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COMMENTARY

Exploring the Clinical Assessment, Guidelines, and Options for the Treatment of Generalized Pustular Psoriasis [Podcast]

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Abstract: Acute episodes of generalized pustular psoriasis (GPP), known as "flares", are characterized by the widespread appearance of pustules with surrounding skin erythema, and are often accompanied by systemic symptoms. The clinical course of GPP is unpredictable, and symptoms vary in extent and severity; the disease may be relapsing-remitting with recurrent episodes of pustulosis, or be more persistent. The triggers that may lead to flares include withdrawal of corticosteroids, stress, pregnancy, and infections. GPP-specific assessment tools, such as the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) and the General Pustular Psoriasis Area and Severity Index (GPPASI), were developed to evaluate the severity of disease, and to monitor the patient's response to therapy during clinical trials. Spesolimab is the first GPP-specific treatment available in the United States for the treatment of GPP flares in adults, and was approved by the US FDA in September 2022. To date, spesolimab has been approved by regulatory agencies in almost 40 countries, including Japan, Mainland China, and the European Union. Spesolimab is a first-in-class humanized monoclonal antibody that targets the interleukin-36 receptor, and blocks the downstream effects of the interleukin-36 pathway, which is associated with GPP pathogenesis. Data from clinical trials demonstrate the safety and efficacy of spesolimab in providing rapid clinical improvement for patients with GPP flares. Standardized international guidelines for the diagnosis and management of GPP are needed, and no recent GPP guidelines are available in the US. This podcast discusses clinical assessment tools for GPP (GPPGA and GPPASI), the evolution of GPP management guidelines, the therapeutic landscape of GPP, efficacy and safety data for spesolimab, and examines important considerations for patients living with this condition.

Keywords: generalized pustular psoriasis, clinical assessment, treatment guidelines, interleukin-36 pathway

Podcast Speakers

This podcast is brought to you by Boehringer Ingelheim.

Moderator: Dr Uwe Wollina

Guests: Dr Eingun James Song and Dr Clive Liu

Dr. Uwe Wollina: Hello and welcome to the podcast series on generalized pustular psoriasis that focuses on different aspects of the disease. Listeners can obtain further information on this condition in other episodes of this podcast series.

I am Uwe Wollina, former head of the Department of Dermatology and Allergology at the Dresden Academic Teaching Hospital in Germany. I have the pleasure of moderating today's podcast, where we will be discussing clinical assessment guidelines and options for the treatment of generalized pustular psoriasis.

I would like to welcome Clive Liu and Eingun James Song, who are both dermatologists in Washington state, and we look forward to discussing their experiences in treating

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generalized pustular psoriasis. Could you please share your background in managing patients with this disease?

Dr. Eingun James Song: Yes, generalized pustular psoriasis, often referred to as GPP, is considered an ultra-rare disease for a reason. We just don't see that much of it, maybe once a year, and I am usually seeing these patients as an inpatient, maybe an ER consult, or an urgent add-on at the end of the day because these patients are often very sick. Now, having said that, I just had a patient with GPP actually wheelchaired through my door the other day.

Dr. Clive Liu: I agree: not only is it rare, GPP is also one of the few dermatologic emergencies that we encounter, and it can be challenging to treat. Clinically, it can be quite striking to visualize. Unlike Dr Song's recent patient, my last case was a little over a year ago.

Dr. Uwe Wollina: It is a pleasure to speak with you both. Today we are going to discuss the clinical assessment tools used to measure disease severity in GPP. We will also talk about treatment guidelines for the management of GPP and consider drugs that may be used in the treatment of GPP.

To start with, would you provide a brief overview of GPP and explain how disease severity is assessed?

[0:02:10]

Dr. Eingun James Song: GPP is a potentially life-threatening skin disease, and it typically presents with rapid widespread sterile pustules with surrounding skin erythema, and it can be associated with systemic symptoms.[1–3] And the disease course is unpredictable, so it can be relapsing-remitting, with recurrent episodes of pustulosis, or it may be more persistent, with symptoms lasting sometimes for several months.

We refer to acute episodes of GPP as "flares", and these are often accompanied by pain in the skin lesions, along with signs and symptoms of systemic inflammation. The triggers that may lead to flares were discussed in this podcast series by Drs. Merola and Amin, and include withdrawal of corticosteroids, exposure to sunlight, stress, pregnancy and infections.

Now you may be wondering who is most affected by GPP. As noted in another podcast publication by Drs. Hawkes and Bhutani, most patients develop symptoms of GPP somewhere between the ages of 40 to 60 years of age, although cases can appear in childhood as well.[4–6] Regarding ethnicity, prevalence data do vary, but GPP appears to affect Asian populations more so than White populations.[7]

As mentioned earlier, the clinical course of GPP is highly variable, and so assessing disease severity is necessary... to determine what level of treatment is needed to control GPP flares. GPP-specific assessment tools, such as the Generalized Pustular Psoriasis Physician Global Assessment Score (often referred to as the GPPGA), and the Generalized Pustular Psoriasis Area and Severity Index (also referred to as the GPPASI) were developed to evaluate the severity of disease and monitor the patient's response to therapy.[8]

The GPPGA is a physician-based assessment that assesses the average severity of pustules, erythema and scaling, and is scored from 0 to 4. A lower score indicates a lesser disease severity. And the validation of the GPPGA score has been published.[9]

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Dr. Clive Liu: The GPPASI is adapted from the Psoriasis Area and Severity Index (which we also know as PASI). It measures the severity of erythema and scaling, but substitutes the degree of pustulation for induration. The percentage of body surface area involved (the head and neck, upper limbs, trunk and lower limbs) is then determined, and a score is calculated and obtained.[8]

It's important to note that these assessment tools are mainly used in a clinical trial setting. Healthcare providers may use other tools to assess disease severity and personalize treatment in GPP, when needed.

Dr. Uwe Wollina: Before we move on, I'd like to recommend that listeners check out the other podcasts in the series that were just mentioned, and provide more detail about GPP – what it is and who is most affected by it – fascinating discussions!

Now, back to our conversation, do we have any existing treatment guidelines for managing GPP?

Dr. Eingun James Song: So guidelines for GPP management from the US National Psoriasis Foundation were published in 2012,[10] so quite outdated, and there are some joint guidelines from the

American Academy of Dermatology and the National Psoriasis Foundation for managing plaque psoriasis with biologics that were published in 2019, but they contained very limited recommendations on the generalized pustular psoriasis section.[11]

In 2017 there was a consensus statement on generalized pustular psoriasis phenotypes that was issued by the European Rare and Severe Psoriasis Expert Network.[1] The consensus definition for the diagnosis of GPP included observing primary sterile, macroscopically visible pustules on non-acral skin (so that excludes palmoplantar pustulosis, and also when pustulation is restricted to the psoriatic plaques); and GPP was further subclassified as being with or without systemic inflammation or plaque psoriasis, and being either relapsing (greater than 1 episode) or persistent disease (lasting greater than 3 months).[1]

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In 2018, the Japanese Dermatological Society issued guidelines on GPP management and treatment.[12] There's also Belgian evidence-based treatment advice for psoriasis that was published in 2020, which included a small section on GPP.[13]

And so, there really is a need to develop standardized international guidelines on GPP diagnosis and management to help with rapid diagnosis and prompt treatment.[14] Recently, there was a Delphi panel of 21 expert dermatologists that established global consensus on the clinical course, diagnosis, treatment goals and disease management of GPP to enable the development of an evidence-based clinical management algorithm.[15]

Dr. Uwe Wollina: Based on your clinical experience, what are some key strategies for managing GPP?

Dr. Clive Liu: I'm glad you mentioned the global consensus publication by Dr Puig and his colleagues.[15] One of the key consensus statements from the publication is on treatment goals, which highlights the need for rapid and sustained clearance of pustules, erythema, scaling and crust, clearance of skin lesions, and prevention of new flares. To put it simply, the goals are to treat the disease as quickly as possible, prevent complications, and prevent further flares. The most important thing, though, is to make the correct diagnosis, which actually can be challenging at times. It involves a thorough clinical history, a physical exam, and sometimes a biopsy may be needed.

As I said before, GPP can be one of the few dermatological emergencies we have, and our goal is to prevent potential complications. These can include infections, sepsis, acute respiratory distress syndrome, cardiovascular shock, and serious electrolyte disturbances.

And once we have made the diagnosis, it's imperative to initiate appropriate therapy as quickly as possible, and to choose a treatment with a rapid onset of action. In addition, we know that GPP can be a chronic condition, and we hope to prevent new flares from occurring.

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Dr. Uwe Wollina: Until recently, no GPP-specific treatment was available in the US. What treatments were used to treat GPP flares?

Dr. Eingun James Song: Today, patients with GPP have spesolimab (sold under the brand name of SPEVIGO®) as a treatment option, which was approved by the US FDA in September 2022 for the treatment of GPP flares in adults.[16]

And before spesolimab, we had to rely on certain treatment options that were really drugs used to treat generalized plaque psoriasis. There were no treatment options specific to GPP.[17] Some of those drugs included oral retinoids, cyclosporine and methotrexate, as well as various biologic agents. But none of these treatments had a US prescribing label for use in patients with GPP.

There are some of these drugs that are approved for treating GPP outside the US, and this includes Japan, Taiwan and Thailand.[18] But the evidence supporting these treatment options are very limited, and include mainly case reports and small open-label single-arm clinical trials.

So, there was really no other choice for us back then, and while there had been successes, this was often a rarity, and patients typically tried many different drugs to find the one that worked best for them, and even then the results were not long-lasting. This makes the FDA approval for spesolimab very exciting, because patients in the US now have access to an approved drug that specifically treats GPP.

Dr. Uwe Wollina: Can you share some learnings from the clinical trials of spesolimab that led to its US FDA approval for the treatment of GPP flares in adults? What does all of this mean for patients with GPP?

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Dr. Clive Liu: Our previous therapies for GPP came from our therapies for psoriasis. However, it is important to remind ourselves that GPP and the most common forms of psoriasis, including plaque psoriasis, are quite different. They each have a distinct pathology, genetic background and clinical presentation.[19] The standard psoriatic therapies are often not always successful in GPP.

Now we have a drug that is approved specifically for GPP, another treatment option exists for our patients. In addition to the US FDA approval of spesolimab, it is also approved by the other regulatory agencies, including Japan, mainland China, and the European Union.[20] One intravenous dose of spesolimab led to complete pustule clearance within a week. What this means for dermatologists in the US is that we may not have to hunt for an off-label treatment to work on our patients, which is very encouraging.

The development of new medications like this began with a new understanding of the interleukin-36 pathway, which is associated intimately with GPP. Spesolimab is a first-in-class humanized monoclonal antibody that binds specifically to IL-36 receptor, and prevents the activation of downstream pro-inflammatory and pro-fibrotic pathways.[21]

Now, let's talk about some of the spesolimab clinical trial data. In the first study, which was a Phase I proof-concept open-label-study ("open label" meaning that the identity of the drug was known to both the patient and the investigator), 7 patients with GPP flare were treated, and 5 of the 7 had acheived the primary endpoint of a GPPGA score of clear or almost clear in just 1 week.[22] What this means is they had clear or almost clear skin, measured during the trial as having a GPPGA score of 0 or 1. At 4 weeks, all 7 patients achieved this milestone of clear or almost clear skin. Spesolimab was safe and well tolerated in all 7 patients who had a GPP flare in this trial.[22]

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The second trial was a Phase II trial called Effisayil™ 1. It was the first multinational, randomized, double-blind, placebo-controlled trial in GPP, and it had enrolled the largest group of patients with GPP to date.[23,24] It was a double-blind study, so no one knew who was taking what, whether they got the drug or the placebo. 53 patients with a GPP flare were divided in a 2:1 ratio to either receive a single intravenous dose of spesolimab at 900 mg (35 patients) or placebo (18 patients) on day 1. They were followed up for 12 weeks. The primary endpoint was a GPPGA pustulation subscore of 0 at week 1, meaning there were no visible pustules.[23]

At week 1 post-treatment, 54% (19 out of 35) of patients who received spesolimab achieved a GPPGA pustulation subscore of 0, compared to only 6% (1 out of 18) of patients who received placebo.[23] When the investigators looked at how many patients had clear or almost clear skin (a GPPGA score of 0 or 1), 43% (15 out of 35) of the participants in the spesolimab group had achieved this, compared to only 11% (2 out of 18) in the placebo group.[23]

Now, it's important to note that these clinical effects were sustained over the duration of the clinical trial, up to the 12 week post-treatment.[23] It is an important result, where we acknowledge that GPP is a chronic disease with intermittent flares.

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Dr. Uwe Wollina: What about the safety data from these trials or, in other words, is this drug safe for patients?

Dr. Eingun James Song: Sure, let's discuss some safety data from Effisayil™ 1, which is the Phase II randomized, double-blind, placebo-controlled study we've been talking about here.[23] According to the results published in the *New England Journal of Medicine*, during the 1-week placebo-controlled period of the Effisayil™ 1 trial, adverse events occurred in 23 of the 35 patients (66%) in the spesolimab group, and in 10 out of 18 (56%) of patients in the placebo group. Serious adverse events were reported in 2 patients receiving spesolimab.[23]

After 12 weeks, adverse events occurred in 42 of 51 (82%) patients who had at least received 1 dose of spesolimab, and that includes those who were initially randomized to

placebo who then received open-label spesolimab at the end of week 1. Infections occurred in 24 of 51 (47%) patients and serious adverse events occurred in 6 of the 51 patients (12%). No deaths occurred during the trial.[23]

I would encourage listeners to refer to the Effisayil™ 1 publication in the *New England Journal of Medicine*, as it contains more information than we can share here and is freely available online at the journal website. A citation and link details are provided below, if you are interested in learning more about that particular study:

- *Bachelez H, Choon SE, Marrakchi S, et al. Trial of Spesolimab for Generalized Pustular Psoriasis. N Engl J Med. 2021;385:2431–2440. Doi: 10.1056/NEJMoa2111563*

Dr. Uwe Wollina: This is an encouraging time for GPP patients, now that they have an approved treatment option to manage their flares. Any other important considerations that our patients should keep in mind?

Dr. Eingun James Song: Yes. So, one consideration for patients accessing spesolimab in a community context is that intravenous administration is needed. This may require patients to receive treatment at hospitals or infusion centers. Working closely with our patients will help them to navigate this potentially challenging pathway to receive treatment, because an effective treatment that is not accessible does not benefit our patients.

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With GPP, patients may receive care from their primary care doctors, nurse practicioners, PAs, or even rheumatologists, genetic counsellors, and infectious disease specialists. Taking a holistic or a multidisciplinary approach to caring for our patients will be key to ensuring they receive appropriate and timely care. It's important to work closely with our patients to help them navigate access to the treatment.

It's interesting to note that spesolimab is also being studied in the Effisayil™ 2 trial for the prevention of flare in patients with GPP using a subcutaneous formulation of the drug.[25] Results show that high-dose spesolimab was superior to placebo in GPP flare prevention: and significantly reduced the risk of a GPP flare and flare occurrence over 48 weeks.[25] Given the chronic nature of GPP, having a treatment for flare prevention is a major shift in clinical management. Patients may soon have an option for complete disease management: that is both treating and preventing GPP flares.

Dr. Uwe Wollina: Now that they have spoken about spesolimab, are any other drugs being investigated to treat GPP?

Dr. Clive Liu: Thank you, Dr Song, for mentioning Effisayil™ 2. Whilst spesolimab is effective in treating GPP flares, there is still a need to address the relapsing nature of GPP. The purpose of Effisayil™ 2 was to determine whether maintenance treatment with a subcutaneous formulation of spesolimab would prevent recurrence and provide sustained disease control.

A second agent that targets the interleukin-36 receptor is currently in clinical development. It is called imsidolimab, formally known as ANB019. Positive results from 8 patients treated with imsidolimab in a single-arm open-label Phase II trial, called GALLOP, was presented at a congress meeting.[26] Phase III trials, called GEMINI-1 and GEMINI-2, are underway in patients with GPP flares,[27] and top-line data are expected possibly in 2023.

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Dr. Uwe Wollina: Based on your clinical experience, what are the main takeaways about GPP that are important for healthcare providers to know about?

Dr. Eingun James Song: The main takeaway about GPP is that it's a rare, chronic, and potentially life-threatening auto-inflammatory skin disease, with an unpredictable and heterogenous clinical presentation and disease course. First and foremost, a greater awareness of this disease is needed to encourage and promote prompt and accurate diagnosis, as well as the appropriate treatment of GPP.

Prior to the approval of spesolimab, off-label use of various drugs in the US were all that we had to care for our patients. Some were approved for plaque psoriasis, and many had limited efficacy in treating GPP. Spesolimab has demonstrated efficacy and safety in

providing rapid and sustained control of GPP flares, and spesolimab is the only GPP-specific treatment that is FDA-approved for use in adult patients with GPP. So, patients now have a treatment option to manage their flares.

Dr. Clive Liu: The approval of spesolimab certainly helps to address an unmet need in GPP. However, even with all this new therapy, the practical problem of access remains, and it's important to work closely with our patients and utilize the various resources available to adequately treat this disease.

Dr. Uwe Wollina: Thank you both for joining us today and for sharing your expertise on GPP.

To our listeners, please join us for the next podcast, when we focus on the patient's perspective in managing GPP.

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