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COMMENTARY

Exploring the Chronic Nature of Generalized Pustular Psoriasis [Podcast]

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Abstract: Generalized pustular psoriasis (GPP) is a rare, chronic, inflammatory skin disease characterized by persistent symptoms and sudden flares of painful, sterile pustules, and may be accompanied by systemic inflammation. Ongoing symptoms of GPP can have a serious impact on patient quality of life, morbidity, and mortality, and severe flares may be life-threatening if left untreated. Guidelines have been developed for the treatment of GPP flares; however, health care professionals and patients are lacking guidance on the management of long-term, persistent symptoms of GPP. Spesolimab is the only FDA-approved treatment for GPP and is approved for use in adults and pediatric patients aged 12 years or older and weighing at least 40 kg. Spesolimab recently gained FDA approval as a subcutaneous injection to treat GPP when patients are not experiencing a flare. In this podcast episode, we discuss what is known about the chronic disease burden of GPP and how persistent symptoms affect quality of life when patients are not experiencing a flare. We address the need for treatment guidelines for chronic GPP and discuss the results of the EFFISAYIL® 2 clinical trial, which led to the approval of the subcutaneous formulation of spesolimab to treat GPP when patients are not experiencing a flare. Finally, we discuss what can be done to improve the treatment of patients with chronic GPP, both while experiencing a flare, and while living with persistent symptoms.

Keywords: generalized pustular psoriasis, rare disease, chronic disease, spesolimab, expert opinion

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Speakers: Dr Boni Elewski, Dr Mark G Lebwohl

Dr Boni Elewski: Hello, and welcome. My name is Dr Boni Elewski, and I am the James Elder Professor and Chair of Dermatology at the University of Alabama. Joining me today is Dr Mark Lebwohl, who is the Dean for Clinical Therapeutics at the Icahn School of Medicine at Mount Sinai Waldman Department of Dermatology. Today we will be discussing generalized pustular psoriasis, or GPP, which is a chronic and potentially life-threatening inflammatory disease. Dr Lebwohl, would you like to give an overview of GPP?

[00:00:37]

Dr Mark G Lebwohl: Certainly. Patients who have GPP experience periodic and sudden flares of painful, sterile pustules on the skin, which are often accompanied by systemic inflammation, and can be life-threatening, as many complications can be severe.[1] In addition to these periodic flares, patients have a substantial chronic disease burden that affects their everyday lives, even when they are not flaring.[2–5] As of right now, however, little guidance is available on how to manage these chronic GPP symptoms. Currently, the only approved medication to treat GPP flares is spesolimab, which is an antibody that specifically blocks interleukin-36 (IL-36) receptor signaling. Spesolimab is currently approved to treat GPP flares in 48 countries.[6] Recently, spesolimab received regulatory approval in the US and China as a subcutaneous injection to treat GPP when patients are not experiencing a flare, in adults and pediatric patients aged 12 years or older and weighing at least 40 kilograms.[7]

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Dr Boni Elewski: That's right. But despite the fact that subcutaneous spesolimab is now approved and available to treat patients who are not experiencing a flare, health care professionals and patients are still

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lacking official guidelines on how to manage chronic GPP. Recently, a DELPHI consensus stated that long-term treatment goals for GPP should focus on minimizing disease severity, preventing flares and controlling signs and symptoms between flares.[data not yet published] Today we will talk about the impact chronic GPP has on patients' lives, the best ways to treat chronic GPP long-term, and what can be done to continue to improve the quality of life in people with GPP. So, Dr Lebwohl, how would you describe the chronic burden of GPP?

[00:02:29]

Dr Mark G Lebwohl: Good question. In a survey, dermatologists reported that patients with GPP experience symptoms like skin scaling, skin lesions, and erythema, even when they are not flaring.[5] Patients themselves, have also reported experiencing at least moderate severity symptoms even when their GPP was under control.[4] Their long-term symptoms can include itching, pain, and fatigue,[8] and these symptoms can severely increase the burden of the disease for these patients. Now, on top of the persistent symptoms' patients experience, they also must deal with the ongoing threat of a GPP flare.

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Dr Boni Elewski: Precisely. One thing that is so difficult about treating patients with GPP is that the clinical course of the disease is highly unpredictable.[1] Flares can occur because the patient encounters a trigger, such as a change in medication, an infection, pregnancy, menstruation, or withdrawal from oral corticosteroid use. But sometimes, there is not any obvious cause at all.[1,3,9–21] Because there are so many potential triggers of a flare, oncoming flares are very difficult to avoid, which is serious, because systemic inflammation is common,[1] and flares can be life-threatening if left untreated.[5] Patients can also experience skin failure during a flare, which is a state of total dysfunction of the skin, or acute skin failure, resulting in a high risk for high-output cardiac failure, renal failure, and sepsis.[22] Flares, themselves, can last over 3 months, and can recur up to 2–3 times per year.[2,4,5,8]

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Dr Mark G Lebwohl: So, patients with GPP experience both persistent chronic symptoms and recurrent, potentially life-threatening flares. And as you have described, because the consequences of GPP can be so severe, it is extremely important for a diagnosis to be made early, and for treatment to be given as quickly as possible. However, because GPP is a rare disease and its presentation can be variable, it may not be easily recognized by clinicians who do not specialize in dermatology. This includes clinicians in the emergency department where patients often go when a serious flare develops.[23] To avoid misdiagnoses and delays in treatment, widespread physician education on the clinical appearance of GPP is imperative. Recently, the International Psoriasis Council and the National Psoriasis Foundation both published consensus statements establishing standardized diagnostic criteria for GPP, and both stressed that the potentially life-threatening nature of GPP necessitates immediate treatment.[24,25] The criteria for identifying GPP included "macroscopically visible sterile pustules on an erythematous base and not restricted to the acral region or within psoriatic plaques." They also emphasized that diagnosis should be made rapidly and should not be delayed by waiting for biopsy results, or results of tuberculosis testing.[26]

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Dr Boni Elewski: These are all great points. Widespread recognition of the disease and rapid diagnosis and treatment are vital when these patients are experiencing a potentially life-threatening GPP flare. Now, let's talk more about what the burden of GPP looks like for patients when not experiencing a flare. Even when not experiencing a flare, the serious and ongoing nature of GPP can have a severe and long-term detrimental impact on patients' quality of life.[9] When surveyed, 36% of patients reported GPP affects their daily well-being in the timescale of months, and 38% reported its impact lasting for years.[4] Patients feel the ongoing impact of GPP physically, mentally, and financially.[27] Persistent symptoms like pain and fatigue can take an immense physical toll on patients, and financially, patients can incur high out-of-pocket costs to travel long distances to see specialists or pay for specialty medications. On top of these stressors, patients have reported feeling debilitating anxiety or depression because the occurrence of their next flare is so unpredictable. Unfortunately, patients have also reported feeling

unsupported by their physicians, and that their physicians do not understand the psychological, emotional, or physical pain caused by their GPP.[4]

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Dr Mark G Lebwohl: And it's not just GPP symptoms contributing to the loss of quality of life. Chronic comorbidities also play a role in long-term patient health and well-being. GPP is often accompanied by chronic comorbidities that contribute to greater overall severity of disease and mortality burden.[9,28–30] The most common include plaque psoriasis, hypertension, cardiovascular comorbidities such as ischemic heart disease and congestive heart failure, psoriatic arthritis, type 2 diabetes, hyperlipidemia, and obesity. A Swedish registry study of 1093 patients with GPP found that as many as 70% of patients with GPP had comorbid conditions, in comparison with 46% of the general population, and 63% of patients with plaque psoriasis.[28]

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Dr Boni Elewski: So, given all the evidence that GPP negatively affects patients long-term, it's clear that guidelines are needed for long-term management of this chronic condition, beyond just treatment of flares. However, currently none exist. Clinicians need official guidelines on flare prevention, and on managing persistent symptoms and chronic comorbidities, even when patients are not experiencing flares. Additionally, measurements of disease severity, quality of life, and pain need to be standardized. A recent DELPHI consensus statement emphasized the importance of managing comorbidities, improving quality of life, and sustained disease control in GPP.[data not yet published] Subcutaneous spesolimab is a new FDA-approved strategy to treat GPP when not experiencing a flare, which could improve quality of life, reduce or improve comorbidities, and reduce the risk of hospitalizations by preventing future flares. Prior to the availability of spesolimab, however, there was a lack of safe and effective treatment strategies for long-term control of GPP.[31,32] Dr Lebwohl, could you describe some of the earlier treatment methods for GPP?

[00:09:23]

Dr Mark G Lebwohl: Certainly. Before the approval of spesolimab, a variety of nonbiologic systemic agents such as retinoids, methotrexate, and cyclosporine have typically been prescribed to treat GPP flares.[33,34] These are used mainly based on their success in treating plaque psoriasis, but none of them are indicated to treat GPP. When prescribed these medications, however, patients are often switched from one therapy to another, suggesting that these methods are ineffective in treating either flares or long-term symptoms.[35] What's more, none of these agents have acceptable safety profiles to be used long-term and are typically only prescribed when flares occur. Cyclosporine, for example, can result in nephrotoxicity and hypertension over time.[36] Methotrexate is associated with liver and hematologic toxicity,[36] and retinoids can lead to side effects like liver toxicity, diffuse skeletal hyperostosis, and osteoporosis.[37] Additionally, both methotrexate and retinoids are contraindicated in pregnancy and must be used with caution in individuals of child-bearing potential due to the risk of birth defects.[37,38] Systemic corticosteroids, while used to treat flares, are also a known flare trigger.[39,40] Topical corticosteroids may also be used to treat flares, although their long-term use can lead to adrenal insufficiency, Cushing's syndrome, and osteoporosis.[39,40] Aside from the nonbiologic therapy options, several biologics have gained approval in Japan to treat GPP flares and have been used off-label in other countries, however their approval was based on small studies without validated measures for end points.[34]

[00:11:04]

Dr Boni Elewski: So, there are a handful of non-GPP-specific treatments that tend to be prescribed to treat GPP. However, because of the high morbidity and mortality of GPP, and the risks you detailed just now with long-term treatment with some off-label medications, it is vital for patients with GPP to be treated with FDA-approved therapies. Now we are going to talk a little more about spesolimab and how subcutaneous spesolimab gained FDA approval to treat GPP when patients are not experiencing a flare. Currently, spesolimab is the only medication approved in the US to treat GPP.[6] EFFISAYIL® 2 was the first randomized, placebo-controlled clinical trial that systematically looked at the prevention of GPP flares with spesolimab.[41] In the study, 123 patients were randomized to receive either subcutaneous spesolimab 300 mg every 4 weeks after a 600 mg subcutaneous loading dose; or 300 mg every 12 weeks after a 600 mg loading dose; or 150 mg every 12 weeks after a 300 mg loading dose; or placebo

every 4 weeks, for 48 weeks. Investigators specifically evaluated the time to first GPP flare by Week 48, and the occurrence of at least one flare by Week 48 in spesolimab versus placebo groups. Dr Lebwohl, can you tell us what they found?

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Dr Mark G Lebwohl: Well, at the end of 48 weeks, among patients treated with 300 mg subcutaneous spesolimab every 4 weeks, only 3 out of 30, or 13% of patients when adjusted for exposure, experienced at least one flare, which was significantly fewer than the 16 of 31, or 52% of patients in the placebo group. Also, patients who received 300 mg every 4 weeks had a significantly lower risk of GPP flare after starting the treatment, compared with placebo. A non-flat dose-response relationship was shown for all three spesolimab treatment groups versus placebo for time to first GPP flare, which achieved the primary trial objective. It was also notable that no flares were observed in the 300 mg every 4 weeks treatment group after the first 300 mg maintenance dose was received at Week 4.

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Dr Boni Elewski: Now, let us take a look at safety. Spesolimab had a similar safety profile in this trial as in EFFISAYIL® 1.[42] In EFFISAYIL® 2, after 48 weeks, the rate of adverse events was similar between treatment arms, with adverse events occurring in 84 of 93, or 90%, of patients across the spesolimab treatment arms and 26 of 30, or 87%, of patients in the placebo arm. Adverse events were not dose-dependent for spesolimab. The incidence of serious adverse events was higher in the spesolimab arm with an overall incidence of 9 of 93 patients, or 10%, compared to 1 of 30 patients, or 3%, in the placebo arm. However, there were no deaths in the study, and infections occurred in 33% of both the spesolimab and placebo arms. Infections were not dose-dependent, and there were no patterns in pathogen or organ system.

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Dr Mark G Lebwohl: The results from EFFISAYIL® 2 suggest that spesolimab is effective and safe to treat patients with GPP, and this is what gained subcutaneous spesolimab FDA approval for treating GPP when patients are not experiencing a flare. The efficacy of spesolimab has held up in subgroup analyses as well, including *IL36RN* mutation status, plaque psoriasis status, and BMI. Another notable finding from EFFISAYIL® 2 was that among 15 of the 30 patients in the placebo group who did not experience a flare, many still reported moderate or very large impacts of GPP on their quality of life. Nearly half reported moderate to severe scores on the Pain Visual Analog Scale, and on the Generalized Pustular Psoriasis Physician Global Assessment, or GPPGA.[43] This goes back to our point about the constant, ongoing, chronic disease burden of GPP, even when patients are not experiencing a flare. With the FDA's approval of spesolimab, flares may now be treated with a single 900 mg intravenous infusion, plus an optional second infusion one week afterwards for persistent flare symptoms. GPP in patients not experiencing a flare can be treated with a subcutaneous 600 mg loading dose followed by 300 mg subcutaneous injections every four weeks.[6]

[00:16:06]

Dr Boni Elewski: I would like to discuss a patient in my own practice who had remarkable improvement in their GPP symptoms following spesolimab treatment. This patient had a long-standing history of plaque psoriasis and psoriatic arthritis and had been receiving guselkumab for more than a year. With guselkumab, her skin was totally clear. However, she developed GPP after receiving a course of oral clindamycin and a steroid injection for a minor infection. Her GPP flare became very serious, and she was air-lifted to a major medical center and admitted to the ICU. On admission, she was erythrodermic, edematous, and covered with small pustules. She was also toxic, tachycardic, and febrile, but her work-up was negative for infection. Despite these very serious symptoms, once the patient was treated with a single IV infusion of spesolimab, she had rapid skin clearance within about 24 hours. This goes to show how vital it is to get FDA-approved medications to patients as soon as possible, and how effective they can be when administered in a timely manner.

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Dr Mark G Lebwohl: And this is precisely why it is so important to make sure patients have timely access to the treatment when they need it. While access to spesolimab may be limited by barriers like difficulty obtaining insurance coverage and challenges locating an infusion center that administers spesolimab, the establishment of official guidelines that recommend therapy for long-term

management of GPP could help ease some of the logistical burden that causes delays in accessing treatment. Collaboration and good communication between health care professionals, infusion centers, and insurance companies will enable patients to gain access to spesolimab with the speed necessary to treat this potentially life-threatening disease.

[00:18:08]

Dr Boni Elewski: Here are some of the takeaways of our conversation today. For patients to receive optimal treatment, GPP *must* be recognized by dermatologists and physicians of all specialties as a chronic disease. Further long-term research and follow-up with patients with GPP will allow for better understanding of the chronic pathophysiology of GPP and may help identify additional flare triggers and how to best avoid them. More research on the long-term effects of GPP treatment is also needed, including a multi-year follow-up of patients taking spesolimab for long-term management, as well as other therapies.

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Dr Mark G Lebwohl: Along with recognition of the disease, patients with GPP should have easier access to long-term therapies that relieve persistent symptoms and ease the mental and physical burden associated with GPP. The approval of subcutaneous spesolimab enables patients to self-administer the medication at home after they receive the loading dose from a health care professional. This route of administration alleviates the burden of traveling to clinics for infusions. Ongoing and future studies should emphasize that GPP is a chronic disease associated with multiple comorbidities, and treatment plans should aim to treat GPP both chronically and acutely, to improve patient outcomes and quality of life.

[00:19:35]

Dr Boni Elewski: Thank you for joining us today. For anyone looking for more information on GPP, we hope listeners will review the previous podcasts in this series, where we discuss the characteristics of GPP, treatment approaches to control flares and improve quality of life, and the patient's perspective on the burden of GPP.

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