraviolet B (UVB) were used in 2 patients each for treatment of GPP flares. On the other hand, acitretin plus ultraviolet light-A therapy (re-UVA) and potassium permanganate bath were used in 1 patient each.

Among the 42 patients with any treatment for GPP flares and outcome data available, 61.9% (n = 26) had a complete response, 61.9% (n = 26) had a partial response, and 16.7% (n = 7) experienced treatment failure/no response to treatment in any flares. Reason for termination of GPP flare treatment was recorded in 37 patients; 24 (64.9%) discontinued the treatment because of flare resolution, 19 (51.4%) due to lack of efficacy (clinician judgment), 4 (10.8%) due to treatment-related adverse events, and 8 (21.6%) due to other causes. A new drug was received, or treatment had been changed since last visit in 75.0% (n = 33) of patients.

Treatment for GPP between Flares

The most commonly used options in the follow-up period were off-label biologics (56.5%, 26 cases out of 46 patients with treatment between flares), including anti-TNF, anti-IL-17, anti IL12/23, and anti-IL-23 agents, followed by conventional systemic agents (47.8%, 22 of 46 patients with treatment between flares), topical treatment (41.3%, 19 of 46 patients with treatment between flares) and antibiotics or other treatments (8.7%, 4 of 46 patients with treatment between flares) (Fig. 2a, c).

By mechanism of action, anti-TNF agents were the most frequently used biologics (n = 13 of 46 patients with treatment between flares; 28.3%) followed by anti-IL-17 (n = 9 of 46 patients with treatment between flares; 19.6%), anti-IL-12/23 (n = 8 of 46 patients with treatment between flares; 17.4%), and anti-IL-23 drugs (n = 5 of 46 patients with treatment between flares; 10.9%). The shortest interval since diagnosis to drug initiation corresponded to anti-TNF treatment, with a mean (SD) of 6.6 (7.8) months (median [Q1-Q3] of 6.6 [0.5–9.3] months). On the other hand, the interval between diagnosis and prescription was longest for anti-IL-23 biologics, with a mean (SD) of 38.6 (33.8) months (median [Q1–Q3] of 58.3 [3–59.8] months). The duration of treatment was 41.8 (32.4) months for anti-IL-12/23 agents, followed by 29.0 (34.1) months for anti-TNF, 14.5 (6.8) months for anti-IL-17, and 13.4 (6.9) months for anti-IL-23 biologic agents.

Regarding non-drug-based treatment for GPP periods between flares, Psoralen plus ultraviolet light-A therapy

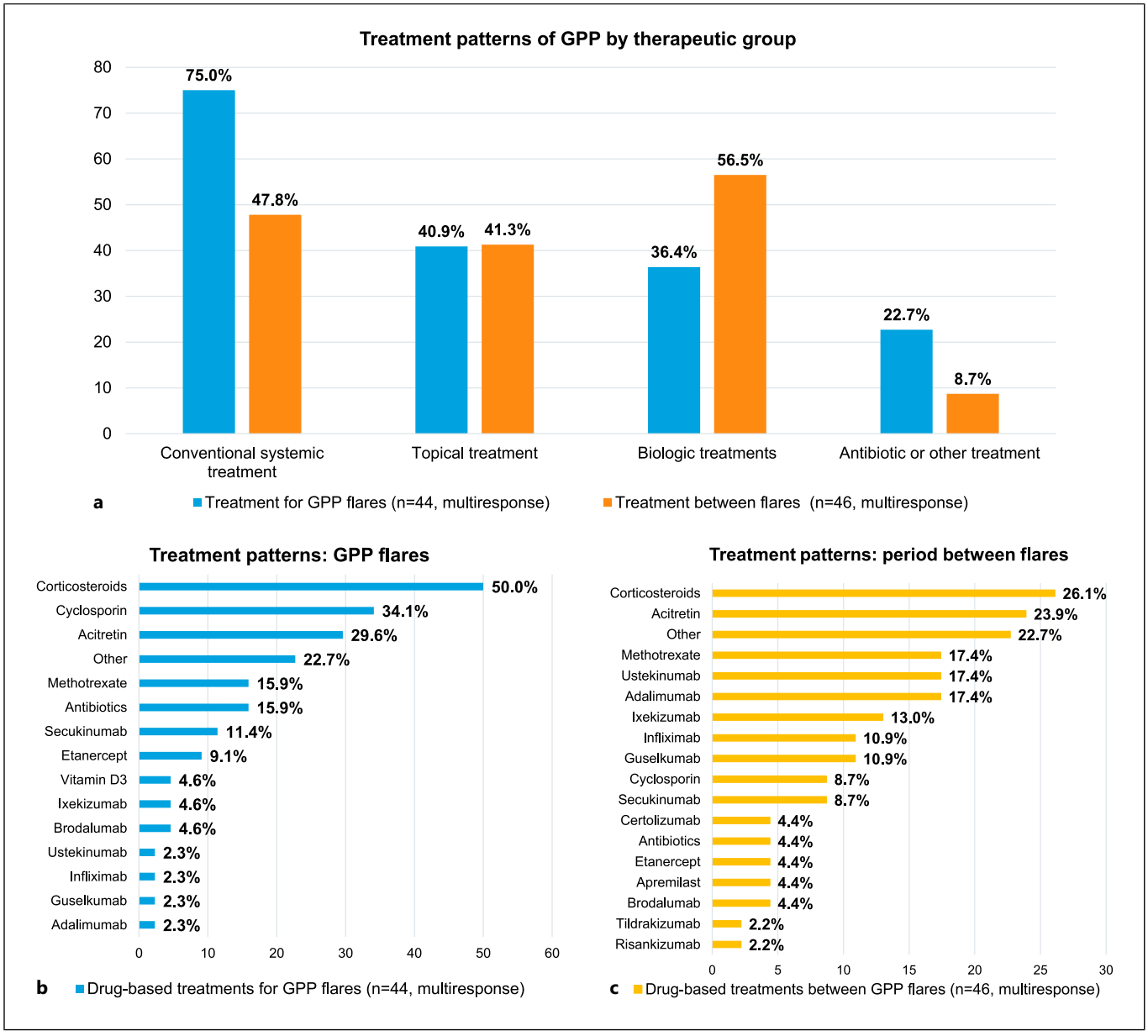

Fig. 2. a Treatment patterns of GPP by therapeutic group (treatment for flare and period between flare). **b** Treatment patterns of GPP flares according to drug-based treatment used. **c** Treatment patterns of GPP in periods between flares according to drug-based treatment used.

(with or without UVB) was used by 2 patients. Emollients were used by seven and narrow-band UVB and coal tar were used by 1 patient each.

Thirty-two patients (69.6%) discontinued their GPP treatment. The reasons for termination were lack of efficacy (according to clinician's judgment) (n = 15, 46.7%), treatment-related adverse events (n = 8, 25.0%), and other causes (n = 14, 43.8%), including disease remission (n = 3; 9.4%), completion of treatment course (n = 2; 6.3%), and patient's decision (n = 2; 6.3%). In 84.8% of patients (n = 39 of 46 that had treatment between flares), a new drug was started, or treatment had been changed since their last visit.

Persistence of treatment for GPP between flares decreased over time for biological and conventional systemic drugs as shown in Fig. 3 by Kaplan-Meier method.

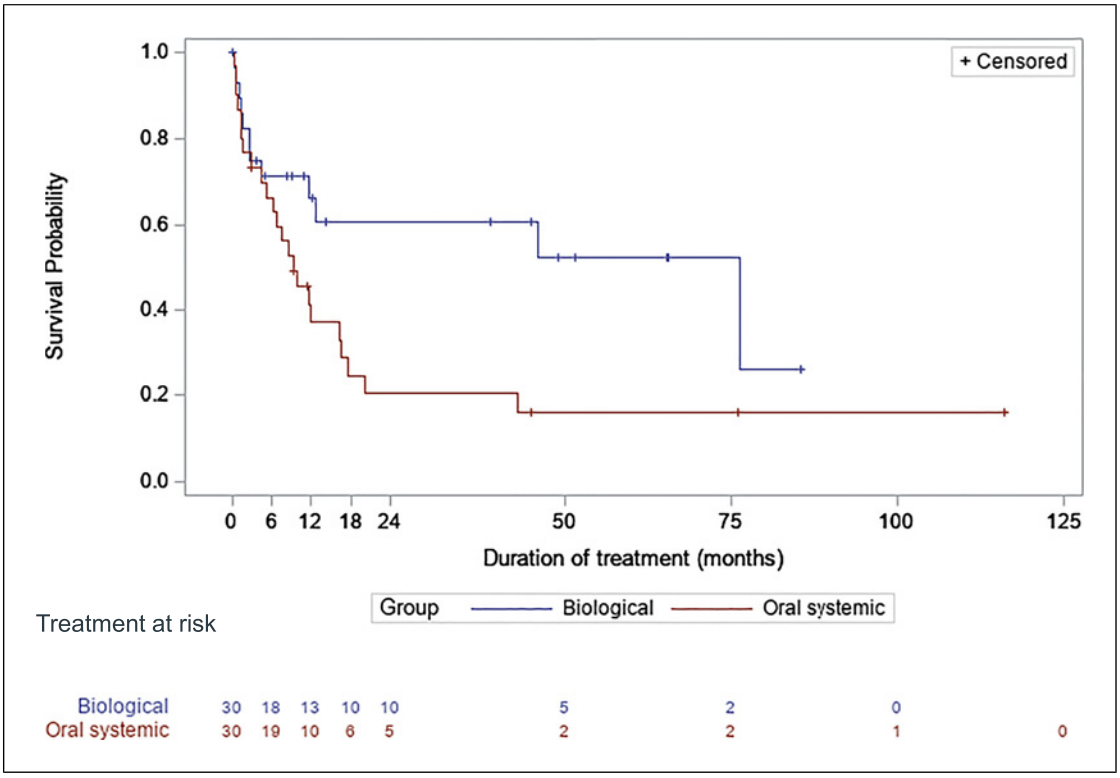

Fig. 3. Time until discontinuation of treatments prescribed between flares, by groups (cumulative probability curves by Kaplan-Meier method).

Persistence rate (95% confidence interval) at 12 months was 66.2% (44.6–81) for biological drugs and 37% (19.6–54.4) for conventional systemics. Persistence rate of treatment at 24 months (95% confidence interval) was 60.6% (38.3–77.0) for biological drugs and 21% (7.7–37.6) for conventional systemics.

Complications of GPP

Nine patients (of the total number of patients, $n = 56$, 16.1%) had at least one complication during the observational period of the study. The complications identified and their management are shown in Table 2. Five out of the 9 (8.9% of all patients) patients who suffered a complication required hospitalization, while 6 (66.7%) required some treatment. The mean (SD) duration of complications was 7.9 (3.7) days.

Comorbidities

Forty-nine of the 56 patients in our study (85.7%) presented at least one comorbidity; they were often multiple and required treatment. The mean (SD) number of comorbidities per patient was 3.5 (2.8) with a median (Q1–Q3) of 3.0 (1–5.5), but 25.0% ($n = 14$) of the patients had 6 or more comorbidities. The most frequent comorbidities were psoriasis ($n = 25$, 44.6%), hypertension ($n = 25$; 44.6%), dyslipidemia ($n = 18$; 32.1%), diabetes mellitus ($n = 14$; 25.0%), psychiatric disorder ($n = 10$; 17.9%), obesity ($n = 6$; 10.7%), liver disease ($n = 6$; 10.7%), endocrinologic disease ($n = 5$; 8.9%), psoriatic arthritis ($n = 5$; 8.9%), neoplastic disease ($n = 5$; 8.9%), or congestive heart failure ($n = 5$; 8.9%), among others. Other less common comorbidities were chronic kidney disease ($n = 4$; 7.1%), renal insufficiency ($n = 2$; 3.6%), or ischemic heart disease ($n = 2$; 3.6%).

Discussion/Conclusion

Because of the low prevalence and high heterogeneity of GPP [40], the existing information regarding its clinical course is limited and there are few studies reporting treatments and outcomes for large numbers of patients. These unmet needs align with the findings of a recent Delphi methodology study involving Italian GPP experts, which revealed a persistent knowledge gap and the necessity for improvement [41]. In addition, data

Table 2. Type of complications identified, and need for hospitalization or treatment due to those complications

Type of complication	Patients with this complication*, *n* (%)	Patients requiring hospitalization*, *n* (%)	Patients requiring treatment*, *n* (%)
Abnormal laboratory	3 (5.4)	2 (66.7)	1 (33.3)
Acute respiratory distress syndrome	1 (1.8)	1 (100)	1 (100)
Arthritis	1 (1.8)	0 (0)	0 (0)
Congestive heart failure	1 (1.8)	1 (100)	1 (100)
Renal failure/renal insufficiency	1 (1.8)	1 (100)	1 (100)
Other	6 (10.7)		
Anorexia + asthenia + fever	1 (1.8)	1 (100)	0 (0)
Herpes zoster	2 (3.6)	1 (67.9)	2 (100)
Pruritus	1 (1.8)	0 (0)	0 (0)
Psoriasis of scalp	1 (1.8)	0 (0)	1 (100)
Rosacea	1 (1.8)	0 (0)	1 (100)
COVID-19 pneumonia	1 (1.8)	1 (100)	1 (100)
Pain	1 (1.8)	0 (0)	0 (0)
Skin lesions (unspecified)	1 (1.8)	0 (0)	0 (0)

*The same patient could have several complications and requirements at the same time.

sources differ widely in the published reports, which used non-standardized methodologies; consequently, there is a lack of more complete factual data at the regional, national, or global level. Our study describes the socio-demographic and clinical characteristics, frequency and management of flares and complications, comorbidities, and treatment patterns in a series of 56 patients with GPP who were managed in 14 centers in Spain with a mean follow-up of 3.7 years (median 3.7, Q1–Q3 [1.2–5.8]).

This is the first multicenter study in GPP patients in Spain, providing new evidence regarding this rare and potentially severe inflammatory skin disease.

According to epidemiological studies, the prevalence of GPP seems higher in females than males, with ratios of 2:1 and 3.7:1 in some studies in Malaysian and Chinese populations, respectively [10, 42]. However, this female preponderance has not been demonstrated in all series due to GPP variation across geographical regions and ancestries; according to some recent studies, GPP is more frequent in male patients [43, 44]. In our study both sexes were equally represented; this is consistent with findings in other previously published Spanish studies, such as the one based on the BIOBADADERM Registry (n = 41 patients), where 46.3% of patients were male [45], or the population-based study on hospital admission of Montero-Vilchez et al. [46], with females accounting for 51.3% of patients.

GPP can present at any age; in most reported cases, it manifests initially at age 50 [16, 47], but there is great variability across studies: 40–45 years of age in Asian populations [10, 42], 50–55 years of age in European populations [48, 49]. The mean age at hospitalization reported in Spanish studies ranges from 62.2 years [45] to 56.8 years [46]; in our study, the mean age at diagnosis of GPP was 53.7 years, but nearly one-third of patients were diagnosed after the age of 65.

Most cases of GPP are idiopathic. However, there are risk factors that might be etiologically relevant, such as a family history of psoriasis, stress, withdrawal of systemic corticosteroids or cyclosporine, infections (viral or bacterial), and pregnancy [8, 10, 14–17]. In our series, two-thirds of patients presented some risk factor that could increase the risk of developing GPP, the most frequent being a personal or family history of psoriasis. In a study including 110 patients in China, a history of psoriasis was even more prevalent than in our series (85.5% vs. 59.5%, respectively) and 10.9% had a history of psoriatic arthritis [33]. On the other hand, a family history of psoriasis was less frequent than in our study (14.5% vs. 44.8%, respectively). This difference may be due to two factors: in our study, this variable was only collected from some of the patients, and our patients' geographic ancestry was European White in >80% of cases.

Regarding other potential risk factors for GPP beyond personal and family medical history, previous publications have identified infections and pregnancy [50]. The presence of previous infections or pregnancy at diagnosis was anecdotal in our study (only 2 and 1

cases, respectively). Metabolic diseases, such as diabetes and cardiovascular diseases, have also been associated with psoriasis [51, 52]. In our series, the mean body mass index (BMI) was high and previous history of overweight or obesity were frequent, as were comorbidities such as hypertension, dyslipidemia, or diabetes, in accordance with the mean age of patients included. Moreover, previous studies have supported the view that metabolic diseases are not only risk factors for the development of GPP, but also determine a worse evolution and response to treatments, increasing the morbidity and total mortality as well as the demands for health care services [53, 54]. Screening for metabolic diseases as well as control of these conditions is therefore highly recommended for GPP patients to avoid cardiovascular events or complications.

Environmental and lifestyle factors such as alcohol consumption and smoking have been associated with pustular lesions (OR = 5.3 for smokers) [55]. In our study, 32.4% of patients had past or current exposure to smoking, 29.4% had stress, and 23.5% consumed alcohol. Thus, once the diagnosis of GPP has been confirmed, it is of great importance not only to control the associated comorbidities but also to encourage patients to follow a series of lifestyle recommendations (non-pharmacological treatment), such as quitting smoking or reducing alcohol consumption to improve the evolution of disease.

Finally, only a few patients received treatments that were considered related to GPP development (n = 6, 1 patient taking two of them: adalimumab in two cases, methotrexate in two, and amoxicillin/clavulanic acid, trastuzumab, and indomethacin in one case each). Overall, even though triggering/external factors were described in our series, the most frequently reported risk factors were intrinsic, such as family or personal medical history.

Diagnosis of GPP is based on clinical features, abnormal laboratory test results, histopathological findings, and genetic evaluations [22, 32, 56]. In our study, using real-world clinical practice data, physical examination was the basis of disease diagnosis in all patients, biopsy specimens were examined in two-thirds of them, and laboratory tests in 50%, while application of the diagnostic criteria described by ERASPEN, national or institutional guidelines, as well as genetic analysis were infrequent. Therefore, although physical (pustules, scaling, erythema, plaques) and histological findings (neutrophilic and lymphocytic infiltration in upper dermis, superficial perivascular mononuclear cell infiltrates, Kogoj's spongiform pustules, etc.) are consistent, a more accurate diagnosis of GPP could also help further personalize treatment and to optimize the management of these patients.

Regarding the burden of GPP, 9 patients (16.1%) had complications that required hospitalization in 5 cases and treatment in 6. Comorbidities were quite frequent and required treatment in many cases, contributing to a high burden of disease and resource consumption. In our study, 85.7% of patients presented at least one comorbidity, but patients usually had several concomitant comorbidities: the mean number of comorbidities per patient was 3.5 and 25.0% of patients had 6 comorbidities or more, with the increasing risk for worse prognosis and disease course this entails. The most frequent comorbidities were psoriasis, hypertension, dyslipidemia, and diabetes mellitus. According to a Japanese study, patients with GPP were more likely to have comorbidities (such as hypertension, type 2 diabetes, obesity, and other forms of psoriasis) than patients with psoriasis [57], suggesting a higher disease burden in GPP [58]. However, some of these comorbidities may be related to lifestyle and might not necessarily be specific to GPP or generalizable to other geographical regions or ancestries [10]. In another study in a Spanish population, hypercholesterolemia, hypertension, and diabetes were the most common comorbidities [46], in line with our findings.

In our series, the mean number of GPP flares per year was 0.55, with a mean duration of 53.4 days. In a GPP Spanish survey, 55.3% of the patients experienced less than one flare/year, while 31.6% and 13.2% experienced 1–2 flares/year or more than 2 flares/year, respectively [59]. On the other hand, Choon et al. obtained results showing that in 57.1% of patients with typical flares, the duration of the flare was more than 3 weeks [60].

GPP flares can be triggered by certain medications, withdrawal of systemic or topical corticosteroids, antibiotics such as amoxicillin, terbinafine, calcipotriol ointment, betamethasone ointment, and TNF- inhibitors), infections (*Streptococcus sp*., *T. rubrum*, cytomegalovirus, Epstein-Barr virus, and *V. zoster* virus), and environmental factors [1, 10, 11, 17, 22–24, 61]. In our study, potential GPP flare triggers were recorded for 40.0% of patients; the most common were viral, bacterial or fungal infections (5 cases), stress (5 cases), and concomitant medication use/withdrawal (2 cases). Other less frequent potential flare triggers (only 1 patient per event) were amoxicillin (provocation allergy tests), low-dose cyclosporine, withdrawal of acitretin, and low-dose acitretin with withdrawal of corticosteroids prescribed for

lumbago, among others. Due to the limited number of cases without flare, a multivariate regression analysis of factors predictive of GPP flare development could not be carried out. Despite this, it is worth taking modifiable variables such as psychological stress into consideration, and clinicians should be alert in the event of infections or treatment modification so as to quickly identify the initial development of a flare.

Objective scales and questionnaires for flare assessment were only used in a few patients. According to those scores, most cases had severe or moderate activity, but no further conclusions can be drawn due to the low number of cases. These data show that awareness of these measures is still scarce and disease severity is not being accurately assessed. Being able to base the diagnosis of flares on homogeneous criteria is worth recommending, since the severity of a flare can determine the evolution of the disease and drive treatment selection.

Although the Spanish evidence-based guideline on psoriasis treatment lists pustular psoriasis among the eligibility criteria for systemic therapy (either conventional or biologic, off-label by default at the time of writing), there is no standard of care for GPP treatment, and the guideline does not provide specific treatment recommendations for the various forms of GPP [31]. The Psoriasis Group of the Spanish Academy of Dermatology and Venereology (GPs) includes GPP among severe variants of psoriasis but does not provide any treatment recommendation [62]. Pharmacological treatment of GPP generally includes off-label use of conventional systemic treatments, biological treatments, and topical therapy [1]. The biological treatments used are mainly anti-TNF-(etanercept, infliximab, adalimumab, certolizumab), anti-IL12/23 (ustekinumab), anti-IL17 (secukinumab, ixekizumab, brodalumab) and anti-IL23 agents (guselkumab, tildrakizumab) [9, 33, 35]. Moreover, other biological medications targeting anti-IL-1 (anakinra), anti-IL-1β (gevokizumab, canakinumab), or IgG (alefacept, itolizumab) have been used for the treatment of GPP [33, 63–65]. Despite the wide variety of therapeutic options, only some biological treatments had been approved in Japan and other Asian countries, and there were no specific treatments for GPP approved in USA or Europe until spesolimab, a humanized anti-IL-36 receptor monoclonal antibody, was approved by the FDA (September 2022) and the EMA (December 2022) for the treatment of GPP flares. This treatment was associated with a rapid modulation of commonly dysregulated molecular IL-36 pathways in these patients [27, 28].

In our study, and in line with previous publications [66], the pharmacological treatments for intercurrent periods between flares were mostly off-label biological drugs, conventional systemic treatments, and topical treatments. Categorized by type of treatment, the most commonly used were corticosteroids and acitretin, followed by adalimumab, methotrexate, and ustekinumab. The time from diagnosis until first main treatment initiation was short (4 months), but this period was considerably longer for topical treatment (1 year) and for biologic treatments (around 8 months).

On the other hand, conventional systemics, including corticosteroids, acitretin, cyclosporine, and methotrexate, have been typically used as first-line options for GPP flares, although with limited evidence [66]. The most common treatments used for flare control in our study were conventional systemics, mostly corticosteroids, cyclosporine and acitretin, although there was not a clear pattern for flare management. Biologics were used in a high percentage of cases, mainly anti-IL-17 and anti-TNF-agents. Although data published confirming the therapeutic effectiveness of IL-17 and TNF-biologics for acute flares is scarce [66], their use in clinical practice is seemingly commonplace due to the previous lack of approved treatments.

Changes in maintenance treatments were also common, with 84.8% of patients receiving a new treatment or changing the drug-based treatment since the last visit. In fact, the probability of continuing with a biological drug or a conventional systemic therapy during the period between flares decreased with time, with a 60.6% and a 21% probability of continuing with these treatments after 24 months from start, respectively. The main reason for changes or withdrawal of treatment was lack of efficacy, both for periods between flares and during flare therapy. This lack of efficacy was observed in almost half of patients and highlights the need of more effective and specific treatments to help control disease flares and maintain the periods of dormancy as long as possible.

Finally, the study had limitations inherent in its design (medical chart review), such as missing data or information and selection bias, which could reduce the validity of our results. To minimize these limitations, a feasibility exercise was conducted to ensure the availability of the minimum essential data (age, date of diagnosis, potential GPP flares, as defined by the inclusion criteria in the study protocol). Moreover, initial training of the investigators followed by continuous remote data monitoring enabled standardization of data collection and entry into the electronic case report form. Besides, only data from routine GPP care were collected and considered in this study, and the selection criteria were clearly defined in the study protocol. Due to the limited number of cases

without flare, a comparison by means of a multivariate regression to confirm these factors as predictive of GPP flare development could not be carried out. Additionally, due to the lack of standardized criteria for differentiating GPP from other similar conditions such as AGEP, which shares common clinicopathological features, misclassification bias may occur, leading to some patients with GPP being misclassified. However, it is estimated that this misclassification was minimal since only dermatologists with expertise in GPP management were selected for participation in this study.

In conclusion, this is the first multicenter study in GPP patients in Spain (n = 56) and provides new real-world evidence on this rare, chronic, severe neutrophilic inflammatory skin disease. Patients were in their fifties, with family and personal history of plaque psoriasis, stress, exposure to smoking and other comorbidities as the main potential triggers. Development of flares was frequent, 0.55 flares/patient/year, although there was variability between patients (0–4). Most patients presented comorbidities and 9 patients (16.1%) had at least one complication of GPP.

There is no standard of care in GPP management in Spain. Our findings indicate that the most common treatments for GPP flares were off-label conventional systemic agents: mostly corticosteroids, cyclosporine and acitretin with no clear pattern regarding flare management. In the follow-up period, off-label biologics were used, including anti-TNF, anti-IL-17, anti IL12/23 and anti-IL-23. In addition, the main cause of treatment discontinuation was lack of efficacy which could lead to inefficiencies for the National Health Systems.

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Statement of Ethics

The study protocol and all other documents related to study were reviewed and approved by the reference Ethic Committee (EC, Hospital Universitario 12 de Octubre, Madrid, Spain), approval no (21/620) and were ratified by the remaining ECs of each participating site. Informed consent form collection was waived by the reference EC.

Conflict of Interest Statement

The authors meet the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE). Dr. L. Puig is the scientific coordinator of the IMPULSE study and has received honoraria from Boehringer Ingelheim. R. Izu Belloso, R. Rivera-Díaz, J. Mollet Sánchez, L. Rodríguez Fernández-Freire, A. Sahuquillo Torralba, and R. Ruiz Villaverde are researchers of the study. The authors did not receive any payment related to the development of this manuscript.

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Author Contributions

This national, multicenter and noninterventional study was conducted by 14 principal investigators (PI) at centers included in the Spanish Public National Health System (NHS) detailed in the list of IMPULSE Investigators Group (Lluís Puig, Rosa Izu Belloso, Raquel Rivera-Díaz, Jordi Mollet Sánchez, Lourdes Rodríguez Fernández-Freire, Antonio Sahuquillo-Torralba, Ricardo Ruiz-Villaverde, María Teresa Abalde Pintos, Mariano Ara Martín, Elena del Alcázar/José Manuel Carrascosa Carrillo, Rosa María Taberner Ferrer, Pablo de la Cueva Dobao, María Isabel Rodríguez Blanco, and Josep Riera Monroig). All of them included patients in the study. Dr. Lluís Puig contributed to the conceptualization, methodology and analysis. All authors collaborated in the writing and original draft preparation and approved the final version for submission.

Data Availability Statement

To ensure independent interpretation of clinical study results, BI grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the ICMJE criteria.

Furthermore, clinical study documents (i.e., study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/.

Prior to providing access, documents will be examined and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel. Clinical Study Reports and Related Clinical Documents can also be requested via the link https://trials.boehringer-ingelheim.com/

All requests will be governed by a Document Sharing Agreement. Bonafide, qualified scientific and medical researchers may request access to de-identified, analyzable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Researchers should use the https://trials.boehringer-ingelheim.com/link to request access to study data. Further inquiries can be directed to the corresponding author.

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