JAMA Dermatology | Original Investigation

Understanding Flares in Patients With Generalized Pustular Psoriasis Documented in US Electronic Health Records

Carla L. Zema, PhD; Wendell C. Valdecantos, MD; Jonathan Weiss, MS; Blake Krebs, MA; Alan M. Menter, MD

IMPORTANCE Other than single-center case studies, little is known about generalized pustular psoriasis (GPP) flares.

OBJECTIVE To assess GPP flares and their treatment, as well as differences between patients with and patients without flares documented in US electronic health records (EHRs).

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included adult patients with GPP (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code L40.1) identified in Optum deidentified EHR data between July 1, 2015, and June 30, 2020. The index GPP diagnosis was the first occurrence in the EHR, with no coded history of GPP for at least 6 months prior. Flare episodes were identified using an algorithm based on diagnosis coding, care setting, type of clinician, GPP disease terms, and flare terms and attributes in the EHR.

MAIN OUTCOMES AND MEASURES Flare episodes were characterized by the frequency of occurrence per patient, the care setting in which they were identified, the type of specialist managing the episode, associated symptoms, and the type of treatment before, during, and after the episode. Patients were divided into groups based on whether or not they had a flare episode documented in their EHR. Comparisons were made between the groups based on demographic characteristics, comorbidity burden, health care use, and treatments.

RESULTS Of 1535 patients with GPP (1018 women [66.3%]; mean [SD] age, 53.4 [14.7] years), 271 had 513 flares documented. Compared with patients without flares, patients with flares had a 34% higher mean (SD) Charlson Comorbidity Index score (2.80 [3.11] vs 2.09 [2.52]), were almost 3 times more likely to have inpatient visits (119 of 271 [44%] vs 194 of 1264 [15%]), were more than twice as likely to have emergency department (ED) visits (126 of 271 [47%] vs 299 of 1264 [24%]), and had higher use of almost all treatment classes. Flares were identified in outpatient (271 of 513 [53%]), inpatient (186 of 513 [36%]), and ED (48 of 513 [9%]) settings. The most common treatments during flares were topical corticosteroids (35% of episodes [178 of 513]), opioids (21% [106 of 513]), other oral treatments, (eg, methotrexate, cyclosporine, tacrolimus; 13% [67 of 513]), and oral corticosteroids (11% [54 of 513]). Almost one-fourth of flare episodes (24% [122 of 513]) had no dermatologic treatment 30 days before, during, or 30 days after a flare episode.

CONCLUSIONS AND RELEVANCE This cohort study suggests that there is significant unmet need for the treatment of GPP and its flares, as evidenced by patients seeking treatment in inpatient and ED settings, as well as the lack of advanced treatments.

Supplemental content

Author Affiliations: Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, Connecticut (Zema, Valdecantos); Optum, Minneapolis, Minnesota (Weiss, Krebs); Department of Dermatology, Baylor University Medical Center, Dallas, Texas (Menter).

Corresponding Author: Wendell Valdecantos, MD, Boehringer Ingelheim Pharmaceuticals Inc, 900 Ridgebury Rd, Ridgefield, CT 06877 (wendell.valdecantos@boehringer-ingelheim.com).

JAMA Dermatol. 2022;158(10):1142-1148. doi:10.1001/jamadermatol.2022.3142
Published online August 10, 2022.

Pustular psoriasis is a rare variation of psoriasis, categorized by generalized and localized forms and characterized by noninfectious, neutrophil-containing pustules on an erythematous background.[1-5] Generalized pustular psoriasis (GPP) is characterized by intermittent flares involving the sudden and widespread formation of sterile pustules with associated erythema and pustules often coalescing to form lakes of pus.[6] Generalized pustular psoriasis flares often occur with systemic symptoms, such as fever, chills, malaise, anorexia, nausea, and severe pain. Moreover, pustules during and after a GPP flare can last for months and lead to life-threatening complications, often requiring emergency care.[1-5] Estimates of mortality associated with GPP vary significantly, with a recent review citing a range of 5% to 32% across 5 studies[7]; however, some studies were outdated or had unclear methods. Numerous studies have shown that patients with GPP have substantially increased health care costs and a higher comorbidity burden compared with patients with plaque psoriasis as well as the general population.[7-10]

Generalized pustular psoriasis can present in patients with a history of plaque psoriasis. However, the pathophysiology and genetic factors that are associated with GPP are distinct from those associated with plaque psoriasis.[6,11] Most cases of GPP with no history of plaque psoriasis are caused by variants of the *IL36RN* gene (OMIM 605507), whereas cases of GPP with a prior plaque psoriasis diagnosis are associated with variants of the *CARD14* (OMIM 607211) or *AP1S3* (OMIM 615781) genes.[11-13]

To our knowledge, few existing studies address GPP flares. The rarity of GPP, its relapsing nature, and unpredictability of flare onset make it challenging to procure meaningful data. Existing studies are limited because many have small sample sizes,[14,15] are single-center studies,[15,16] include only hospitalized patients,[16-18] are survey-based studies only,[19,20] or are from decades ago.[21-23] The objectives of this study are to characterize GPP flares and their treatment and to describe differences between patients with and patients without documented GPP flares in US electronic health records (EHRs).

Key Points

Question What are the differences in treatment between patients with generalized pustular psoriasis (GPP) with flares and those without flares?

Findings In this cohort study comprising 1535 patients with GPP, with 271 of them having 513 documented flares, patients with flares had a higher comorbidity burden, were almost 3 times more likely to have inpatient visits, were more than twice as likely to have emergency department visits, and had higher use of almost all treatment classes. Despite this high level of severity, advanced treatments for GPP were very rarely used during flare episodes.

Meaning This study suggests that there is a significant unmet need in the current treatment of GPP and its flares.

Methods

This is a retrospective observational cohort study conducted from July 1, 2015, to June 20, 2020, including adult (aged ≥18 years) patients with GPP (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] code L40.1) identified in Optum deidentified EHR data between January 1, 2016, and December 31, 2019. This database of more than 89 million US patients includes commercial, Medicare, and Medicaid payers and self-pay and represents data from 150 000 clinicians, 2000 hospitals, and 7000 clinics. The mean (SD) follow-up time for patients is 4.3 (4.4) years (median follow-up time, 2.9 years [range, 0-14.8 years]). The index GPP diagnosis was the first GPP occurrence between 2016 and 2019 with no other GPP diagnosis in the 6 months prior (back to July 1, 2015). Only patients with at least 12 months of health care activity documented in the EHR after the index diagnosis (through June 30, 2020) and with EHR notes were included. Our institution does not require institutional review board review or patient consent for retrospective analyses using deidentified data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Natural language processing of EHR notes was conducted to identify GPP flares. The method accounted for documented signs, disease, and symptoms (terms such as *rash*); descriptions of the signs, disease, and symptoms terms (attributes such as "worsening" rash); and care settings. To ensure that flares were GPP flares, literature reviews were conducted and clinical expert input was obtained to develop the method. The terms to identify GPP flares represented key characteristics: (1) *rash or erythema*, (2) *pustule or lesion*, (3) *other GPP symptoms*, and (4) *flares*. Lists of clinically relevant synonyms of these terms were identified for each of these key characteristics (eTable 1 in the Supplement). Flares were identified by searching for records of each health care visit beginning on or after the index date of the GPP diagnosis with documented notes that met at least 1 of any of the following criteria:

For visits with a primary diagnosis of GPP (*ICD-10* code L40.1):

1. An encounter with place of service = emergency department, observation, inpatient, or urgent;
2. Any term in the "flare" category (eg, *flare*, *eruption*);
3. Any term in the "pustule or lesion" category plus any flare attribute;
4. Any term in the "rash" category plus any flare attribute; and
5. Any term in the "other GPP symptoms" category plus any flare attribute.

For dermatology-related visits (ie, type of clinician was a dermatologist or primary reason for visit was any skin-related diagnosis defined by *ICD-10* L* or R2* code):

1. Any term in the "flare" category and any term in the "pustule or lesion" category; and
2. Any term in the "pustule or lesion" category plus any flare attribute.

Flare episodes were defined as consecutive days that flares were documented in the EHR and were characterized by the frequency of occurrence per patient, the setting of care where

Table. Baseline Characteristics of Patients With GPP

Characteristic	Patients, No. (%)		
	With GPP (N = 1535)	With documented GPP flares (n = 271)	Without documented GPP flares (n = 1264)
Age, mean (SD), y	53.4 (14.7)	53.5 (15.2)	53.3 (14.5)
Age category, y			
18-34	190 (12.4)	32 (11.8)	158 (12.5)
35-44	224 (14.6)	44 (16.2)	180 (14.2)
45-54	332 (21.6)	58 (21.4)	274 (21.7)
55-64	450 (29.3)	74 (27.3)	376 (29.7)
≥65	339 (22.1)	63 (23.2)	276 (21.8)
Sex			
Male	517 (33.7)	90 (33.2)	427 (33.8)
Female	1018 (66.3)	181 (66.8)	837 (66.2)
Race and ethnicity			
African American	118 (7.7)	25 (9.2)	95 (7.4)
Asian	25 (1.6)	9 (3.3)	16 (1.3)
Hispanic	85 (5.6)	14 (5.2)	71 (5.5)
White	1236 (80.5)	209 (77.1)	1027 (81.3)
Other or unknown[a]	71 (4.6)	14 (5.2)	57 (4.5)
Insurance type			
Commercial	748 (48.7)	108 (39.9)	640 (50.6)
Medicaid	327 (21.3)	74 (27.3)	253 (20.0)
Medicare	328 (21.4)	67 (24.7)	261 (20.6)
Uninsured	28 (1.8)	4 (1.5)	24 (1.9)
Other or unknown	104 (6.8)	18 (6.6)	86 (6.8)
Charlson Comorbidity Index score, mean (SD)	2.22 (2.65)	2.80 (3.11)	2.09 (2.52)
Comorbid conditions			
Anxiety	324 (21.1)	66 (24.4)	258 (20.4)
Asthma	176 (11.5)	30 (11.1)	146 (11.6)
Depression	308 (20.1)	58 (21.4)	250 (19.8)
Type 2 diabetes	304 (19.8)	63 (23.2)	241 (19.1)
Coronary artery disease	151 (9.8)	32 (11.8)	119 (9.4)
COPD	184 (12.0)	43 (15.9)	141 (11.2)
Hypercholesterolemia	119 (7.8)	17 (6.3)	102 (8.1)
Hypertension	679 (44.2)	131 (48.3)	548 (43.4)
Obesity	355 (23.1)	80 (29.5)	275 (21.8)
Other autoimmune disorders			
Plaque psoriasis	199 (13.0)	46 (17.0)	153 (12.1)
Other psoriasis	969 (63.1)	211 (77.9)	758 (60.0)
Psoriatic arthritis	220 (14.3)	52 (19.2)	168 (13.3)
Rheumatoid arthritis	103 (6.7)	24 (8.9)	79 (6.3)
Ulcerative colitis	18 (1.2)	6 (2.2)	12 (0.9)
Crohn disease	34 (2.2)	11 (4.1)	23 (1.8)

Abbreviations: COPD, chronic obstructive pulmonary disease; GPP, generalized pustular psoriasis.

[a] Other or unknown race and ethnicity was taken from the Optum database with no further detail available.

the flare was identified, the type of specialist identifying the episode, associated symptoms, and the type of treatment before, during, and after the episode.

Results

Of 48.6 million patients with EHR notes available, 1535 with GPP (1018 women [66.3%]; mean [SD] age, 53.4 [14.7] y) were identified; 271 of those patients had at least 1 flare episode documented in their EHR, accounting for 513 flare episodes during the study period. Age and sex were similar among patients with or without documented GPP flares (**Table**). Patients with documented flares were more likely to be enrolled in Medicare and Medicaid and less likely to be enrolled in commercial insurance. Patients with documented flares also had a higher comorbidity burden than those without documented flares, as evidenced by a 34% higher mean (SD) Charlson Comorbidity Index score (2.80 [3.11] vs 2.09 [2.52]). Similarly, more patients with documented GPP flares had common comorbid conditions, including autoimmune conditions, compared with patients without documented flares.

Figure 1. Number of Documented Generalized Pustular Psoriasis (GPP) Flares

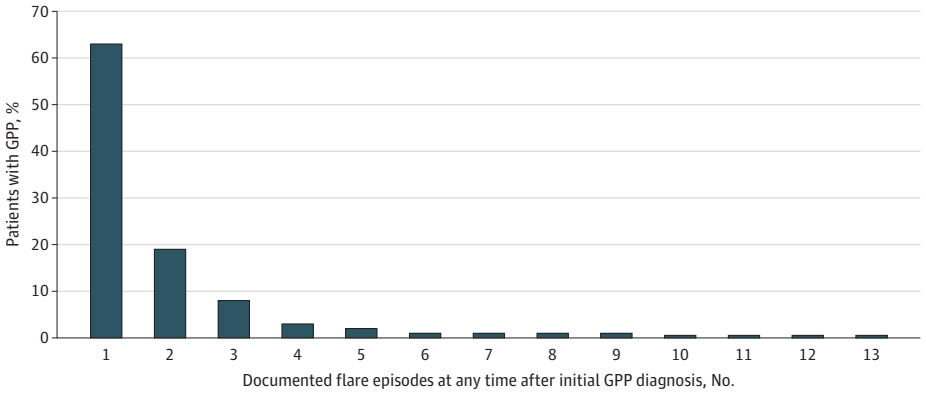
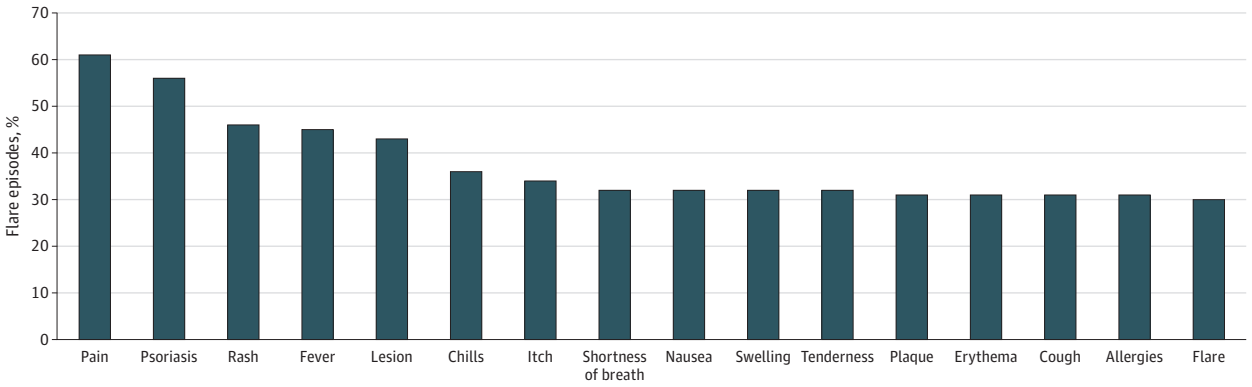


Figure 2. Most Commonly Documented Signs, Diseases, and Symptom Terms During a Generalized Pustular Psoriasis Flare



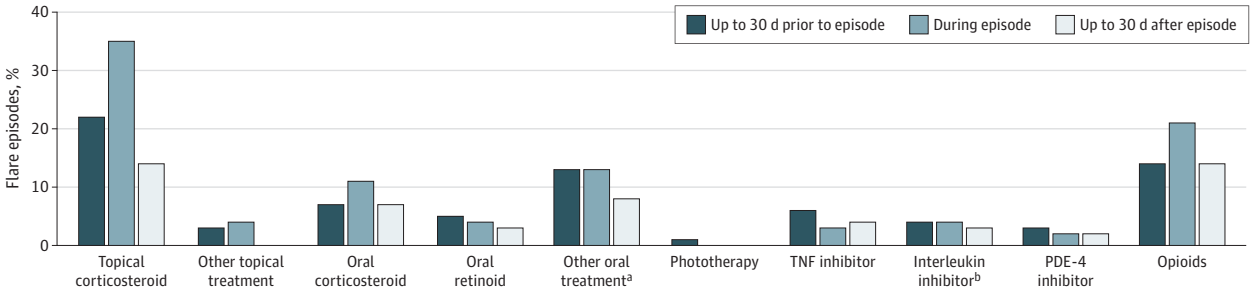
Of the 271 patients with documented GPP flares, 182 (63%) had only 1 flare documented in the follow-up period. **Figure 1** shows the distribution of the number of flares documented among the patients who sought care for the flares. The mean number of flare episodes per patient per year was 0.88, and the mean follow-up time was 724.8 days (median follow-up time, 698 days).

For the 513 documented GPP flares among the 271 patients, 271 (53%) were identified in outpatient settings, 186 (36%) in inpatient settings, 48 (9%) in emergency department settings (ED), and 8 (2%) in other settings. For the 271 flare episodes identified in outpatient settings, 198 (73%) were documented by dermatologists, 28 (10%) by rheumatologists, and 24 (9%) by primary care professionals. Most flare episodes were documented within the same month as the index GPP diagnosis (182 of 271 patients with flares or first flare episode [67%]), with 87% of those flares (158 of 182 patients with flares or first flare episode in same month as index GPP diagnosis) documented within the same month, representing 58% of all flares (158 of 271 patients with flares or first flare episode). Fourteen percent of flares (38 of 271) occurred in months 1 to 6 after the index GPP diagnosis, 6% (16 of 271) in months 7 to 12, 5% (13 of 271) in months 13 to 18, 4% (12 of 271) in months 19 to 24, 3% (8 of 271) in 2 to 3 years, and 1% (2 of 271) in more than 3 years. The most common signs or symptoms documented during flare episodes were pain (61% of flare episodes [312 of 513]) followed by rash (46% [236 of 513]) and fever (45% [229 of 513]) (**Figure 2**).

The most common dermatologic treatment during a flare episode was topical corticosteroids (35% of flare episodes [178 of 513]) followed by other oral dermatologic treatments (eg, methotrexate, cyclosporine, tacrolimus; 13% [67 of 513]), and oral corticosteroids (11% [54 of 513]) (**Figure 3**). Opioids were prescribed during 21% of flare episodes (106 of 513). Almost one-fourth of all flare episodes (24% [122 of 513]) had no dermatologic treatment initiated 30 days before, during, or 30 days after a flare episode. Specific medications under each treatment class can be found in eTable 2 in the Supplement.

With regard to overall treatments, patients with documented flares had greater use of drug treatments across almost all classes compared with patients without documented flares, including topical corticosteroids (194 of 271 [72%] vs 606 of 1264 [48%]), oral corticosteroids (105 of 271 [39%] vs 344 of 1264 [27%]), other oral dermatologic medications (82 of 271 [30%] vs 186 of 1264 [15%]), tumor necrosis factor inhibitors (41 of 271 [15%] vs 97 of 1264 [8%]), other topical medications (39 of 271 [14%] vs 91 of 1264 [8%]), and interleukin 17 (IL-17), IL-12/23, or IL-23 inhibitors (39 of 271 [14%] vs 72 of 1264 [6%]) (**Figure 4**). In addition, more than half of patients with documented flares (137 of 271 [51%]) were pre-

Figure 3. Treatments Initiated Before, During, or After Generalized Pustular Psoriasis Flare Episodes

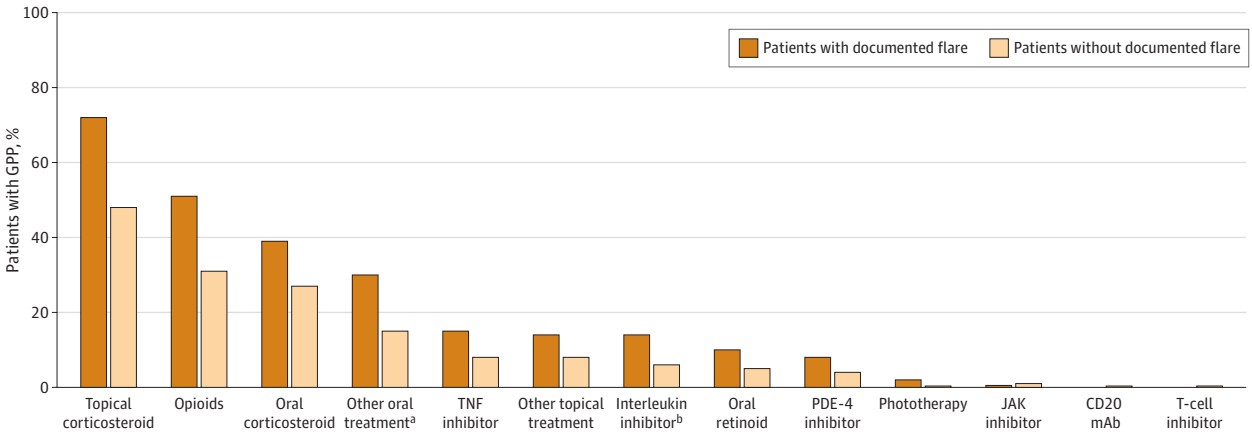


PDE-4 indicates phosphodiesterase 4; and TNF, tumor necrosis factor.

[a] Includes methotrexate, cyclosporine, and tacrolimus.

[b] Includes interleukin 17, interleukin 12/23, and interleukin 23 inhibitors.

Figure 4. Comparison of Treatments Between Patients With Generalized Pustular Psoriasis Who Did Have Documented Flare Episodes and Those Who Did Not



CD20 mAb indicates anti-CD20 monoclonal antibody; JAK, Janus-kinase; PDE-4, phosphodiesterase 4; and TNF, tumor necrosis factor.

[a] Includes methotrexate, cyclosporine, and tacrolimus.

[b] Includes interleukin 17, interleukin 12/23, and interleukin 23 inhibitors.

scribed opioids during the study period compared with 390 of 1264 patients (31%) without documented flares.

Use of biologics and other advanced treatments (eg, phosphodiesterase 4 and Janus-kinase inhibitors) was low. Many patients with GPP also have comorbid autoimmune conditions (ie, plaque psoriasis, other psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn disease, ulcerative colitis, and uveitis) that are also indicated for use of biologics. Among those with biologics use, 99% of patients with documented flares (67 of 68) and 94% of patients without documented flares (144 of 153) also had a comorbid autoimmune condition. When excluding the category of other psoriasis, these percentages decreased to 75% (51 of 68) and 73% (112 of 153), respectively.

Although little to no differences were observed between the groups in outpatient visits (93% vs 98%), patients with documented flares were almost 3 times more likely to have any inpatient visits (119 of 271 [44%] vs 194 of 1264 [15%]) and twice as likely to have any emergency department visits (126 of 271 [47%] vs 299 of 1264 [24%]) than patients without documented flares. Moreover, the mean (SD) number of inpatient stays for patients with documented flares was 2.63 (2.40), which was 32% higher than those without documented flares, with a mean (SD) number of inpatient stays of 1.99 (1.82).

Discussion

Patients with GPP who had documented flares in this study have a greater disease burden than those who did not have flares. They have more comorbid conditions, as evidenced by not only higher percentages of common conditions but also higher scores on the Charlson Comorbidity Index. They also had higher all-cause inpatient and emergency department use. This study provides greater evidence of the potential severity of flares, given that 36% of all flares were identified in inpatient settings and 9% were identified in emergency department settings. In addition, pain was the most common symptom documented during flare episodes; thus, many patients

were treated with opioids. However, despite the severity of the flare episodes, topical corticosteroids were the most common treatment during flares, and use of biologics or similar advanced treatments was low. Moreover, 24% of patients received no additional treatment prior to, during, or immediately after the medical care they sought for their flare.

To our knowledge, few studies have documented flares in patients with GPP and their treatment, and none have compared differences between patients with documented flares and patients without flares. Anecdotal accounts of GPP flares and patient surveys suggest that flares are quite severe, often requiring acute care.[16,20] Although several previous large population-based administrative data analyses have documented the clinical and economic burden of GPP, these studies were unable to identify GPP flares.[8,24] Current evidence of flares comes from case reports or single-center studies. To obtain a significant number of patients, some studies have included patients identified as having GPP for 2 decades or more,[16,18,20] which undermines the ability to examine current practice. Given the effect of flares on the lives of patients with GPP, it is important to gain knowledge of GPP, its flares, and current treatments beyond anecdotal accounts, case reports, or studies with small sample sizes.

Therefore, this study provides insights into GPP, its flares, and the patients who have flares documented in their EHR, given the number of patients included in the study and the ability to identify flares in the EHRs. With the large study population, this study focused on current treatments within the past several years. The algorithm to identify flares is an important contribution to the ability to identify GPP flares consistently in administrative data in a manner that can be replicated across studies. Moreover, the findings are consistent with previous smaller studies and care reports as well as anecdotal accounts and results from physician and patient surveys. The findings of greater acute care and emergency department burden are also consistent with other studies of patients with GPP compared with the general population as well as those with plaque psoriasis.[8,24]

Limitations

Like other studies using clinical data, this study had several limitations. The algorithm to identify GPP flares needs to be validated in future research. To ensure that only GPP flares were included in the study, the algorithm was intentionally conservative; key disease characteristics and flare terminology were necessary for the classification of flares. The method also captured only flares documented in the EHRs. Given the number of patients with no treatment initiated during or immediately after a flare, patients likely do not seek medical care for flares, knowing that no treatment changes are possible. In addition, most EHR data sources in the US, including Optum EHR data, are derived primarily from integrated-delivery health systems. If patients receive care outside of the health system, it is possible that this care is not captured in the database. Given this conservative approach, it is likely that the study underestimates the number of flares experienced by patients with GPP and that the flares identified are likely to be of higher severity than those not documented. Validation of the flare identification algorithm is warranted to ensure misclassification does not present bias in the results.

Another limitation was that the study population included only patients with a GPP diagnosis during the study period. Owing to the rarity and unawareness of GPP, additional patients with true GPP remain undiagnosed or are miscoded with other forms of psoriasis. This finding is further supported by the high percentage of patients with GPP who also have visits coded with "other psoriasis." Therefore, it is likely that some patients with GPP have never had visits coded with GPP specifically and would not have been included in this study.

Requiring 12 months of follow-up as an inclusion criterion is standard for these types of studies to ensure that patients included in the study have sufficient time in the data for follow-up care and treatment. However, excluding patients who are lost to follow-up, as defined by having at least 12 months of follow-up, also excludes patients who have died prior to 12 months after the index GPP diagnosis. In addition, treatments were based on prescriptions written or administered in the office or facility. Written prescriptions may not indicate whether the prescription was filled or actually taken by the patients. Moreover, changes in prescriptions that did not result in a new prescription being written or administered would not be captured. This is especially important when interpreting treatments before, during, and after flare episodes. The eFigure in the Supplement breaks down Figure 3 for flare episodes with or without treatment during a flare episode. Across almost all treatment categories, the percentage of flare episodes with treatment before an episode was higher for those without treatment during the episode than those with treatment during the episode. It is possible that dosing of existing treatments was increased without the need to write an additional prescription during the episode. This limitation of not being able to capture dosing escalations and the simplification of treatments that do not include combination therapy also contributes to the potential to underestimate flare episodes. Further research and refinement of the flare identification algorithm should examine treatment escalation as a potential indicator of flare episodes. In addition, the duration of flare episodes could not be assessed with this study method because episode duration is not commonly documented in the EHR. Similarly, the 30-day period after the last day of flare documentation in the EHR is likely not after the actual flare episode because flares can last for months. Moreover, subsequent flare episodes were not examined in association with the first flare episode in the data. Although this study offers new information regarding treatments for patients with GPP who do or do not have flares documented in their EHR and by flare episodes, additional research is needed to build on this initial examination of treatments, including the use of combination treatments. Despite these limitations, this study offers important insights into GPP flares.

Conclusions

To our knowledge, little is known about GPP flares and the differences between patients with GPP who seek care for

flares and those who do not. This cohort study examined GPP flares among a large population of patients with GPP. Generalized pustular psoriasis flares can be severe, often requiring emergency department care or acute care. Despite this high level of severity, advanced treatments are very rarely used during flare episodes, leaving a significant unmet treatment need for patients with GPP and for health care professionals.

ARTICLE INFORMATION

Accepted for Publication: June 13, 2022.

Published Online: August 10, 2022. doi:10.1001/jamadermatol.2022.3142

Author Contributions: Drs Zema and Valdecantos had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Zema, Weiss, Menter.
Acquisition, analysis, or interpretation of data: Zema, Valdecantos, Weiss, Krebs.
Drafting of the manuscript: Zema, Valdecantos.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Zema, Weiss, Krebs.
Obtained funding: Zema.
Administrative, technical, or material support: Zema, Valdecantos, Weiss, Menter.
Supervision: Zema, Weiss.

Conflict of Interest Disclosures: Dr Zema reported serving as a contractor for Boehringer-Ingelheim Pharmaceuticals Inc during the conduct of the study. Dr Menter reported being an investigator for AbbVie, Boehringer Ingelheim, Incyte, Janssen Biotech, Merck, Mindera, Novartis, Pfizer, Sun Pharma, and UCB; receiving research funds from AbbVie, Allergan, Amgen, Boehringer Ingelheim, Incyte, Janssen Biotech, Merck, Novartis, Pfizer, Sun Pharma, and UCB; and serving as an advisor, consultant, and/or speaker for and receiving honoraria from AbbVie, Allergan, Amgen, Boehringer Ingelheim, Eli Lilly, Janssen Biotech, LEO Pharma, Novartis, Pfizer, Sun Pharma, and UCB. No other disclosures were reported.

Funding/Support: This study was sponsored by Boehringer Ingelheim Pharmaceuticals Inc.

Role of the Funder/Sponsor: Through authors who are employees or contractors, Boehringer Ingelheim Pharmaceuticals Inc contributed to the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank Marianne Laouri, PhD, Boehringer Ingelheim Pharmaceuticals Inc, for her input and expertise in study design, analysis protocol, and interpretation of results; and Maya Hanna Lloyd, PhD, formerly with Boehringer Ingelheim Pharmaceuticals Inc during the study, for contributions towards study design, analysis protocol, and interpretation of results.

REFERENCES

1. Bachelez H. Pustular psoriasis: the dawn of a new era. *Acta Derm Venereol*. 2020;100(3):adv00034. doi:10.2340/00015555-3388

2. Menter A, Van Voorhees AS, Hsu S. Pustular psoriasis: a narrative review of recent developments in pathophysiology and therapeutic options. *Dermatol Ther (Heidelb)*. 2021;11(6):1917-1929. doi:10.1007/s13555-021-00612-x

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

4. Twelves S, Mostafa A, Dand N, et al. Clinical and genetic differences between pustular psoriasis subtypes. *J Allergy Clin Immunol*. 2019;143(3):1021-1026. doi:10.1016/j.jaci.2018.06.038

5. Ly K, Beck KM, Smith MP, Thibodeaux Q, Bhutani T. Diagnosis and screening of patients with generalized pustular psoriasis. *Psoriasis (Auckl)*. 2019;9:37-42. doi:10.2147/PTT.S181808

6. Benjegerdes KE, Hyde K, Kivelevitch D, Mansouri B. Pustular psoriasis: pathophysiology and current treatment perspectives. *Psoriasis (Auckl)*. 2016;6:131-144. doi:10.2147/PTT.S98954

7. Kharawala S, Golembesky AK, Bohn RL, Esser D. The clinical, humanistic, and economic burden of generalized pustular psoriasis: a structured review. *Expert Rev Clin Immunol*. 2020;16(3):239-252. doi:10.1080/1744666X.2019.1708193

8. Hanna ML, Singer D, Valdecantos WC. Economic burden of generalized pustular psoriasis and palmoplantar pustulosis in the United States. *Curr Med Res Opin*. 2021;37(5):735-742. doi:10.1080/03007995.2021.1894108

9. Okubo Y, Kotowsky N, Gao R, Saito K, Morita A. Clinical characteristics and health-care resource utilization in patients with generalized pustular psoriasis using real-world evidence from the Japanese Medical Data Center database. *J Dermatol*. 2021;48(11):1675-1687. doi:10.1111/1346-8138.16084

10. Morita A, Kotowsky N, Gao R, Shimizu R, Okubo Y. Patient characteristics and burden of disease in Japanese patients with generalized pustular psoriasis: results from the Medical Data Vision claims database. *J Dermatol*. 2021;48(10):1463-1473. doi:10.1111/1346-8138.16022

11. Liu ZJ, Tian YT, Shi BY, Zhou Y, Jia XS. Association between mutation of interleukin 36 receptor antagonist and generalized pustular psoriasis: a PRISMA-compliant systematic review and meta-analysis. *Medicine (Baltimore)*. 2020;99(45):e23068. doi:10.1097/MD.0000000000023068

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

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

14. Perez-Barrio S, Luz Garcia Vivar M, Galindez-Agirregoikoa E, et al. Pustular psoriasis and psoriatic arthritis: 13 cases reported in a multidisciplinary unit. *J Eur Acad Dermatol Venereol*. 2016;30(suppl 6):33-34.

15. Shmidt E, Wetter DA, Ferguson SB, Pittelkow MR. Psoriasis and palmoplantar pustulosis associated with tumor necrosis factor-α inhibitors: the Mayo Clinic experience, 1998 to 2010. *J Am Acad Dermatol*. 2012;67(5):e179-e185. doi:10.1016/j.jaad.2011.05.038

16. Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. *Int J Dermatol*. 2014;53(6):676-684. doi:10.1111/ijd.12070

17. Miyachi H, Konishi T, Kumazawa R, et al. Treatments and outcomes of generalized pustular psoriasis: a cohort of 1516 patients in a nationwide inpatient database in Japan. *J Am Acad Dermatol*. 2022;86(6):1266-1274. doi:10.1016/j.jaad.2021.06.008

18. Borges-Costa J, Silva R, Gonçalves L, Filipe P, Soares de Almeida L, Marques Gomes M. Clinical and laboratory features in acute generalized pustular psoriasis: a retrospective study of 34 patients. *Am J Clin Dermatol*. 2011;12(4):271-276. doi:10.2165/11586900-000000000-00000

19. Strober B, Kotowsky N, Medeiros R, et al. Unmet medical needs in the treatment and management of generalized pustular psoriasis flares: evidence from a survey of Corrona Registry dermatologists. *Dermatol Ther (Heidelb)*. 2021;11(2):529-541. doi:10.1007/s13555-021-00493-0

20. Kawada A, Tezuka T, Nakamizo Y, et al; Japanese Society for Psoriasis Research. A survey of psoriasis patients in Japan from 1982 to 2001. *J Dermatol Sci*. 2003;31(1):59-64. doi:10.1016/S0923-1811(02)00142-1

21. Ohkawara A, Yasuda H, Kobayashi H, et al. Generalized pustular psoriasis in Japan: two distinct groups formed by differences in symptoms and genetic background. *Acta Derm Venereol*. 1996;76(1):68-71.

22. Roth PE, Grosshans E, Bergoend H. Psoriasis: development and fatal complications. Article in French. *Ann Dermatol Venereol*. 1991;118(2):97-105.

23. Ryan TJB, Baker H. The prognosis of generalized pustular psoriasis. *Br J Dermatol*. 1971;85(5):407-411. doi:10.1111/j.1365-2133.1971.tb14044.x

24. Kotowsky N, Gao R, Singer D, Garry EM, Golembesky AK. Clinical burden and healthcare resource utilization in patients with generalized pustular psoriasis: a claims database study. Presented at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management, September 16-17, 2020; virtual.