Quick **TAKES**

- Generalized pustular psoriasis (GPP) is characterized by recurrent acute flares.
- The FDA accepted a biologics license application and granted priority review of spesolimab for the treatment of GPP.
- Education is imperative in GPP treatment and disease management.

New Treatment Shines Light on Generalized Pustular Psoriasis

Patients with this rare and severe skin disorder may soon have a new therapeutic option.

KATIE HOBBINS | *Editor*

First the skin becomes dry, red, and tender. Within hours, 2- to 3-mm sterile pustules appear and, after a day, form lakes of pus-filled lesions. Then the pustules dry out, leaving a peeled and glazed-looking surface on which more pustules may appear and erupt every few days or weeks.[1]

This describes the experience of a patient with generalized pustular psoriasis (GPP), a rare and serious skin disorder distinct from psoriasis and characterized by recurrent acute flares. GPP flares may cause fever, chills (or hypothermia), headache, rapid pulse rate, loss of appetite and nausea, thirst and dehydration, muscle weakness, and leg swelling.[1]

Factors that may trigger or exacerbate the disorder include the following, according to the authors of a continuing education activity paper published in *StatPearls*:[2]

INFECTION: Viral or bacterial infections "were reported in 12 of 16 patients with known [GPP] in one series," the authors wrote.

DRUGS: Corticosteroids seem to be the most common drug provocation. "There is substantial evidence that withdrawal of systemic corticosteroid therapy can precipitate [GPP], and topical therapy with potent corticosteroids under occlusion has also been implicated," the authors wrote. Additionally, withdrawal of cyclosporine has been reported to induce flares. Other systemic drugs occasionally implicated include terbinafine, propranolol, bupropion, lithium, phenylbutazone, salicylates, and potassium iodide. "Coal tar and dithranol may provoke pustulation if applied injudiciously when the disease is unstable," they continued.

PSYCHOLOGICAL STRESS: Patients have reported disease deterioration during times of psychological stress.

HYPOCALCEMIA: Although GPP itself may lead to low levels of calcium in the blood, hypocalcemia caused by hypoparathyroidism can also trigger active disease.

PREGNANCY: Recognized risk factors include pregnancy.

PATIENT PROFILE CHARACTERISTICS

The estimated incidence and prevalence rates for this rare disorder are 0.64 and 1.76 per million in the French population and prevalence is 7.46 per million in the Japanese population, according to authors of the paper, which was last updated in September 2021. In the United States, GPP appears especially rare. In a recent study 5 of 20 referral centers in the United States had less than 5 GPP patients over the past 10 years.[3]

The mean age of disease onset is 31 years, according to findings of a study in the *Journal of Allergy and Clinical Immunology*.[4] Children also can develop the disease—often because of genetic changes or mutations—and women are slightly more likely than men to develop GPP.[4,5]

The National Psoriasis Foundation reported that 54.4% of patients with GPP also have plaque psoriasis.[4] About 10% of patients also reported a history of psoriasis.[1]

GPP is a serious disease that often results in hospitalization and, without effective treatment, can cause death in its acute stage.[2] In the US it is estimated that 37% will need hos-

“The key thing to emphasize is how sick these patients are. These are amongst the sickest patients we see in dermatology, and this life-threatening disease requires urgent medical management. It’s a horrible disease with no approved therapy.”

Joel M. Gelfand, MD, MSCE, *Philadelphia, Pennsylvania*

pitalization at the initial encounter and that patients will experience on average, one GPP hospitalization every 2 years.[3] Biologics that inhibit tumor necrosis factor (TNF) α, IL-17, and IL-23 are approved for the treatment of GPP in Japan, Taiwan, and Thailand. Currently, there are no FDA approved therapies for the orphan disease in Europe or in the United States, where disease management has included cyclosporine, retinoids, methotrexate, and biologic agents.

Now a new drug aims to expand the treatment tool kit.[6] Boehringer Ingelheim announced in December 2021 that the FDA accepted a biologics license application and granted priority review of its drug spesolimab (BI655130) for the treatment of GPP.[7]

Spesolimab is a novel, humanized, selective antibody that blocks activation of the IL-36 receptor (IL-36R). This pathway within the immune system is shown to be key in the pathogenesis of the disorder, among several other autoimmune diseases, according to the company.

Deleterious germline mutations in IL-36RN have also been reported in familial and sporadic GPP in patients from the United Kingdom, Germany, Tunisia, Malaysia, China, and Japan. Mutations differ between those populations, “with evidence of a founder effect; in Europeans the most common mutation in IL-36RN results in the substitution p.Ser113Leu and is present in 0.03% of the healthy European population,” according to the authors of the *StatPearls* paper. “[GPP] patients with IL-36RN mutations also are more likely to have the early-onset disease and a systemic inflammatory response.[2]

“IL-36-RN encodes the IL-36 receptor antagonist (IL-36-Ra), which is expressed primarily in the skin and is the antagonist of 3 pro-inflammatory cytokines of the IL-1 family (IL-36 alpha, beta, and gamma),” the authors continued. “These cytokines activate signaling pathways, such as NF-kB and mitogen-activated protein (MAP) kinase, and are interrelated by Th17 cytokines and TNF-alpha. IL-36 cytokines also are overexpressed in the skin of plaque psoriasis, consistent with the concept that abnormal IL-36 signaling has a significant role in establishing cutaneous inflammation but presumably by a different mechanism than in [GPP].”

Investigators in a recent phase 2 randomized trial (Effisayil 1; NCT03782792) published in the *New England Journal of Medicine* examined the use of spesolimab to treat GPP flares.[6] The multicenter, double-blind, placebo-controlled study was conducted between February 20, 2019, and January 5, 2021, with patients enrolled at 37 sites across 12 countries. “Because GPP is a rare disorder, and because estimates of prevalence at the time of planning the trial suggested that GPP was approximately 5 times more common in Asia than in Europe and the United States, the trial sites were chosen accordingly,” study investigators wrote.

The investigators also noted that although published literature on ethnicity prevalence is lacking, their clinical experience anecdotally exhibited that the disease occurs less frequently in Black than Caucasian individuals.

Patients from 18 to 75 years of age were enrolled if they had a history of GPP consistent with the European Rare and Severe Psoriasis Expert Network diagnostic criteria and currently had a moderate to severe flare. Although patients were analyzed for the 3 main GPP-associated genes—*IL-36RN*, *CARD14*, and *AP1S3*—through DNA extracts from blood samples, they were enrolled regardless of *IL-36RN* mutation status.

Patients with active GPP flares were randomized 2:1 to receive a single IV dose of 900 mg of spesolimab or placebo on day 1.

On day 8, patients from both groups were eligible to receive a single open-label, 900-mg IV dose of spesolimab if they had persisting symptoms according to the threshold of a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score of 2 or higher (range, 0 [clear skin] to 4 [severe disease]) and a clinician assessment of GPP severity based on a modified Physician Global Assessment and a GPPGA pustulation subscore of 2 or higher (range, 0 [no visible pustules] to 4 [severe pustulation]) at week 1. This resulted in a crossover from placebo to open-label spesolimab for some patients.

After week 1, rescue treatment of a single 900-mg IV dose of spesolimab could be administered in the case of flare reoccurrence. Patients who clinically improved or completed the trial without flare symptoms were than eligible to take part in a 5-year open-label extension study. Those who needed escape treatment—defined as standard-of-care therapy—were considered to not have a response (nonresponse) for both primary and secondary evaluation at week 1.

EXAMINING THE END POINTS

The primary end point for the study was a GPPGA pustulation subscore of 0 (no visible pustules) at the end of week 1, the investigators

wrote. At that point, 19 of the 35 patients (54%) assigned to the spesolimab group and 1 of the 18 patients (6%) assigned to the placebo group had a subscore of 0 (difference, 49% points; 95% CI, 21-67; $P < .001$).

"The key secondary end point was a GPPGA total score of 0 or 1 (clear or almost clear skin) at the end of week 1," the investigators wrote. "Secondary end points were mostly assessed at week 4. Secondary end points at week 4 (after the randomized phase of the trial) included a 75% or greater decrease in the score on the Psoriasis Area and Severity Index (PASI) for Generalized Pustular Psoriasis (GPPASI 75); the change from baseline in the assessment of pain on a visual analog scale (pain VAS; scores range from 0 [no pain] to 100 [severe pain]); the change from baseline in the score on the Psoriasis Symptom Scale (PSS, which involves patient-reported psoriasis pain, redness, itching, and burning; scores range from 0 to 16, with higher scores indicating more severe symptoms); and the change from baseline in the score on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue, which involves the patient-reported effect of fatigue on daily activities; scores range from 0 to 52, with lower scores indicating a greater effect)."

Fifteen patients (43%) in the spesolimab group and 2 (11%) assigned to placebo had a GPPGA score of 0 or 1 (difference, 32% points; 95% CI, 2-53; $P = .02$).

Secondary end points at week 4 were descriptively reported in groups of 4 that reflected the treatment paths after day 8. This was done because after week 1, 15 of 18 patients initially in the placebo group received open-label spesolimab on day 8, making planned hierarchical testing noninformative.

"All 35 patients [were] randomly assigned to receive spesolimab (patients who received 1 dose [day 1 only] or 2 doses [day 1 plus day 8]), 23 patients randomly assigned to receive spesolimab who did not receive open-label spesolimab on day 8 (day 1 only), 12 patients randomly assigned to receive spesolimab who received open-label spesolimab on day 8 (day 1 plus day 8), and 15 patients randomly assigned to receive placebo who received open-label spesolimab on day 8," wrote the authors.

Their conclusion, based on the results: "This randomized trial of a single intravenous dose of the humanized anti–interleukin-36 receptor monoclonal antibody spesolimab in patients with a flare of GPP showed that at 1 week there was better clearance of lesions with spesolimab than with placebo." However, infections were more frequent.

To further discuss the study findings and highlight physician perspectives, Boehringer Ingelheim held an expert roundtable in partnership with *Dermatology Times*®. The physicians present at the discussion, which was recently held onsite at the Maui Derm for Dermatologists 2022 meeting in Hawaii, included:

- Bruce E. Strober, MD, PhD, co-founder of Central Connecticut Dermatology in Cromwell and a clinical professor of dermatology at Yale University School of Medicine in New Haven, Connecticut;
- Michael Gold, MD, founder of Gold Skin Care Center, Advanced Aesthetics Medical Spa, the Laser & Rejuvenation Center, and Tennessee Clinical Research Center in Nashville; and
- Joel M. Gelfand, MD, MSCE, James J. Leyden Endowed Professor in Clinical Investigation, professor of dermatology and of epidemiology, vice chair of clinical research, senior scholar in the Center for Clinical Epidemiology and Biostatistics, medical director of the Department of Dermatology clinical studies unit, and medical director of the Psoriasis and Phototherapy Treatment Center at the University of Pennsylvania Perelman School of Medicine in Philadelphia.

The experts highlighted the findings, noting specific educational needs for the dermatology community.

Wendell C. Valdecantos, MD, executive director of clinical development and medical affairs at Boehringer Ingelheim, started off the ad board by highlighting the severe need for an FDA-approved GPP treatment. "Despite it being a rare disease, we do know that there's significant morbidity and mortality among patients with the disease," he said.

INCREASING EDUCATION

After discussing the *New England Journal of Medicine* study, the roundtable focused on specific questions prepared by the company and Strober about awareness and education. Gold emphasized that although a disease is rare, it is important to have a treatment available when a patient needs it. "Even for the dermatologists that don't see 1 of these [cases] every 10 years…[they'll] know that this exists and not get scared of it," he said.

Educating physicians and allied health care professionals will be key for increasing the understanding of disease manifestations, treatment, and misdiagnosis, Strober said.

Strober suggested having regional company representatives visit and educate practice staff on potential procedures to follow for patients with GPP. "Basically, the [representative] needs to be present, saying, 'Look, if this patient walks in, here's how we get the process rolling.' And at least there's a concept that you contact a person who's in that geographic area quickly and ask, 'How do we get this process moving from prior authorization to referral to treatment?' because it's really time dependent," he said. "There needs to be a very immediate 4-alarm-fire approach to these patients."

Gelfand noted the importance of education not only in individual practices but in hospital settings as well. "The biggest benefit of this drug is through the hospital, right? [These patients] generally get admitted to the hospital; they get a sepsis work-up, and they get covered in a sauna suit," he said, highlighting the severe nature of the disease and the fact that many patients get sent directly to a hospital, not to a dermatologist.

"The key thing to discuss is how sick these patients are," Gelfand said. "These are amongst the sickest…patients we see in dermatology, and [this life-threatening disease] requires urgent medical management. The data clearly underscore that, given the pain scores and the systemic inflammation. It's a horrible disease with no therapy."

Gold emphasized the need to teach physicians in specialties outside dermatology about

"Longer and larger trials are warranted. That's an obvious one. Who's going to say 'No, you don't need any more studies; we're done'?"

Bruce E. Strober, MD, PhD, *New Haven, Connecticut*

> “We’ve got to teach the primary care [physicians], rheumatologists, [emergency room] docs.”

Michael Gold, MD, *Nashville, Tennessee*

the management of GPP due to its acute onset: “We’ve got to teach the primary care [physicians], rheumatologists, [emergency room] docs.”

Gelfand discussed including patients in the education process. Because GPP is so rare, creating an engaged network could foster awareness of spesolimab, according to Gelfand. “You can create a network of patients,” he said. “The idea would be that the patient knows what to ask for and knows who to go to and say, ‘I have this horrible pustular disease, and I need this drug.’”

Disease awareness may also call for partnerships with psoriasis organizations. “I think you could do it through the National Psoriasis Foundation,” Gold said. “Work with them and say, ‘Hey, we need a center of excellence in every major metropolitan area.’”

DRILLING DOWN THE DATA

The 3 experts highlighted the study findings that make the most impact when talking with other physicians about spesolimab as a treatment for the skin disorder.

Data such as GPPGA scores and pustulation may need additional explanation for dermatologists, according to Strober. However, he said, focusing on pain and Dermatology Life Quality Index (DLQI) scores could be of more interest.

“The GPPGA and pustulation scores are not easily understandable right now,” Strober said. “They’ll need some education. But you also may want to anchor back to the DLQI improvement and pain improvement, because it’s probably more important when you’re reporting these data.”

Gelfand continued: “You tend to be excited by the fact that their pustular score goes to zero, and then focus on the resolution of the systemic inflammatory processes. The main thing is [that there are] no more pustules after a week—that’s heavily powerful—and the fatigue scores.”

These positive outcomes do come with the potential for adverse events (AEs), but Strober noted that AEs need to be put in context with how sick the patients are. “This is such a severe disease; there’s a greater tolerability for some AEs—maybe infection that could result from the drug,” he said. “I actually thought the study showed a pretty good safety outcome. In this kind of disease state, you would anticipate that with a sick population, there are going to be negative AEs at a higher rate.”

> “The main finding is that a high percentage of patients had resolution of pustules within one week.”
>
> Joel M. Gelfand, MD, MSCE
> **Philadelphia, Pennsylvania**

PARTNERING WITH INFUSION CENTERS

Many dermatology offices partner with infusion centers to administer IV treatments, including the practices of Strober, Gelfand, and Gold. A similar procedure may be followed for using spesolimab. However, health care professionals would need to understand the process for administration because of the agent’s orphan drug status and the associated rare skin disorder.

“We all use infusion centers now and are happy to have a program and get the [physicians] and say, ‘OK, we have a new drug for something you may never see, or we may see 2 or 10 times this year. You may have seen it and not known what you were treating,’” Gold said.

Due to the acute nature of GPP and its rapid onset, the experts highlighted the need to get patients into an infusion center for treatment as quickly as possible. “I can get them [there] in an hour if I need to,” he said. “It could take a week or 2 normally, but if it was an emergency, I’d get them in immediately.”

Insurance can complicate the situation. “There’s variability based on their insurance too,” Strober pointed out. “I mean, how quickly can you get the prior authorization? Through some insurers it’s almost instantaneous. And others? It’s weeks.”

At his practice, Strober said, he created a “hotline approach” with a nearby infusion center: “The one we work with is highly motivated to have patients. They’re very easy to work with, and we’ve developed a hotline approach with them. Every medically oriented dermatology practice has to have a hotline approach in the private practice setting with the nearby infusion center.”

What’s next, according to the round table experts? Additional studies.

“Longer and larger trials are warranted,” Strober said. “That’s an obvious one. Who’s going to say ‘No, you don’t need any more studies; we’re done’? Also, the subcutaneous formulation is vital to the long-term use of the drug, so that a ‘non-IV’ option becomes a viable and effective choice.”

Gold added, “Once the drug is out there and approved, it requires podiums. It requires papers, and it’s going to require meetings.”

Disclosures:

Strober is a consultant for Boehringer Ingelheim. Gelfand is a consultant and receives research grants from Boehringer Ingelheim. Gold reported no relevant disclosures.

References

1 Ngan V. Generalised pustular psoriasis. DermNet NZ. Updated September 2014. Accessed February 3, 2022. https://dermnetnz.org/topics/generalised-pustular-psoriasis

2 Mirza HA, Badri T, Kwan E. Generalized pustular psoriasis. In: StatPearls. StatPearls Publishing; September 14, 2021. https://www.ncbi.nlm.nih.gov/books/NBK493189/

3 Noe MH, Wan MT, Mostaghimi A, et al. Evaluation of a case series of patients with generalized pustular psoriasis in the united states. JAMA Dermatol. 2022;158(1):73.

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 Generalized pustular psoriasis. National Psoriasis Foundation. Accessed February 3, 2022. https://www.psoriasis.org/generalized-pustular-psoriasis/

6 Bachelez H, Choon SE, Marrakchi S, et al. Trial of spesolimab for generalized pustular psoriasis. N Engl J Med. 2021;385(26):2431-2440. doi:10.1056/NEJMoa2111563

7 U.S. FDA grants priority review for spesolimab for the treatment of flares in patients with generalized pustular psoriasis (GPP), a rare, life-threatening skin disease. Boehringer Ingelheim. News release. December 15, 2021. Accessed February 3, 2022. https://www.boehringer-ingelheim.us/press-release/us-fda-grants-priority-review-spesolimab-treatment-flares-patients-generalized