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## Breakthroughs in Generalized Pustular Psoriasis Treatment: Exploring Current & Emerging Approaches

### Dr. Chovatiya:

Generalized pustular psoriasis is a rare inflammatory skin disease that can be life-threatening if left untreated. Fortunately, current therapies are emerging for this disease state, which is what we'll be talking about in today's program.

You're listening to *DermConsult* on ReachMD. I'm Dr. Raj Chovatiya coming to you from the Greater Chicagoland area. And joining me today is Dr. Jason Hawkes, who is a medical dermatologist in the Greater Sacramento area who also sits on the National Psoriasis Foundation Medical Board and Scientific Advisory Committee.

Dr. Hawkes, welcome to the program.

### Dr. Hawkes:

Thanks, Raj. Happy to be here.

### Dr. Chovatiya:

So happy to have you. Let's start off with a little bit of background, Dr. Hawkes. Could you give us an overview of generalized pustular psoriasis? What is it? Is it different than the psoriasis that we think about? And how is it actually diagnosed?

### Dr. Hawkes:

Yeah, this is a really important topic because we talk about psoriasis as if it's one bucket with one clinical scenario, and what we find is that within that bucket of psoriasis, there are multiple variants, and these variants have different clinical features, they have different genetic features, and the treatments can often vary. GPP is one of these variants of psoriasis that is very distinct from plaque psoriasis, and it's distinct from its primary lesions, which are primarily pustules, and also its presentation. This is a disease that is characterized with both pustules and widespread erythema, desquamation. These patients can go from clear to 95 percent involved, very similar to our pustular psoriasis patients or erythrodermic patients, and so these are patients that can present very quickly. They get these repeated, recurrent flares, this relapsed or remitting flare of pustules, desquamation, erythema, and that may accompany these systemic symptoms, so fever, skin pain, malaise, fatigue, and so these are patients who can present very severely. They often show up in emergency rooms, emergency care, and these are patients that—different from plaque psoriasis who can very fairly stable, chronic disease—these are patients that we need to make the diagnosis quickly and act quickly because the implications of insufficient treatment can lead to a lot of secondary complications, like secondary organ failure or even death.

### Dr. Chovatiya:

Great point. And I think that it can be tricky if you're not really familiar with what the entity is and what the diagnosis is because, as you mentioned, sterile pustules are really the foundation of what we look at from a dermatologic setting. And I guess I might follow that up with just asking you about how do you go about making that diagnosis knowing that not all cases of GPP may be 0 to 100 going to 100, but also, there's other pustular eruptions to think about?

### Dr. Hawkes:

Yeah. So what's made this difficult, I think, in dermatology is that, again, we talk about buckets as if they're all homogeneous, but pustular psoriasis can mean a number of things, and the nomenclature around pustular psoriasis has been pretty poor, actually. But the nomenclature is only part of the problem. The other part of the problem is that there is a number of situations or sort of immune drivers which can cause pustules in the skin, and they overlap with sort of the underlying pathogenesis of GPP, but they can mimic or sort of interfere with the dermatologist's ability to make the diagnosis of GPP, and so there are features that are going to be helpful. Obviously,

an acute eruption that's pustular and erythrodermic could represent AGEPE, for example, or a drug reaction characterized by similar pustules that can be very difficult, so their history is going to be helpful. These patients that either have or don't have a history of plaque psoriasis or a family history of plaque psoriasis can be helpful. And so we really need to take all that information from the history to the clinical exam to the family history and look for that pattern of sort of these recurrent flares of GPP and making sure that we're not missing a primary infection and working through that differential diagnosis of conditions that can present in a similar way where pustules are the primary skin lesion.

**Dr. Chovatiya:**

Really, really good point. And the history sometimes is really a lot of what we do even more so than what we see. But just kind of transitioning into treatment, you know, I am really excited to talk about some of the newer treatments, but let's stick with what we sort of have had at our disposal for that GPP patient. What are some of the current therapies and standard of care we follow right now knowing that maybe there might be a lot of differences in terms of how people handle these cases?

**Dr. Hawkes:**

Yeah. You know, when you talk about what have we historically done from treatment, we have basically had to use therapies that were FDA approved for plaque psoriasis. We were using them off label because there were no approved therapies for pustular psoriasis and other variants, and that includes the use of broad-acting systemic immunosuppressants, so cyclosporin, some of the retinoids, acitretin, for example, methotrexate, and even apremilast as medications that we've been trying for GPP. And part of that has been the regulatory process that drugs are approved for specific indications, which is bad for patients who don't have that approved indication, and two, most of our research has been driven on the IL-23/17 signaling axis, which is predominant plaque psoriasis. And it's just now that we've started uncovering that there is some unique immunology to some of these variants, and I think pustular psoriasis, GPP in particular, is a really great template of why studying these variants is critical because we have identified IL-36 as a really central role in this variant compared to, say, plaque psoriasis, which has directly led and translated to a very novel therapy for this condition.

**Dr. Chovatiya:**

For those of you that are just tuning in, you're listening to *DermConsult* on ReachMD. I'm Dr. Raj Chovatiya, and I'm speaking with the wonderful Dr. Jason Hawkes about therapies for patients with generalized pustular psoriasis.

So, Dr. Hawkes, if we do turn our attention to IL-36, really exciting development that we've had and really kind of a big scientific and medical story and breakthrough in psoriasis, what role does IL-36 play in the disease pathogenesis and treatment? How does it help us better understand what's going on in GPP?

**Dr. Hawkes:**

Yeah, so I think it's helpful just very quickly to take that high-level approach to what's the immune framework for plaque psoriasis. So what we know with plaque psoriasis is that it's a T-cell-mediated disease, so its T-lymphocyte central works in collaboration with the dendritic cells to create signals that are going to drive chronic disease. We know IL-23 and TNF coming from the dendritic cells is going to help the T-cells make high levels of IL-17, and it's really IL-17 driving the clinical phenotype because it's driving the hyperproliferation of the keratinocytes. In response to the high IL-17 levels, we know the skin becomes hyperproliferative, and it starts to make a whole host of signals: antimicrobial peptides, chemokines like CCL20, IL-19, which helps drive that thickening of the skin, and then interestingly IL-36. So what we start to find is that there's this interaction between the adaptive immune response, primarily the dendritic cells with T-cells with IL-23 and IL-17 really driving the skin phenotype, which acts as the innate arm of the immune system, so it makes sense your skin is at the surface it's there to protect it and leads to these quick, nonspecific rapid responses. So IL-36, like IL-1, really falls into this innate category of our immune response, and they're really designed to be a fast-acting immune response on that surface that's exposed to a whole bunch of external factors that potentially threaten our health.

What's interesting with plaque psoriasis is that while we see increased levels of IL-36—which are helping drive in the recruitment of cells like the neutrophils in the skin, so we might see pustules in the skin biopsy of patients who have plaque psoriasis—it's not the predominant signal, which is why we talk about IL-23 and 17. Now in contrast we have GPP, which is very different. Its predominant signal is IL-36, which is why we see these widespread pustules because IL-36's function is as a keratinocyte-derived signal, it's really driving the formation of pustules, the recruitment of neutrophils which make the pustules, but what it does also is that it signals to both itself—so it's autocrine signaling, so if a cell secretes IL-36, it activates that cell—but it also activates its neighboring keratinocytes to really increase that hyperproliferative response. And very interestingly, it also stimulates the production of IL-17, and so what we have is we have this overlap between the IL-23 proinflammatory response overlapping with IL-36, but IL-36 isn't predominant in plaque psoriasis. We have the exact opposite in GPP where IL-36 is driving that pustular response, but it's also feeding back into the IL-23/17 pathway, and so that's why you can kind of see some similar features, but they are distinct entities based on the predominant signal.

**Dr. Chovatiya:**

And so on that end, maybe sort of the last big question I really want to get out of you is spesolimab. Maybe you can tell us a little bit about it and how this really is an important move forward for one of these orphan psoriasis diseases where we didn't have much targeted options.

**Dr. Hawkes:**

So we think of these key cytokines we talk about: IL-23, IL-17, and IL-36. These are all primarily proinflammatory cytokines. So within the IL-36 family, which it falls under the IL-1 family, so IL-1 and IL-36, have similar function in driving this innate immune response—we have IL-36 alpha, beta and gamma, and those are on switches, or they hit the gas pedal for that immune response, but we have an innate sort of a biologically endogenous brake system, and that brake system is the IL-36 receptor antagonist, and it does exactly that. It antagonizes the receptor, which prevents IL-36 isoforms from driving inflammation.

Patients with GPP, we know that fundamentally they have dysregulated IL-36 signaling, but that could be the result of multiple things. So, 1) you can have some inherent genetic change, for example, that drives high levels of IL-36, and that would keep the gas on, which would drive the widespread inflammation of pustules, but alternatively, you could also have a mutation in the gene which codes for the protein that's the brake or the receptor antagonist. So the IL-36 receptor antagonist is encoded by the IL-36 RN gene, and that, in fact, was the gene that was first discovered in the Tunisian families, which was in the big publication *The New England Journal of Medicine*, which highlighted that this mutation in that brake or the receptor antagonist was the predominant mutation driving disease in these patients. And so the idea that IL-36 is sort of unabated because you don't have the ability to shut it off, then that made sense why IL-36 would become a target and that's where IL-36 receptor inhibitors like spesolimab make sense because they are effectively functioning as the brake. And so by giving spesolimab, we're able to block the receptor, which is going to block the ability for the immune system to be activated by these IL-36 cytokines.

Now alternatively, you could create a therapy to block the IL-36 cytokines themselves, so say like an IL-36 gamma inhibitor, but right now as a first FDA-approved medication for GPP in the US is this receptor antagonist, spesolimab, which is an intravenous medication, which has been very promising from the phase II clinical trial data that we've seen as working very quickly and very effectively, which I think also underscores this idea that IL-36 is truly the basis of disease in this variant of psoriasis.

**Dr. Chovatiya:**

It seems like we're at a very exciting time for those of us who treat generalized pustular psoriasis, and I'm sure there's going to be more to tell about this story in the near future. So I just really want to thank my guest, Dr. Jason Hawkes, for sharing these latest advancements. Dr. Hawkes, thanks so much for joining me today.

**Dr. Hawkes:**

Thanks for having me, Raj.

**Dr. Chovatiya:**

For ReachMD, I'm Dr. Raj Chovatiya. To access this episode and others from the series, visit [ReachMD.com/DermConsult](https://ReachMD.com/DermConsult) where you can Be Part of the Knowledge. Thanks for listening.