Drug survival in the treatment of generalized pustular psoriasis: A retrospective multicenter study

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Abstract

Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening inflammatory skin disease. Our aim was to assess patient and disease characteristics and analyze drug survival rates in the treatment of GPP in a real-life setting. In this retrospective study, 201 treatment series of 86 patients with GPP treated at five University Medical Centers were analyzed. Overall, excellent response was reached in 41.3% of all treatment courses, partial response in 31.4%, and nonresponse in 27.3%. Biological treatment was significantly more effective than non-biological therapies (excellent response: 47.4% vs 35.9%; P = .02). Overall, the median drug survival was 14.0 months (biologics: 36.0 months vs nonbiologics: 6.0 months; P < .001).

The crude probability of survival was highest for secukinumab (hazard ratio [HR] of drug discontinuation compared with acitretin: 0.22), followed by ixekizumab and ustekinumab (HR: 0.38 each), adalimumab (HR: 0.59), etanercept (HR: 0.62), infliximab (HR: 0.69), cyclosporine (HR: 1.00), acitretin (reference for HR), fumaric acid esters (HR: 1.06), methotrexate (HR: 1.26), and apremilast (HR: 3.44); no drug discontinuation with guselkumab. Our results reveal high efficacy and drug survival, particularly for IL-17 and IL-12/23 antagonists. Thus, these biologics may be considered early in the therapeutic algorithm of GPP.

KEYWORDS
GPP, IL-12/23, IL-17, TNF-alpha, Zumbusch

1 INTRODUCTION

Generalized pustular psoriasis (GPP) is a rare inflammatory skin disease with an often chronic-relapsing course of disease.1 GPP is nowadays considered a phenotype of pustular psoriasis which also comprises palmoplantar pustulosis (PPP) and acrodermatitis continua of Hallopeau (ACH). GPP clinically presents with multiple coalescing sterile pustules on erythematosus skin, associated with general symptoms such as fever and malaise.3 Laboratory test alterations comprise leukocytosis and elevated C-reactive protein (CRP).3 Extracutaneous manifestations may consist of cholestasis, neutrophilic cholangitis, arthritis, acute respiratory distress syndrome, and mucosal involvement.4-8

Since GPP is a chronic-relapsing and potentially life-threatening disorder, therapeutic long-term control is required.8,9 The therapeutic...
Armamentarium mostly used comprises topical corticosteroids, phototherapy, oral retinoids (acitretin), methotrexate, and cyclosporine.\textsuperscript{9,10} Recently, antipsoriatic biologicals targeting tumor necrosis factor (TNF)-\(\alpha\), interleukin (IL)-17(R), and IL-(12)/23 have been applied for the treatment of GPP in small open trials.\textsuperscript{11} Due to the rarity of the disease, larger clinical studies with high methodological quality are currently not available.\textsuperscript{9}

“Drug survival,” defined as the interval between drug initiation and discontinuation is a relatively new concept for the measurement of therapeutic success in a real-word setting because it incorporates the drug’s effectiveness over time, tolerability, quality-of-life, and further patient-oriented and physician-oriented factors.\textsuperscript{12,13} Drug survival has been extensively studied in systemic treatment of psoriasis (PsO)\textsuperscript{14-20} and recently of palmoplantar pustulosis.\textsuperscript{21} Kishimoto et al investigated drug survival of biologicals in psoriatic patients in Japan.\textsuperscript{22} Among 205 included patients 13 patients suffered from GPP with a total of 25 treatment courses. The authors identified GPP compared with PsO as predictor for drug discontinuation of biologicals with a hazard ratio (HR) of 1.87. However, no further subgroup analysis with regard to GPP patients was reported.\textsuperscript{22}

The aim of this study was to assess patient and disease characteristics and analyze therapy regimens and particularly drug survival in the treatment of GPP in a real-life setting.

\section{MATERIALS AND METHODS}

\subsection{Study cohort}

Patients with GPP treated in the Dermatology Departments of five German University Medical Centers between 01/2005 and 05/2019 were identified retrospectively by their ICD-10 code (L40.1). Medical records were reviewed. Patients with merely localized pustular psoriasis phenotypes, that is, PPP or ACH, and patients with manifestation of GPP under treatment with TNF-\(\alpha\) antagonists as a paradoxical reaction were excluded. Exclusive treatment with systemic glucocorticoids (n = 8) or phototherapy (n = 21) were not included in analysis as those treatment options serve as short-term therapy (mean drug survival: 2.9 months and 1.2 months, respectively). Treatments with only one treatment course (ie, anakinra: treatment response: partial response, drug survival: 60 months, then therapy was switched to secukinumab, the patient was reported on previously,\textsuperscript{23} brodalumab: treatment response: excellent response, drug survival: 9 months, then therapy was switched to ustekinumab due to diarrhea and arthralgia; and tofacitinib: no follow-up data available) were excluded. The study was performed according to the principles of the Declaration of Helsinki,\textsuperscript{24} and approved by the ethics committee of all participating medical centers.

\subsection{Data extraction}

Patient characteristics extracted from medical records comprised sex, age at onset of disease, and age at last visit, clinical features (subtype of GPP, trigger factors, complications, and course of disease), laboratory findings at time of first presentation to the respective University Medical Center, family history, number of biopsies, and comorbidity (PsO, PPP, psoriatic arthritis [PsA], alcohol and tobacco consumption, metabolic diseases, psychiatric disorders, and neoplastic diseases). Treatment characteristics were assessed with regard to type of treatment, dosage, concomitant therapy, adverse events, number of previous therapies, drug survival, and the reason for treatment discontinuation (ie, ineffectiveness, adverse events, remission, or a combination of those). Treatment response at the end of a treatment course (if discontinued) or at last observation (if not discontinued) was categorized into (a) excellent response, implied by a respective phrasing: “complete” or “marked response”, “remission”, “dramatic improvement”, and “near” or “complete clearance”, for example in the medical records and/or photographic evidence, (b) partial response, implied by the phrasing “some improvement”, for example and (c) nonresponse, including exacerbation of disease.

\section{RESULTS}

\subsection{Patient characteristics}

Overall, 86 patients were identified; 65.1\% were female (Table 1). Onset of disease was on average at the age of 51.2 years with a mean disease duration of 8.7 years. Most frequently, infections were reported as trigger factors of first manifestation of GPP (24.7\% of all patients), followed by withdrawal of an antipsoriatic treatment (18.8\%, particularly systemic glucocorticoids) and intake of new medication (8.2\%, most frequently nonsteroidal antiinflammatory drugs and antihypertensive medication). About 88.8\% of patients presented with erythrodermia or suberythrodermia and fever was present in 45.3\%. About 57.7\% of patients complained about fatigue. Laboratory examination at time of first presentation to the respective University Medical Center revealed elevated inflammation parameters in 75.3\% (CRP) and 62.4\% (leukocytosis) of patients and electrolyte imbalance in 38.1\% (hypocalcemia), 26.3\% (hypokalemia/hyperkalemia), and
| Cohort characteristics |
|-------------------------|
| **Characteristic** | **n of patients (%)**<sup>a</sup> |
| Total number of patients | 86 (100) |
| Female gender | 56 (65.1) |
| Age at symptom onset (years), mean (SD) | 51.2 (19.2) |
| Age at last visit (years), mean (SD) | 57.9 (18.4) |
| Disease duration (years), mean (SD) | 8.7 (11.7) |
| Deceased patients<sup>b</sup> | 2 (2.3) |

### Clinical features at initial presentation

- **Von Zumbusch type of GPP**: 66 (80.5)
- **Annular form of GPP**: 16 (19.5)

### Trigger factors of first flare of GPP

| Trigger factor | n of patients (%)<sup>c</sup> |
|---------------|-------------------------------|
| Infection | 21 (24.7) |
| Medication<sup>d</sup> | 7 (8.2) |
| Withdrawal of an antipsoriatic treatment<sup>d</sup> | 16 (18.8) |
| Other<sup>e</sup> | 8 (9.4) |

### Laboratory findings<sup>f</sup>

| Laboratory finding | n of patients (%)<sup>a</sup> |
|--------------------|-------------------------------|
| Erythrodermia/suberythrodermia | 73 (88.0) |
| Fever | 29 (45.3) |
| Fatigue | 41 (57.7) |
| Mucosal involvement | 1 (1.6) |
| Biopsy performed | 55 (64.0) |

### Flare-related complications

| Complication | n of patients (%)<sup>a</sup> |
|--------------|-------------------------------|
| Infection | 25 (36.2) |
| Septicemia | 4 (6.7) |
| Heart failure | 3 (5.1) |
| Acute renal failure | 7 (11.3) |
| Complication requiring IMC/ICU treatment | 8 (12.9) |

### Course of disease

| Course of disease | n of patients (%)<sup>a</sup> |
|-------------------|-------------------------------|
| Predominantly chronic persistent | 12 (14.1) |
| Predominantly relapsing | 46 (54.1) |
| Persistent and relapsing | 7 (8.2) |

### Comorbidity

| Comorbidity | n of patients (%)<sup>a</sup> |
|-------------|-------------------------------|
| Psoriasis vulgaris | 43 (50.0) |
| Interval between diagnosis of PsO and GPP (years), mean (SD)<sup>g</sup> | 10.5 (11.2) |
| Psoriatic arthritis | 15 (17.4) |
| Interval between diagnosis of PsA and GPP (years), mean (SD)<sup>g</sup> | −1.9 (10.6) |

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<sup>a</sup> Number and percentage of all patients with clear documentation, if not indicated otherwise.

<sup>b</sup> One female patient died aged 39 after a disease duration of 14 years due to a myocardial infarction. Another female patient died due to pneumonia at the age of 71 after a flare of GPP which required hospitalization.

<sup>c</sup> Medication with a temporal connection to onset of GPP comprised ramipril and clopidogrel in one patient, nonsteroidal antiinflammatory drugs in two patients, and calcium antagonist, betablocker, trazodone, and hydroxychloroquine in one patient each.

<sup>d</sup> Manifestation of GPP occurred in patients with psoriasis vulgaris who discontinued or tapered treatment with methotrexate (n = 1), fumaric acid esters (n = 1), cyclosporine (n = 1), or systemic corticosteroids (n = 11; maximum dosage: mean: 75.6 mg/day; documented for n = 8).

<sup>e</sup> Other trigger factors comprised UVB311nm phototherapy (n = 1), seasonal exacerbation in spring (n = 1), psychological stress (n = 3), alcohol withdrawal (n = 1), and usage of several illicit drugs (not further specified, n = 1).

<sup>f</sup> Depicted is the number of patients in whom at least one biopsy was performed and, as a percentage of those, in whom histological findings were compatible with GPP.

<sup>g</sup> The following limits of laboratory results were assumed: elevated C-reactive protein: >5 mg/L, leukocytosis: >11 000/μL, hyponatremia: <136 mmol/L, hypokalemia/hyperkalemia: <3.5 and >4.6 mmol/L, hypocalcemia: <2.2 mmol/L, and elevated retention parameter (creatinine): >1.2 mg/dL.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; PsA, psoriatic arthritis; PsO, psoriasis.

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(Continues)
20.0% (hyponatremia), respectively. Flare-related complications comprised infections in 36.2% of patients, acute renal failure (11.3%), septicemia (6.7%), and heart failure (5.1%); 12.9% of patients required IMC or ICU treatment due to a GPP flare. About 74.1% of patients had evidence of disease at time of last observation. Patients received on average 2.3 systemic therapies for GPP. PsO was diagnosed in 50.0% and PsA in 17.4%. Alcohol and tobacco consumption as well as metabolic and frequent comorbidities are presented in Table 1.

3.2 | Treatment characteristics

Overall, 201 treatment courses were identified (Table 2). Most frequently, methotrexate was administered (n = 42; 20.9% of all treatment courses), followed by acitretin (n = 28; 13.9%), fumaric acid esters (n = 19; 9.5%), etanercept and infliximab (n = 18 each; 9.0%), adalimumab and cyclosporine (n = 17 each; 8.5%), secukinumab and ustekinumab (n = 14 each; 7.0%), ixekizumab (n = 7; 3.5%), guselkumab (n = 5; 2.5%), and apremilast (n = 2; 1.0%). 17.9% and 25.0% of treatment courses with acitretin were combined with PUVA and UVB 311 nm phototherapy, respectively. TNF-α antagonists were frequently combined with methotrexate (32.1%; 17/53 treatment courses). Acitretin was dosed on average 0.4 mg/kg body weight/day, methotrexate was given in a mean dosage of 13.0 mg/week, and cyclosporine 2.6 mg/kg body weight/day. Biologicals were usually given in the standard maintenance dose for PsO. Patients had on average 0.8 previous systemic therapies before initiation of cyclosporine and 2.9 before prescription of biologicals. 15.1% of secukinumab and ixekizumab: n = 1 each).

3.3 | Treatment outcomes

Overall, 41.3% of all treatment courses (50/121) led to excellent response, while in 31.4% (38/121) and 27.3% (33/121) partial response and nonresponse were reached, respectively (Table 3). Among nonbiologials, one clearly documented treatment course with apremilast was highly efficacious (excellent response: 100%, 1/1), followed by cyclosporine (excellent response: 45.5%, 5/11) and acitretin (excellent response 40.9%, 9/22). Biological treatment was significantly more effective than nonbiological therapies (excellent response: 47.4%, 27/57 vs 35.9%, 23/64; P = .02 χ²-test). Among biologicals, excellent response was reached in 60.0% (6/10) of treatment courses with secukinumab, followed by ixekizumab and etanercept (50.0% each, 3/6 and 6/12, respectively), infliximab (46.7%, 7/15), and adalimumab (42.9%, 3/7). At time of last observation, excellent response was overall reached in 47.4% (27/57) of all treatment courses, partial response in 31.6% (18/57), and nonresponse in 21.1% (12/57) for all biologicals. Combination therapy of the most frequent combinations was by tendency—but not significantly—more successful than the respective monotherapy (excellent response rate: acitretin + UVB 311 nm phototherapy/PUVA vs acitretin: 60% [6/10] vs 25.0% [3/12], P = .10; TNF-α antagonists + MTX vs TNF-α antagonists: 57.1% [8/14] vs 40.0% [8/20], P = .32). Subgroup analysis with regard to presence or absence of comorbidities (psoriasis vulgaris, diabetes mellitus II, arterial hypertension, cardiovascular disease, and depression) showed no significant differences for efficacy data (data not shown). Adverse events occurred in 27.9% of all treatment courses (56/201). At time of last observation, 73.1% of nonbiologials (79/108) had been discontinued, compared with 53.8% (50/93) of biological therapies (P = .004 χ²-test). Reasons for drug discontinuation comprised ineffectiveness in 38.0% of all treatment courses (49/129), followed by adverse events (36.4%, 47/129), other reasons such as patient’s request, for example (19.4%, 25/129), and remission (3.4%, 5/129) and did not differ significantly between biologicals and nonbiologials.

3.4 | Drug survival

The median drug survival for all systemic treatment courses was 14.0 months (95% CI: 7.5-20.5; Table 4). Among nonbiologials, acitretin was applied for a median of 12.0 months, followed by fumaric acid esters (10.0 months), cyclosporine (7.0 months), methotrexate (4.0 months), and apremilast (1.0 months). Treatment duration with biologicals was significantly longer than for nonbiologials (median: 36.0 months vs 6.0 months; P < .001 log-rank test, Figure 1). Among biologicals, drug survival was on average highest for ustekinumab (median: 36.0 months), followed by secukinumab (35.0 months), adalimumab (17.0 months), infliximab (13.0 months), and etanercept (20.0 months). The median for guselkumab and ixekizumab was not calculated because the cumulative number of events was too small. Cumulative 1-year and 2-year survival rates of all agents—based on life tables—are presented in Table 4. According to theoretically predicted survival curves by Cox regression, the crude probability of survival was highest for secukinumab (HR of drug discontinuation compared with acitretin: 0.22, P = .02), followed by ustekinumab (HR: 0.38, P = .07), ixekizumab (HR: 0.38, P = .38), adalimumab (HR: 0.59, P = .23), etanercept (HR: 0.62, P = .23), infliximab (HR: 0.69, P = .38), cyclosporine (HR: 1.00, P = .99), acitretin (HR: 1.06, P = .89), methotrexate (HR: 1.26, P = .51), and apremilast (HR: 3.44, P = .11). There was no drug discontinuation of treatment courses with guselkumab (n = 5). When grouping biologicals according to their target cytokine, drug survival was highest for IL-17A antagonists (HR of drug discontinuation compared with acitretin: 0.09, P = .001), followed by IL-(12)/23 antagonists (HR: 0.13, P = .003), and TNF-α antagonists (HR: 0.45, P = .032). Treatment duration of these three groups was also significantly longer compared with the group of all nonbiologials (IL-17A antagonists HR: 0.12, P < .001, IL-(12)/23 antagonists HR: 0.16, P = .001, and TNF-α antagonists HR: 0.41, P = .001; Figure 2).

In the Cox regression model, adjusted for the variables age, gender, PsA, and number of previous systemic antipsoriatic treatments, drug discontinuation was significantly lower in patients with one
TABLE 2  Treatment characteristics

| Characteristic, n (%) | ACI | MTX | CyA | FAE | APR | ADA | ETA | INX | UST | GUS | SEC | IXE |
|----------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Number of treatment courses | 28 | 42 | 17 | 19 | 2 | 17 | 18 | 18 | 14 | 5 | 14 | 7 |
| +PUVA* | 5 (17.9) | 1 (2.4) | - | - | - | - | - | - | - | - | - | - |
| +UVB 311 nm phototherapy* | 7 (25.0) | 6 (14.3) | - | - | 3 (15.8) | - | - | 2 (11.1) | - | - | - | - |
| +MTX* | 1 (3.6) | NA | 3 (17.6) | - | - | - | 5 (29.4) | 3 (16.7) | 9 (50.0) | 1 (7.1) | - | 2 (14.3) | 1 (14.3) |
| +Prednisolone* | 2 (7.1) | 10 (23.8) | 1 (59) | - | - | 1 (59) | 3 (16.7) | 2 (11.1) | 2 (14.3) | - | 2 (14.3) | - |
| Mean dosage (SD)b | 0.4 mg/kg/day (0.2) | 13.0 mg/week (4.7) | 2.6 mg/kg/day (1.2) | 1.5 tablets as 120 mg/day (1.0) | 2 (100) as LIC'D | 15 (88.2) as LIC'D | 18 (100) as LIC'D | 13 (72.2) as LIC'D | 12 (85.7) as LIC'D | 5 (100) as LIC'D | 14 (100) as LIC'D | 7 (100) |
| Number of previous therapies, mean (SD) | 0.8 (1.0) | 0.9 (1.1) | 1.1 (1.3) | 1.4 (1.9) | 2.5 (2.1) | 2.3 (1.6) | 3.6 (3.0) | 1.6 (1.7) | 3.4 (3.1) | 3.4 (2.4) | 3.9 (2.4) | 3.3 (2.1) |

Abbreviations: ACI, acitretin; ADA, adalimumab; APR, apremilast; as LIC'D, as licensed; CyA, cyclosporine; ETA, etanercept; FAE, fumaric acid esters; GUS, guselkumab; INX, infliximab; IXE, ixekizumab; MTX, methotrexate; NA, not applicable; SEC, secukinumab; UST, ustekinumab; kg, kilogram body weight.

*Number of treatment courses combined with PUVA, UVB 311 nm phototherapy, methotrexate, or prednisolone, respectively.

bFor apremilast and biologicals, the number of patients (%) who received the standard maintenance dosage for psoriasis is depicted.

TABLE 3  Treatment outcomes and reasons for discontinuation

| ACI | MTX | CyA | FAE | APR | ADA | ETA | INX | UST | GUS | SEC | IXE | TNF-α | IL-12/23 | IL-17A |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------|---------|--------|
| Number of treatment courses | 28 | 42 | 17 | 19 | 2 | 17 | 18 | 18 | 14 | 5 | 14 | 7 | 53 | 19 | 21 |
| Nonresponse, n (%) | 6 (27.3) | 10 (41.7) | 3 (27.3) | 2 (33.3) | 0 (0.0) | 4 (57.1) | 3 (25.0) | 2 (13.3) | 1 (16.7) | 0 (0.0) | 1 (10.0) | 1 (16.7) | 9 (26.5) | 1 (14.3) | 2 (12.5) |
| Partial response, n (%) | 7 (31.8) | 8 (33.3) | 3 (27.3) | 0 (0.0) | 0 (0.0) | 3 (15.8) | 2 (10.5) | 3 (16.7) | 2 (11.1) | 2 (14.3) | - | 2 (14.3) | - |
| Excellent response, n (%) | 9 (40.9) | 6 (25.0) | 5 (45.5) | 2 (33.3) | 1 (100) | 3 (42.9) | 6 (50.0) | 7 (46.7) | 2 (33.3) | 0 (0.0) | 6 (60.0) | 3 (50.0) | 16 (47.1) | 2 (28.6) | 9 (56.3) |
| Response not reported, n (%) | 6 (21.4) | 18 (62.9) | 6 (35.3) | 13 (68.4) | 1 (50.0) | 10 (58.8) | 3 (15.7) | 6 (33.3) | 3 (16.7) | 8 (47.4) | 4 (28.6) | 2 (14.3) | 9 (35.8) | 12 (63.2) | 5 (23.8) |
| Adverse events, n (%) | 3 (13.0) | 13 (31.0) | 4 (23.5) | 9 (47.4) | 0 (0.0) | 1 (59.0) | 6 (33.3) | 10 (55.6) | 3 (21.4) | 1 (100) | 4 (28.6) | 2 (26.5) | 17 (32.1) | 4 (21.1) | 6 (28.6) |
| Treatment discontinued, n (%) | 17 (60.7) | 31 (77.5) | 13 (76.5) | 16 (88.9) | 2 (100) | 12 (70.6) | 14 (77.8) | 13 (72.2) | 6 (46.2) | 0 (0.0) | 3 (23.1) | 2 (28.6) | 39 (73.6) | 6 (33.3) | 5 (25.0) |
| Reason for treatment discontinuationb | | | | | | | | | | | | | | |
| Adverse events, n (%) | 3 (17.6) | 12 (38.7) | 2 (15.4) | 9 (56.3) | 0 (0.0) | 1 (8.3) | 6 (42.9) | 9 (69.2) | 2 (33.3) | NA | 2 (66.7) | 1 (50.0) | 16 (41.0) | 2 (33.3) | 3 (60.0) |
| Ineffectiveness, n (%) | 7 (41.2) | 14 (45.2) | 5 (38.5) | 2 (12.5) | 0 (0.0) | 9 (75.0) | 5 (35.7) | 3 (23.1) | 2 (33.3) | NA | 1 (33.3) | 1 (50.0) | 17 (43.6) | 2 (33.3) | 2 (40.0) |
| Remission, n (%) | 3 (17.6) | 0 (0.0) | 0 (0.0) | 1 (6.3) | 0 (0.0) | 0 (0.0) | 1 (7.1) | 0 (0.0) | 0 (0.0) | NA | 0 (0.0) | 0 (0.0) | 1 (2.6) | 0 (0.0) | 0 (0.0) |
| Other, n (%) | 4 (23.5) | 3 (9.7) | 6 (46.2) | 2 (12.5) | 2 (100) | 1 (8.3) | 2 (14.3) | 2 (15.4) | 2 (33.3) | NA | 1 (33.3) | 0 (0.0) | 5 (12.8) | 2 (33.3) | 1 (20.0) |

Abbreviations: ACI, acitretin; ADA, adalimumab; APR, apremilast; CyA, cyclosporine; ETA, etanercept; FAE, fumaric acid esters; GUS, guselkumab; IL-12/23, UST and GUS; IL-17A, SEC and IXE; INX, infliximab; IXE, ixekizumab; MTX, methotrexate; SEC, secukinumab; TNF-α, TNF-α antagonists (ie, ADA, ETA, INX); UST, ustekinumab.

bPercentage of all patients who discontinued the respective treatment. Multiple reasons could be stated. Other reasons comprised non-adherence, patient's request, diagnosis of psoriatic arthritis, and planned discontinuation due to long exposure (cyclosporine).
## TABLE 4  Drug survival of systemic therapies

|                      | ACI | MTX | CyA | FAE | APR | ADA | ETA | INX | UST | GUS* | SEC | IXE | TNF-α | IL-(12)/23 | IL-17A |
|----------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-------|-------------|--------|
| Number of treatment courses | 28  | 42  | 17  | 19  | 2   | 17  | 18  | 18  | 14  | 14   | 5   | 14  | 7     | 53          | 19     | 21     |
| Median of drug survival in months (95% CI)* | 12.0 | 4.0 (0.0-8.3) | 7.0 (1.6-12.4) | 10.0 (0.0-22.0) | 1.0 (NA) | 17.0 | 0.0-46.7 | 10.0 | 0.0-28.3 | 13.0 | 0.0-48.4 | 36.0 | NC | 35.0 (3.9-66.1) | 17.0 | 36.0 (22.7-49.3) | 35.0 (3.9-66.1) |
| Mean of drug survival in months (95% CI)* | 19.1 | 15.4 | 22.0 | 19.1 (1.9-36.4) | 2.5 (0.0-5.4) | 28.7 | 14.3-43.0 | 32.1 | 16.4-49.7 | 30.8 | 13.5-48.2 | 38.4 | NA | 32.0 (24.6-39.5) | 15.7 | 33.1 (22.5-43.7) | 38.4 (25.0-51.8) | 30.2 (23.4-37.0) |
| Patients with treatment duration ≥12 months, n (%) | 6 (30.0) | 7 (21.9) | 6 (35.3) | 3 (30.0) | 0   | 7 (50.0) | 8 (47.1) | 8 (50.0) | 8 (66.7) | 0   | 10 (76.9) | 2 (28.6) | 23 (48.9) | 8 (47.1) | 12 (60.0) |
| Patients with treatment duration ≥24 months, n (%) | 2 (10.0) | 4 (12.5) | 2 (11.8) | 2 (20.0) | 0   | 6 (42.9) | 7 (41.2) | 6 (37.5) | 5 (41.7) | 0   | 7 (53.8) | 0   | 19 (40.4) | 5 (29.4) | 7 (35.0) |
| HR for drug discontinuation with the reference acitretin (95% CI) | Ref | 1.26 | 1.00 | 1.06 (0.43-2.62) | 3.44 | 0.59 (0.76-15.64) | 0.62 | 0.25-1.41 | 0.69 | 0.30-1.58 | 0.38 | 0.13-1.07 | NA | 0.22* (0.06-0.78) | 0.38 | 0.08-1.70 | 0.45* (0.22-0.93) | 0.13** (0.04-0.49) | 0.09*** (0.02-0.39) |

Notes: *: P < 0.05; **: P < 0.01. NC: not calculated (median for guselkumab and ixekizumab could not be calculated due to insufficient number of cumulative events); NA: not applicable (no treatment course with guselkumab was discontinued; thus, drug survival and hazard ratio for drug discontinuation could not be calculated).

Abbreviations: ACI, acitretin; ADA, adalimumab; APR, apremilast; CI, confidence interval; CyA, cyclosporine; ETA, etanercept; FAE, fumaric acid esters; GUS, guselkumab; HR, hazard ratio; IL-(12)/23, UST and GUS; IL-17A, SEC and IXE; IXE, ixekizumab; INX, infliximab; MTX, methotrexate; Ref, reference; SEC, secukinumab; TNF-α, TNF-α antagonists (ie, ADA, ETA, INX); UST, ustekinumab.

Cumulative proportion surviving at the time according to Kaplan-Meier analysis. Significant differences in drug discontinuation compared with acitretin are displayed in bold.

Mean treatment time with guselkumab until last observation was 5.2 months (SD: 3.5).
previous therapy compared with those with two or more previous therapies (HR: 0.44, P = .01; Table 5) and numerically lower in patients with no previous therapies compared with two or more previous therapies (HR: 0.68, P = .25). Treatment with secukinumab was by tendency more sustainable compared with acitretin (HR: 0.14, P = .07).

4 | DISCUSSION

This study is one of the larger case series adding to the growing evidence on treatment of GPP and, to our knowledge, is the first in-depth analysis of drug survival in GPP in a real-life setting. Sociodemographic patient characteristics were in line with published literature. We found a female predominance with a ratio of approximately 3:2 which was also reported by Baker and Ryan25 and in the European ERASPEN cohort (female proportion: 62.5%).26 The mean age at symptom onset was 51.2 years, comparable to reported onset of disease in the fifth decade of life.25,27,28 In our cohort, infections, withdrawal of antipsoriatic medication, particularly systemic glucocorticoids, and intake of new medication were suspected trigger factors of GPP manifestation by the treating physicians, consistent with previous reports.1,8 According to diagnostic criteria, persistence of pustular rash for at least 3 months or at least one relapse is required for a definite diagnosis of GPP.2,3,10 Thus, during the first flare, acute generalized exanthematous pustulosis (AGEP) cannot be ruled out as differential diagnosis which may lead to a different systemic treatment of the first flare.10 Fever and fatigue were present in at least half of all patients and 75.3% and 62.4% had elevated CRP levels and leukocytosis, respectively, as signs of systemic inflammation, which has been reported previously.1,8 Half of all our patients had a concomitant diagnosis of PsO, compared with 59.6% in the cohort of Baker and Ryan25 and 54.4% in the ERASPEN cohort26 and PsA was present in approximately one fifth of our patients, compared with reported
rates of 23.8%-34.7%. One third of our patients were current smokers, compared with 28.3% in the ERASPEN cohort. Interestingly, frequency of metabolic comorbidities was comparable to patients with PsO and PPP. We found that 74.1% of all patients had symptoms of disease at time of last observation. Due to the chronic-relapsing course of disease and the high rate of flare-related morbidity and mortality, an efficacious therapeutic long-term strategy is necessary.

In our cohort, 35.9% of treatment courses with non-biological therapies led to excellent response. Among nonbiologicals, cyclosporine (excellent response: 45.5%) and acitretin (40.9%) were particularly successful, while 25.0% of treatment courses with methotrexate were highly efficacious. Except for corticosteroids, acitretin is the only systemic drug licensed for GPP in Germany and thus considered standard first-line treatment. According to the Japanese guidelines on GPP, etretinate, cyclosporine, and methotrexate were effective in 87.1%, 87.6%, and 84.9% of treated patients with GPP (Japanese national clinical database) and are recommended as systemic therapies. In accordance, the Medical Board of the National Psoriasis Foundation of the United States suggested a treatment algorithm starting with acitretin, cyclosporine, methotrexate, or infliximab as first-line therapy. About 47.4% of biological therapies were highly efficacious in our cohort (IL-17 antagonists: 56.3%, TNF-α antagonists: 47.1%, and IL-(12)/23 inhibitors: 28.6%). In a recent systematic review, treatment response to biologicals has been compiled from case reports, case series, and clinical trials with a complete response rate of 66.7% for IL-17(R) antagonists, 58.1% for TNF-α antagonists and 85.7% for the IL-12/23 antagonist ustekinumab. The relatively high response rate might be partly explained by the bias of selective publication of positive results and the high number of reports on patients with Asian ethnicity who might differ from European patients. We detected an overall good efficacy in patients at time of last observation (excellent response: 52.9%, partial response: 41.2%, 25.9% of patients in remission). Thus, control of disease activity was achieved eventually in most of our patients. The US Medical Board of the National Psoriasis Foundation recommends infliximab as first-line therapy, and adalimumab and etanercept as second-line therapies for GPP. However, since treatment recommendations were published in 2012, evidence on treatment with biologicals targeting IL-17/IL-17R and IL-(12)/23 was not available then. The Japanese guidelines from 2018 on GPP recommend TNF-α inhibitors, secukinumab, ixekizumab, brodalumab, and ustekinumab for the treatment of GPP. Of note, most antipsoriatic biologicals are approved for treatment of GPP in Japan.

Overall, drug survival in our patients was 14.0 months, which is higher than drug survival of systemic medication in the treatment of PPP patients (median: 8.0 months) and of ACH patients (median: 7.0 months), and comparable to PsO patients (median: 14 months). In contrast, Kishimoto and colleagues identified GPP compared with PsO as predictor for drug discontinuation with biologicals with a HR of 1.87 in Japan. They found highest drug survival with ustekinumab (overall: n = 66 treatment courses with ustekinumab of which n = 2 were GPP patients). When compared with acitretin as reference, secukinumab showed a significantly higher drug survival and ustekinumab was by tendency given for a longer period of time. If grouped according to the target cytokine, IL-17A antagonists yielded the best retention time, followed by IL-(12)/23 inhibitors and TNF-α blockers (all significant vs acitretin). Similarly, drug survival in PPP was reported to be higher for biologicals than for nonbiologicals. Drug survival in PsO has been extensively studied and showed high retention rates for biologicals. Among biologicals, IL-17(R) antagonists and ustekinumab were found to yield a higher drug survival compared with TNF-α blockers in PsO. Regression analysis in our study revealed that patients with one previous systemic therapy had a significantly longer drug survival compared with patients with two or more prior therapies, and for patients with no prior therapy, drug survival was numerically, but not significantly longer than in patients with two or more previous therapies. Possibly, patients with two or more previous therapies were more severely affected which might decrease drug survival.

Based on our experience, we suggest acitretin as first-line treatment due to excellent response in 40.9% of patients. A combination with photo(chemo)therapy should be considered. Cyclosporine may be considered in a small subgroup of patients for short term control
due to its good efficacy and fast onset. However, its unfavorable safety profile, particularly in older and comorbid patients, limits its use. Methotrexate yielded a lower response rate in our cohort and evidence of apremilast therapy is based on very few patients. Moreover, methotrexate should only be used with caution in patients with certain comorbidities such as diabetes mellitus and renal or hepatic impairment which are observed frequently in patients with GPP. In accordance with previous reports, we found higher efficacy and longer drug survival with biologicals which we recommend as second-line treatment. Among biologicals, particularly IL-17A antagonists and IL-(12)/23 inhibitors yielded a favorable response rate and high drug survival in our cohort. Considering the morbidity and mortality associated with GPP flares, biologicals may be considered as first-line therapy in patients with severe disease which is already performed in clinical practice (15.1% of all biological treatment courses were applied as first-line therapy in our cohort). A summary of our proposed therapy algorithm, that takes into account published data and our own data as well as the great heterogeneity of the disease course and severity including systemic symptoms, is given in Figure 3.

Results of this study should be interpreted cautiously. First, retrospective data collection may introduce selection bias and lead to missing data in some categories. Second, due to the rarity of the disease, 86 patients were identified, and some subgroups contained small numbers of treatment courses. Third, some of the biologicals were available very recently, which may lead to shorter drug survival. Fourth, evaluation of treatment response was based on physicians’ description and/or photographic evidence. Due to the retrospective study design, recently established parameters of disease severity such as the Generalized Pustular PASI (GPPASI) and the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) were not consistently available. Therefore, response had to be classified into “nonresponse,” “partial response,” and “excellent response” as best estimates. Moreover, it has to be noted that response was not clearly reported in a considerable number of patients.

A major strength is the multicenter design of the study and the cohort size, considering the rarity of the disease. A wide range of systemic treatments was investigated in a real-life setting over a sufficiently long period of time using different outcome measures for efficacy.

In conclusion, we found good effectiveness and drug survival of all biologicals in the treatment of GPP, particularly for IL-17 and IL-(12)/23 antagonists. We suggest a treatment algorithm starting with acitretin as first-line therapy, escalating to cyclosporine for short-term control or methotrexate, followed by biologicals, particularly IL-17/IL-17R antagonists, IL-(12)/23 inhibitors, or TNF-α blockers, as second-line treatment or first-line in severely affected patients. More research is needed to further evaluate traditional and also particularly newer drugs in GPP.

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**CONFLICT OF INTEREST**

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**AUTHOR CONTRIBUTIONS**

Christian Kromer, Emilia Loewe, Marthe-Lisa Schaarschmidt, Andreas Pinter, Sascha Gerdes, Sietske Poortinga, Röttraut Moessner, Dagmar Wilsmann-Theis: Cared for the patients; Christian Kromer and Emilia Loewe: Acquisition of data. Christian Kromer and Raphael Herr: Analysis of data. All authors were responsible for interpretation of data, drafting the manuscript, and gave their final approval of the version to be published.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available from the corresponding author upon reasonable request.
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