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Recent Advances in the Management of Pustular Psoriasis

Announcer:
Welcome to CME on ReachMD. This activity titled “Recent Advances in the Management of Pustular Psoriasis” is provided by Clinical Care Options, LLC and the Partners for Advancing Clinical Education (PACE), and is supported by an educational grant from Boehringer Ingelheim Pharmaceuticals, Incorporated. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Kucera:
I’m Kristine. I’m pleased to be joined by Dr. Alice Gottlieb. Dr. Gottlieb is a Clinical Professor of Dermatology at the Icahn School of Medicine at Mount Sinai and the Medical Director of Dermatology at Mount Sinai Union Square in New York, New York. She is also a rheumatologist, so she brings a plethora of information to us today, and we are here to discuss the management of pustular psoriasis. So, faculty disclosures – Dr. Gottlieb’s is listed there. Kristine – mine – is listed after hers. We’re going to learning objectives. Today we plan to identify patients with pustular psoriasis early in the course of disease, and now we’re going to get rolling with our presentation.

So, introduction and overview of pustular psoriasis. We’re going to start with our overview. So, pustular psoriasis is a group of heterogenous inflammatory skin diseases, which include three phenotypes. We have the generalized pustular psoriasis, also known as GPP. That can either be acute or generalized. We have the Acrodermatitis continua of Hallopeau, and that can actually – you can see on the right-hand side the letter B – is usually on the fingertips. And then we have palmoplantar pustulosis. It can be on the palms and soles.

Systemic signs and symptoms – what do we see? Widespread sterile pustules. It could be pain, scaling, erythema, dryness, itching, burning. Multiple different symptoms can occur, but also some systemic systems as well as swelling, malaise, joint pain, leukocytosis, headache, fever, high output cardiac failure, tachycardia, and fatigue. So, you can see that it can not only affect outside but inside.

What about the epidemiology? It is much rarer than plaque psoriasis, mostly affects men and women age 40 to 60, occurs in 1% of children, varies by ethnicity – you can see Asian about 7.46 per million, white 1.76 per million, and black less than 1.3 – and the mortality rate is anywhere between 3 and 25%.

So, let’s talk a little bit about the etiology. Definitely genetic and age, environmental influences as well, infections, upper respiratory tract infections, group A Streptococcus bacteria, cytomegalovirus, varicella zoster, Epstein-Barr, acute respiratory syndrome. So, many, many infections can bring it on. Drugs are another thing to consider – sudden withdrawal if systemic glucocorticosteroids, cyclosporine, ustekinumab, topical steroids. Pregnancy is one, trauma, and also sunburn.

Now let’s get into a case study, and this is Brian. Brian is a 58-year-old Asian male. He had plaque psoriasis since age 37 – no serious flares until now. Medical history – he does have hypertension, which is controlled, and psoriasis. He runs 5 miles a day at least 5 times a week, nondrinker, and he quit smoking 30 years ago. He has no surgical history, and the medications – he has been on infliximab for 2 years, and that’s for his psoriasis, propanolol – he’s taken that for 10 years – and he does not take any over-the-counter or recreational drugs.

Now, Brian says the flares started on his trunk a day after swimming at the lake with friends. He initially thought the pustules were

blisters due to sunburn. He's complaining of pain from spreading erythematous plaques. It woke him up early in the morning. His wife urged him to go to the emergency department. He compromised by going to an urgent care center, and physical exam showed pustules covering chest and back, tender to touch. He was tachycardic and hypertensive at that time.

Now, let's talk about this – how pustular psoriasis differs from plaque psoriasis. Generalized pustular psoriasis – it is an innate immune inflammation, neutrophilic. It is driven by IL-36 pathway, and it is associated with a mutation in the IL36RN gene. What about plaque psoriasis? This is an innate and adaptive immune process. It is an immune disease that is driven by the IL-23 pathway.

Now, looking at quality of life talking about plaque psoriasis versus pustular psoriasis. Overall quality of life – this is based on 5 dimensions in 3 severity levels. Pustular psoriasis is in the blue, and plaque psoriasis is in the orange, and you can see across the board, pustular psoriasis ranks much higher in not only walking and self-care, usually daily activities, pain and discomfort, as well as anxiety and depression, so overall a much higher impact on quality of life.

Patient perspectives on the particular patients that have had to deal with pustular psoriasis, they're saying it has a significant impact on daily activities, such as physical activity, wearing shoes, important life events, running errands, intimacy with partner, and household chores, symptom severity often worse than plaque psoriasis as far as pain, itching, and fatigue. It is associated with more anxiety and depression and likely to experience more trials of treatment.

So, next we're going to look at disease severity and the diagnosis of pustular psoriasis. So, starting with diagnosing, it's usually based on clinical and histologic findings, a very good history and review of symptoms with pustular psoriasis and with any type of psoriasis, very important to do an entire full body skin examination. You have to see what's going on with these patients. Skin biopsy is possible – you can use this to distinguish pustular psoriasis from other pustular eruptions – and some basic blood tests. Remember there can be systemic symptoms here. The patient can have fever, chills, pain, malaise, nausea, diarrhea, dehydration, arthralgias, tachycardia, seizures, high cardiac output – a lot of things can be going on with these patients. Very important to remember that pustules are usually sterile unless an infection is present, and if a suspected infection is there, need to culture the skin or the blood.

Now, moving back to Brian, let's talk about his case a little more. So, while the urgent care team was waiting for results of his labs, Brian fainted. He appears weaker than when he first walked in, he's nauseated, he's dehydrated, and he's not drinking water when he's offered. Laboratory results did come back. They did show leukocytosis, lymphopenia, and an elevated ESR. Renal and liver function are borderline abnormal, and no skin biopsy was performed.

Now, moving along and talking about laboratory tests for pustular psoriasis. No blood tests definitively confirm this diagnosis – keep that in mind. A CBC with differential can show anemia, leukocytosis, lymphopenia. A CMP – you can find hypocalcemia, some electrolyte abnormalities, iron and ferritin possible, liver and renal function could be a little abnormal, and hypoalbuminemia. Now, you can also see a CRP and an increased ESR, if secondary infection is suspected, of course, we're going to culture the pustule, and genetic testing if possible and if it's available.

So, looking at our differential diagnosis, we have acute generalized exanthematous pustulosis that's called AGEP. Now, what differentiates this from our pustular psoriasis is this is usually an abrupt onset, short duration, absence of arthritis, and eosinophils and necrotic keratinocytes on the skin biopsy. The other differential we can look at is dermatitis with a secondary infection. You can have a spongiotic dermatitis, and you can have bacteria on a skin biopsy, and, of course, a patient's history might give this away as well. We also can look at subcorneal pustular dermatosis. This often occurs in middle-age women, affects trunk flexors of the extremities, intertriginous areas. It can occur with pyoderma gangrenosum and multiple myeloma. The next one is IgA pemphigus – this you would check with direct immunofluorescence, and this is found in middle-aged or elderly men and women – and then, of course, tinea corporis. There's no systemic symptoms, but you will find fungal hyphae on a skin biopsy or a potassium hydroxide preparation.

So, pustular psoriasis pretty much needs a scale of its own. There's a number of disease measures. We have what we call the physician global assessment, which measures disease severity on a 7-point scale from 0 to 6 – 0 being clear, 6 being severe. There's a PASI – Psoriasis Area and Severity Index – this measures redness, thickness, and scaling, and it's a mathematical equation that gives us a number as to how severe the patient's psoriasis is. There's also Clinical Global Impression Scale called the CGI, clinician's view of patients' global function before and after treatment, and we have a Japanese Dermatological Association Severity

Index of GPP, and this measures skin symptoms, systemic symptoms, lab findings, and disease severity altogether, and then we have patient-reported outcomes. We have the PSS, Psoriasis Symptom Scale, which this is patient-reported on pain, redness, itching, and burning, the Pain Visual Analog Scale, the pain VAS, which measures pain severity, we have the Functional Assessment of Chronic Illness Therapy – fatigue, this is self-reported fatigue – and then the Dermatology Quality of Life Index, the DLQI, which a lot of us actually use in our clinical setting, and this measures health-related quality of life.

Now, Generalized Pustular Psoriasis Physician Global Assesment – GPPGA, very long – it is a clinical assessment that looks at not only

erythema, pustules, and the scaling of all the different lesions, but it's also scored by a clinician on a scale of 0 to 4, with 0 being clear, 4 being severe, and then the total GPPGA score is determined based on the composite score. Patients either are a 0 to 4 and clear to severe.

The next thing is looking at the Generalized Pustular Psoriasis Area and Severity Index. So, instead of a PASI, we have a GPPASI, and this again looks at the entire body, the severity, the erythema, pustules, and desquamation, and that is a score, a percent involvement, and that is a score, and then the percent of the body which surface its on, and then everything is calculated up, and the individual score is for by region plus the severity, involvement, and you get a sum, and that is our GPPASI score.

So, moving into now pustular psoriasis subtypes and clinical features – lot of different subtypes here. We have our generalized pustular psoriasis, also called von Zumbusch. These are sterile subcorneal pustules, they expand into lakes of pus, they are associated with systemic symptoms. Some diagnostic clues here – macroscopically visible pustules with or without evidence of systemic inflammation, male-to-female ratio there, and the mean age of onset is 31 to 57. We also have impetigo herpetiformis. This is pustular psoriasis of pregnancy. These are subcorneal pustules on erythematous patches. Systemic symptoms can be with this, and there is an elevation in inflammatory markers as well as leukocytosis. Look for this in pregnancy and postpartum flare-ups, and third trimester is typical. Annular pustular psoriasis – milder systemic symptoms than those of generalized pustular psoriasis, usually no history of psoriasis, and the mean onset here is 39 to 43. We have juvenile pustular psoriasis, and it affects children. They can exhibit systemic findings like those in the adult patients, 2-to-1 male-to-female, and age of onset is 4.6 to 6.9. Now, palmar plantar pustulosis – these are sterile pustules on the palms and soles, and they have yellow-brown discoloration. The hands and feet, you can either have it with or without classic plaque psoriasis, and the mean age of onset is 42 to 43 and females much higher than in males. And then our Acrodermatitis continua of Hallopeau, and this is sterile pustules that is affecting the tips of the fingers and the toes, definitely nail involvement there, it's frequently unilateral, a little bit higher in females than males but almost even, and this mean onset of age is 49 to 51.

So, the features of palmar plantar pustulosis versus palmar plantar pustular psoriasis – so, two separate things here. Common sites – both can be on the palms and soles, and some can have psoriasis in other areas and some do not. Skin changes – there can be sterile pustules, well-demarcated papules in patches, and associated conditions. With the palmar plantar pustulosis, there can be some upper respiratory infections, psoriatic arthritis, usually female, thyroid. Palmar plantar pustular psoriasis – there can be psoriatic arthritis associated with that. Pain and itching is seen. Positive family history is not in palmar plantar pustulosis, but it is in the palmar plantar psoriasis. Histology is there, and then genetic susceptibility is in both types.

Now, one more thing we'll just touch on here is comorbidities associated with palmar plantar pustulosis. Patients can have thyroid disease, parathyroid disease, metabolic syndrome, arthritis, celiac disease, anemia, hypocalcemia, high output cardiac failure, definitely diminished quality of life, and some psychiatric disorders as well. This is when it shows that it's very, very important to do a really good history on any patient that has psoriasis.

Okay, moving into just our Q&A. Dr. Gottlieb, what should the patient, when they present to the ER, will, and, of course, I know how I feel about this, but the patient may be really sick. Will the ER doctor know what the heck to do? Or are they going to have to try to get a dermatologist in?

Dr. Gottlieb:
You've answered the question. I think there's a great gap in that the ER physician, the primary care physician, the hospitalists have no idea what it is, and, in fact, they will be cultured in every orifice and place, they will be assumed to be septic, they will be put on multiple antibiotics. The ER doc may have a question is this AGEP, but even that, they may not, but this really needs to get a dermatologist there or, you know, a physician's associate such as yourself, an expert in the area, but you need to get somebody who's a specialist in this area. This is – there are not that many life-threatening dermatoses – this is one of them – and I can recite a patient that I had sort of, but this is a patient who when I was at the Rockefeller – this is many years ago, we're talking 1980s, okay – when I was at the Rockefeller, the patient was given systemic corticosteroids for a rheumatoid arthritis and a swollen knee. It turned out that the patient was given high-dose corticosteroids that were stopped abruptly. The patient did not have rheumatoid arthritis. They had psoriatic arthritis, and they very quickly developed generalized pustular psoriasis with fevers of 106, vital sign instability, hypocalcemia, anemia, developed sepsis because of their poor barrier function and died, and the only treatment that we had at that time was called etretinate, which was a precursor to acitretin, but that person died because they were misdiagnosed, given a prednisone. The abrupt cessation led to GPP, and there were very little treatments available at that time and they died, and they died from a complication of sepsis. So, this is a life-threatening dermatosis. You really need to get the expert there. It's easy for me to say because I live in the New York metropolitan area, you live in the Dallas area, and you could always find a dermatologist who will come in. What are you going to do if you live in Nowhere, United States and there isn't a dermatologist? Or you can't find someone who's willing to come in? I think we absolutely have to educate the emergency room staff so they can recognize what this is.

Dr. Kucera:
It will only help the patient. Okay, so we have a question here – would telehealth have benefited here in consulting with a dermatologist with one is not available in the area?

Dr. Gottlieb:
Who's doing the consulting? I mean, if the ER – do I think to manage generalized pustular psoriasis, a telemedicine visit with the patient and the doctor and the dermatologist is adequate? No, I don't, and I think that if the consulting physician is an ER doctor talking to a dermatologist, but this patient needs to be seen by a doctor somewhere. They really could be in trouble in terms of heart failure, you know, fluid electrolyte counts. You will not get that from a tele derm visit, and you won't be able to do anything about it. So, I do think it's important to have an ER doctor to call a dermatologist, but it is not adequate to do GPP by telemedicine. I'll take that stand on that one.

Dr. Kucera:
Yes, and dermatology in general is so difficult telemedicine. You know, when the pandemic hit us, it was very difficult because we're touchy-feely, and you really have to be in front of a patient a lot of times to diagnose some things. So, just overall, just putting my two cents in there, it was really – it's really been difficult just doing telemedicine for those patients.

I'm Kristine. I'm pleased to be joined by Dr. Alice Gottlieb. Dr. Gottlieb is a Clinical Professor of Dermatology at the Icahn School of Medicine at Mount Sinai and the Medical Director of Dermatology at Mount Sinai Union Square in New York, New York. She is also a rheumatologist, so she brings a plethora of information to us today, and we are here to discuss the management of pustular psoriasis. So, faculty disclosures – Dr. Gottlieb's is listed there. Kristine – mine – is listed after hers.

We're going to learning objectives. Describe the pathophysiology of pustular psoriasis and how it's different from that of plaque psoriasis. So, now we're going to move into a little bit deeper dive. We're going to go into pathophysiology, and I get to turn it over to Dr. Gottlieb to take us through all of this.

Dr. Gottlieb:
Thank you very much, Kristine. So, I think most of this audience knows what the pathogenesis of plaque-type psoriasis, but it involves features of the innate and adaptive immune response. The inflammatory mediators that are playing a very important role are IL-23, Th17, TNF alpha, and molecules that depend on their existence on these particular cytokines. Multiple cell types are involved. The typical story is there's a danger signal, which activates the plasmacytoid dendritic cell, which releases alpha interferon, which activates the dendritic cell. The dendritic cell makes – in this particular case, we'll talk about interleukin-23, which causes a CD4-positive T cell to become a Th17-positive T cell, making – no surprise – IL-17, but other molecules like TNF alpha, IL-23, IL-21, IL-22, which has effects not only on keratinocytes, but we also have effects on different elements of the joint. So, that's plaque-type psoriasis, which I believe this audience is familiar with already. However, in pustular psoriasis, the players can be somewhat similar, but what's really important is that there's overexpression of interleukin-1 beta, interleukin-36 alpha, and interleukin-36 gamma, and there are 3 genes of the innate skin immune system that play an important role in pustular psoriasis – the IL-36 receptor antagonist gene – roughly I think between 25 and 30% of patients with generalized pustular psoriasis have some kind of a defect in this gene. There's CARD14, and there's something called AP153.

Dr. Kucera:
So, going back to Brian. Brian is diagnosed with generalized pustular psoriasis, which surprises him because he is adherent to his infliximab regimen. He wants to know how to prevent another flare like this episode. He admits he never had eruptions so severe and so sudden with his plaque psoriasis.

Dr. Gottlieb:
Okay, so we're next going to talk about current management strategies. It's very important. Most of these patients with generalized pustular psoriasis are really very sick. They show up in the dermatologist's office, but they more often show up in the emergency room/urgent care. They are sick, and so the first thing you need to do is stabilize them, and so due to their illness, and if they have severe illness, they have fluid and electrolyte imbalance, their vital signs are unstable, they can have very high fevers, tachycardia, and if their hearts are not perfect, they can have high output cardiac failure that could ultimately lead to death. They also have high fevers as I mentioned. They can be secondarily infected. It's important to identify the drugs that may have induced the flare and discontinue them. Of course, the most common drug – the disease is caused by the discontinuation of the oral or parenteral corticosteroids, but yes, it's important to do that.

Now, if you're sitting in a hospital emergency room, what do you have at your disposal immediately because the operative word is fast because these people are sick. Okay, so what can you do about the pustular psoriasis? Most hospitals are able to get acitretin or cyclosporin very, very quickly. Biologics take longer, but there're certain biologics now – we have spesolimab, we also have the IL-17 blockers, and especially infliximab. They work very fast and are other choices, but again, they're not sitting around in the hospitals. The

approach is obviously based on disease severity and drug availability. It's very important not to focus only on the skin because organ dysfunction can happen. I have seen it, especially pre-biologics. I have seen high output cardiac failure. I've seen sepsis due to an abnormal barrier function with eventual death from infection. Other things that can happen are anemia, hypocalcemia, renal hepatic dysfunction, so one has to do real internal medicine when you have a patient with a pustular psoriasis.

I am going to focus only on the right, but this is generalized pustular psoriasis. First-line therapy I would say right now, if spesolimab is available – spesolimab, I, too, have trouble with those S words because I have a lisp, so I apologize with that – so if spesolimab was available within 12 hours, I'd say go for it. Okay, what if we don't have spesolimab? The first-line treatments I would say would be acitretin or cyclosporin. Why do I say that? Well, not everyone can have cyclosporin. Look at our case here of Brian who has hypertension. It's not an ideal drug for somebody with hypertension. Obviously acitretin is not at all okay for somebody who's pregnant. So, usually in most parts of the world, you can get acitretin or cyclosporin. In the case of a pregnant woman, you might be forced to use prednisone. However, as I would mention now as of a few days ago, the spesolimab – that would be my first choice. Now, the biologics, other biologics that work quite well are the IL-17 inhibitors – they are approved for this indication in Japan actually – although TNF blockers, especially infliximab, would be other choices. I believe ustekinumab and the IL-23 blockers would be too slow. I don't think phototherapy is an option.

This goes over what I just said, only with a complicated schema. We talked about the IL-17 blockers. We talked about TNF blockers. We should put here spesolimab somewhere, maybe in a pustule. Interleukin-1 antagonizing drugs have been tried. Canakinumab is an anti-IL-1 beta, which I think anakinra is not potent enough but people have used it, and as I mentioned, I believe ustekinumab is too slow.

Conventional treatments that have been used – acitretin and cyclosporin, which I would say worldwide are the most common. Methotrexate is way too slow to be useful. Apremilast has not nearly been tried in any kind of study, and the JAK inhibitors have not been tried yet, either. TNF antagonists – yes. As I mentioned, the fastest one is infliximab. We talked about ustekinumab, all the IL-17 inhibitors – these three, at least. I don't know about bimekizumab abroad where it is approved, but these three certainly are approved in Japan. This is an anti-IL-17 receptor. I mentioned there are IL-23 blockers – I think they work too slowly. And, of course, spesolimab – that is very recently approved.

And then one can use topicals, but topicals alone I'm going to tell you right now are just totally inadequate. So, moisturizers, topical corticosteroids, vitamin D analogs, vitamin A analogs, not sure coal tar is a great choice since it causes folliculitis by itself, but these – I do not think these are generally going to be enough to be used alone.

Now, how did the targeting IL-36 pathway actually get its start? And it got its start with a disease of nature, which is a deficiency of the interleukin-36 receptor antagonist. So, normally what happens is you get IL-6 interactions with receptors, which through intracellular messengers activates two systems, the NF kappa B and MAP kinase system, which together are responsible for making a highly inflammatory response. This red thing that looks like a candy corn represents the receptor antagonist. When it is present, the IL-36 cannot activate this system, and we don't get inflammation. However, the disease sends these rare genetic defects. What happens is there is no IL-36 receptor antagonist, or it doesn't work well, and then you get unopposed inflammatory responses that are mediated by the NF kappa B and MAP kinase system, and this is called DITRA. Now I hit return to Kristine, please.

Dr. Kucera:
Let's go back to our case. This is conclusion. So, after Brian stabilizes on acitretin, he follows up one week later with his dermatologist. The dermatologist recommends he try an IL-17 blocker instead of infliximab. Brian receives a prescription for a topical vitamin D analog for the few remaining recalcitrant plaques. Brian's dermatologist cautions him about long-term use of corticosteroids, stopping medications abruptly, which could prompt another flare.

Okay, so moving into just our Q&A, how would you manage a generalized pustular psoriasis patient in pregnancy?

Dr. Gottlieb:
So, obviously this is a worrisome complication. Again, I can't say to use spesolimab because I don't think it hasn't been tested in pregnancy. So, I think that that would be risky, but IL-17 blockers could be used, TNF blockers could be used, cyclosporin can be used. There's a large registry in transplant cyclosporin. Obviously, don't use acitretin. I would like to avoid prednisone since that's how they may have gotten there to begin with, and by the way, prednisone is not totally safe in pregnancy, either. So, I guess that would be my answer, although I don't think prednisone is absolutely contraindicated, but it certainly wouldn't be my first choice.

Dr. Kucera:
There's a question here regarding the case study. Now that we have an FDA approved for palmar plantar or pustular psoriasis, would you have used that first? And yes, absolutely. I will tell you that this pustular, especially palmar plantar, is so difficult to treat. Even

though in the clinical trials, palmar plantar did not do as well as generalized pustular, I would still go for it because the patient definitely needs some relief, and you're kind of just out there grabbing at things trying to get them relief as soon as possible.

And, okay, so Dr. Gottlieb, what should the patient when they present, to the ER, will – and, of course, I know how I feel about this – but the patient may be really sick. Will the ER doctor know what the heck to do? Or are they going to have to try to get a dermatologist in?

Dr. Gottlieb:
You've answered the question. I think there's a great gap in that the ER physician and the primary care physician, the hospitalists have no idea what it is, and, in fact, they will be cultured in every orifice and place, they will be assumed to be septic, they will be put on multiple antibiotics, and the ER doc may have a question is this AGEP, but even that, they may not, but this really needs to get a dermatologist there or, you know, a physician's associate such as yourself. I'm an expert in the area, but you need to get somebody who's a specialist in this area. There are not that many life-threatening dermatoses. This is one of them, and I can recite a patient that I had sort of, but this is a patient who when I was at the Rockefeller – this is many years ago, I'm taking 1980s, okay - when I was at the Rockefeller, the patient was given systemic corticosteroids for a rheumatoid arthritis knee and had a swollen knee. It turned out that the patient was given high-dose corticosteroids that were stopped abruptly. The patient did not have rheumatoid arthritis. They had psoriatic arthritis, and they very quickly developed generalized pustular psoriasis with fevers of 106, vital sign instability, hypocalcemia, anemia, developed sepsis because of their poor barrier function and died, and the only treatment that we had at that time was called etretinate, which was a precursor to acitretin, but that person died, and that person died because they were misdiagnosed, given a prednisone, the abrupt cessation led to GPP, and there were very little treatments available at that time and they died, and they died from a complication of sepsis. So, this is a life-threatening dermatosis. You really need to get the expert there. It's easy for me to say because I live in the New York metropolitan area, you live in the Dallas area, and you could always find a dermatologist who will come in. What are you going to do if you live in Nowhere, United States and there isn't a dermatologist? Or you can't find one who's willing to come in? I think we absolutely have to educate the emergency room staff so they can recognize what this is.

Dr. Kucera:
I totally agree. So, question here about smoking cessation in PPP. Let me just say smoking cessation in any type of psoriasis is a great idea. We actually, you know, just with the American Heart Association getting on board saying that, you know, there's a higher risk of cardiac problems in patients that have this inflammatory disease, anything that you can do to make your patients' lifestyle more healthy will help your psoriasis patients no matter what type of psoriasis they have. So, we always say that definitely smoking cessation, definitely diet, exercise, I mean, they really need to get themselves healthy, and then just to kind of piggyback on that, patients with any type of psoriasis should have yearly physicals, they should have yearly blood tests, they should have yearly, you know – they have to have a PCP. If they have heart problems, they need to follow up with cardiologists. A lot of times they need a rheumatologist. This is a very multidisciplinary patient that we're taking care of. So, yes, make sure your patients are doing everything they can to have and live a healthy lifestyle. It will only help the patient.

Okay, so we have a question here – would telehealth have benefited here in consulting with a dermatologist with one is not available in the area?

Dr. Gottlieb:
Who's doing the consulting? I mean, if the ER – do I think that to manage generalized pustular psoriasis, a telemedicine visit with the patient and the doctor and the dermatologist is adequate? No, I don't, and I think that if the consulting physician is an ER doctor talking to a dermatologist, but this patient needs to be seen by a doctor somewhere. They really could be in trouble in terms of heart failure, you know, fluid electrolyte counts. You will not get that from a tele derm visit, and you won't be able to do anything about it. So, I do think it's important for the ER doctor to call a dermatologist, but it is not adequate to do GPP by telemedicine. I'll take that stand on that one.

Dr. Kucera:
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Okay, so we have another question here, Dr. Gottlieb, about TNF alpha inhibitors. How often do you see them inducing pustular psoriasis? And would you avoid them in patients that have pustular psoriasis?

Dr. Gottlieb:
So, I actually thought about this with Brian's case. I said, you know, this could also be TNF – even the TNF blocker-induced psoriasis, and so I would not have picked it for him particularly. I would stop the infliximab and stayed away from it because you don't know at the time which situation it is, and I actually was just called to emergency last night actually during synagogue services about such a case, and so it does happen. So, the answer is this could be a presentation of TNF blocker-induced psoriasis, and I would not pick TNF

blockers as first-line in Brian's case specifically.

Dr. Kucera:
So, I can totally agree with that. You know, TNF alpha inhibitors have been wonderful in our practice, but, you know, there's a few things I've seen. I've seen a change in morphology of psoriasis with them, so you really, you know, they always ask what drug you pick for what patient and why. It really depends on the entire patient, and you have to take so many things into account. This is where it's important again to do a really good history on your patients and also physical exam. Get all their medication history, all of their psoriasis history, etcetera.

Dr. Gottlieb:
So, very much appreciate your joining us.

Dr. Kucera:
Yes, absolutely.

I'm Kristine. I'm pleased to be joined by Dr. Alice Gottlieb. Dr. Gottlieb is a Clinical Professor of Dermatology at the Icahn School of Medicine at Mount Sinai and the Medical Director of Dermatology at Mount Sinai Union Square in New York, New York. She is also a rheumatologist, so she brings a plethora of information to us today, and we are here to discuss the management of pustular psoriasis. So, faculty disclosures – Dr. Gottlieb's is listed there. Kristine – mine – is listed after hers.

We're going to learning objectives. Today we plan to apply recent evidence of emerging agents into the clinical context of evolving paradigms in the field of pustular psoriasis treatment.

Now let's get into a case study, and this is Brian. Brian is a 58-year-old Asian male. He had plaque psoriasis since age 37 – no serious flares until now. Medical history – he does have hypertension, which is controlled, and psoriasis. He runs 5 miles a day at least 5 times a week, nondrinker, and he quit smoking 30 years ago. He has no surgical history, and the medications – he has been on infliximab for 2 years, and that's for his psoriasis, propanolol – he's taken that for 10 years – and he does not take any over-the-counter or recreational drugs.

Now, Brian says the flares started on his trunk a day after swimming at the lake with friends. He initially thought the pustules were blisters due to sunburn. He's complaining of pain from spreading erythematous plaques. It woke him up early in the morning. His wife urged him to go to the emergency department. He compromised by going to an urgent care center, and physical exam showed pustules covering chest and back.

So, while the urgent care team was waiting for results of his labs, Brian fainted. He appears weaker than when he first walked in, he's nauseated, he's dehydrated, and he's not drinking water when he's offered. Laboratory results did come back. They did show leukocytosis, lymphopenia, and an elevated ESR. Renal and liver function are borderline abnormal, and no skin biopsy was performed.

Brian is diagnosed with generalized pustular psoriasis, which surprises him because he is adherent to his infliximab regimen. He wants to know how to prevent another flare like this episode. He admits he never had eruptions so severe and so sudden with his plaque psoriasis.

So, Dr. Gottlieb, if you'll take us through new and emerging therapies.

Dr. Gottlieb:
Yes, thank you. There are case reports that the IL-1 antagonists, which is this – these two are antibodies to interleukin-1 beta. This one is a IL-1 receptor antagonist, but then remember, these are case reports. Spesolimab is now FDA-approved for treating generalized pustular psoriasis, and there are some benefit in palmar plantar pustulosis. This one is called imsidolimab, and it is also an IL-36 receptor antagonist. It's not yet FDA-approved, but there're phase 2 clinical trials that show benefit in generalized pustular psoriasis.

Spesolimab isn't actually its name now, but let's use just the generic name. This was a phase 2 study, randomized placebo-controlled of adults with generalized pustular psoriasis, and this was a single dose of spesolimab and 900 mg IV versus placebo, and it was repeated on day 8 if persistent symptoms happened in both groups – this is now open-label dosing – and the primary endpoint was a Generalized Pustular Psoriasis Physicians Global Assessment pustulation subscore of 0. Okay, that means no visible pustules, and you know this could range from 0 (no visible pustules) to 4 (severe pustulation) at the end of week 1. This shows the design, which is somewhat – I know there's a total of only 53 patients, but this is a very rare disease, and so 2-to-1 randomized in favor of spesolimab versus placebo. As I point out, day 1, get a placebo shot or IV, or you get a spesolimab, and then 1 or day 8 is the primary endpoint. If people aren't doing well, they get another, whether they had placebo or they had the real drug, they get another infusion. I think this is quite complicated, and I think I'm going to skip it because we're running late.

Well, here's the results that were published in New England Journal. 54% of spesolimab-treated patients versus placebo patients of only 6% achieved a generalized pustular PGA pustulation score of 0 at week 1, and this is, of course, significant. If you're looking at the total score of 0 at week 1, then it's 43% versus 11% in the placebo. The adverse events which are reported in these clinical trials included fever, dizziness, DRESS syndrome, urinary tract infection, hepatic injury, and arthritis.

Now, this is a separate study in palmar plantar pustulosis, multicenter with adults, and the intervention here – spesolimab 900 mg IV every 4 weeks over 12 weeks or spesolimab 300 mg IV every 4 weeks over 12 weeks. Primary endpoint was this palmar plantar pustulation PASI 50 score at week 16, so it's kind of similar to, tried to make similar to like a PASI 50 score, and it's defined as achieving a 50% decrease from baseline in that palmar plantar pustulation PASI score. That's a mouthful.

Okay, this shows graphically between 2 different doses of spesolimab versus placebo, and the results here are that the percentage of that palmar plantar pustulation PASI 50 responder, placebo at the high rate – 23.8% - in the 300 mg dose, 31.6% of patients achieved the primary endpoint at week 16, and at the 900 mg dose, 31.6% of patients achieved that dose.

And showing this in picture use of placebo, here is the 900 mg dose, and here is the 300 mg dose, and this is the 50% improvement mark.

Now, we're talking here about spesolimab in palmar plantar pustulosis.

Now, I'm going to – this is already a little bit out of date – I mean, spesolimab clearly has done phase 2B, they're doing phase 3, and it's approved right now in the United States.

Switch to imsidolimab. This was a GPP study, and this is a different endpoint. It's looking at improvement in the Clinical Global Impression score, which was devised by the Japanese Dermatology Association, and they're looking – patients are dosed at baseline and then IV, and then subcu of 100 mg at week 4, 8, 12, primary endpoint at week 16, and the results here that you divide the patients into responders versus non-responders, and responder's defined as somebody who on that CGI score is either minimally, much, or very much improved. When you add it all up, 75% of patients, which is, by the way, 6 patients, achieved that at week 4, and that's maintained at week 16. If you're looking at non-responders – that means no change, worsened, or the patient lost to follow-up – the 2 patients, which represents 25%, are at week 4, and 2 patients, which is 25%, at week 16. So, obviously these case studies are very small because, again, this is a rare disease.

Now, the results were not so good with palmar plantar pustulosis with imsidolimab. They did not reach primary endpoint. Imsidolimab is in phase 3 studies now in GPP, and expected completion is in June of 24.

And now I turn back to my esteemed colleague, Kristine, for another question.

Dr. Kucera:
Yes, thank you, and I will second what Dr. Gottlieb says. This is very rare. Everything we're talking about here is rare. We both have been in practice for many, many years, and you don't see a lot of this in clinical practice, but again, it's very difficult to treat, so it's nice that we have some things that we can use.

Okay, Dr. Gottlieb will go through the summary slide, and then I will take it back over for some more questions.

Dr. Gottlieb:
So, in summary, widespread sterile pustules and erythematous plaques are hallmarks of pustular psoriasis. Acute episodes and plaques of pustular psoriasis can be fatal, and certain drugs may cause flares. We do have treatment options. I personally think topical and systemic are the ones. Phototherapy – I can't imagine somebody who is that sick standing up in a light box, and a light box will take probably 10 weeks when they actually do anything, so I think it's topical and systemic. No agents – that's not true anymore – but spesolimab is now indicated in the United States for this indication. In Japan, the IL-17 blockers are all approved for this indication, and IL-36 I think has kept its promise as a target for pustular psoriasis treatment.

Dr. Kucera:
Okay, we're going to go through a quick case study discussion. I will go through this case. This was a patient, actually a patient of mine, and like I said, we don't see a lot of palmar plantar pustulosis – it's very hard to find – or palmar plantar psoriasis. This is a case of a 57-year-old female, and she presented with a painful eruption on her right palm times one week. She had a similar episode. It occurred 3 months prior. She was treated by her PCP. They gave her oral prednisone for 10 days, and then she discontinued. Initially responded – we all know treating psoriasis patients that everything usually responds to prednisone, but what happens after the patient comes off of prednisone? So, she initially responded to treatment. She stayed clear for a while and recently started to flare back up. Medical history – she's 5'2", she's 120 pounds, she has a perfect BMI, she's very healthy except cholesterol, but it's 100% under control on atorvastatin. She doesn't smoke, she does yoga daily, and she hadn't had any recent illnesses/infections, no new medication, skincare products, or

stress. Remember, that's all the things we have to ask our patients. If they have a new onset or flare of psoriasis, we have to find if something is causing it. No other previous dermatology complaints. She's a teacher. She said it was having a big impact on her quality of life. It was her right hand – she's right-handed. She was having a hard time grading papers, shaking parents' hands, even driving into school. Her hand was really bothering her. Now, our differential diagnosis – of course, we think about is this palmar plantar pustulosis? Dyshidrotic eczema? Herpes simplex virus? A fungus on the hand? Tinea manuum? Or is it a contact dermatitis? Now, we did do a biopsy on her. The results were of her skin right palm – it did say it was pustular psoriasis. They actually did do some stains, and it was negative for fungus.

Now, just kind of walking through this case, at the initial visit, patient was very hesitant to start a systemic treatment. She really was skeptical about the diagnosis of palmar plantar psoriasis because she had a very small area. She had no family history of psoriasis. The previous eruption was the first she had ever had experienced. At that appointment, she was given clobetasol. We did a topical strong steroid to see if we could get her some relief. She did that for 14 days, but it just became more inflamed, enlarged, and developed more pustules. We then switched her to a topical combination, halobetasol, which is a very strong steroid, and a tazarotene lotion. She used this for 6 weeks. She did say the pustules cleared, but it caused skin irritation, and her skin felt raw. When she discontinued, the pustules reoccurred.

Here is just some pictures. Her second visit after 14 days of clobetasol use – nothing really is looking any better. It's actually looking worse. We then put her on the combination halobetasol/tazarotene, and it did get better, but again, her hand was getting very raw, and so she stopped medication, and, of course, the pustules started to recur. So, what did we do with her? We did talk her into then doing some systemic treatment. She was initiated on secukinumab, which is an IL-17. The rationale for choice of treatment – secukinumab does have a heavy loading dose that can lead to a rapid onset of action of the efficacy data. She was prescribed a mid-potency steroid to calm the irritated skin and told to use topical moisturizers, and after 3 months, she was considered a non-responder. Her hands were not getting any better, they were getting worse, and she was miserable. So, then we initiated her on apremilast, told to continue topicals as needed. She was cleared for 3 month follow-up except for some post-inflammatory and being evaluated at 3, 6 months, 9 months, and a year later she's doing very well, and here's just the follow-up visit with systemic treatment. On the left-hand side, that was initiation of secukinumab. She waited 3 months, nothing was really helping, so then we put her on apremilast, and she cleared except for just the minor erythema.

So, again, just kind of pointing out this case and that this is a very difficult disease to treat, thank goodness we have something that's specifically for pustular psoriasis now. This can be a significant effect in patients' quality of life, as you can see, if it's on your hands and feet. Sometimes not a lot that you can do on a daily basis to get any relief, and it can interfere with your daily quality of life.

Okay, so moving into just our Q&A. We're going to have a few questions here. Okay, so the first one we're going to look at here is when you're doing a combination therapy to treat PPP or GPP, what are some typical combinations that you'll try? And, Dr. Gottlieb, you want to tackle that one?

Dr. Gottlieb:
Well, as I think you heard from both of us, the key thing other than making sure that the patient has normal vital signs, not dehydrated, not infected, but if you're talking about the treatment specifically is to use a fast-acting systemic, as there are multiple choices. There's spesolimab, there's IL-17 blockers, there is TNF blockers, especially infliximab. For palmar plantar pustulosis only, I think apremilast was a nice idea. I would not use that as my systemic of choice for GPP. And then if – one can use topicals that are not too occlusive, right? You don't want to be using high occlusive ones, but one can use topicals as adjunctive treatment. I think other things to make the patient comfortable is if they have high fever, you give them some acetaminophen to lower the fever. Make sure you hydrate them because many of them come dehydrated. If they're hypocalcemic or they're anemic, you may have to deal with those things, too.

Dr. Kucera:
And Dr. Gottlieb, is – how do you think that phototherapy does in pustular psoriasis – in generalized?

Dr. Gottlieb:
I wouldn't use it.

Dr. Kucera:
I agree.

Dr. Gottlieb:
I wouldn't use it for multiple reasons. These patients – they're sick. They can hardly stand up, so you're going to stand them up in a light box where they'll fall over and burn themselves? I mean, that's one. Two, it's too slow. I mean, it takes like, you know, we're talking in probably 12 weeks, I mean, and the patient doesn't have 12 weeks. I don't think it's an option.

Dr. Kucera:
I agree.

Dr. Gottlieb:
It's certainly not available in an emergency room or in an inpatient service.

Dr. Kucera:
There's a question here regarding the case study. Now that we have an FDA-approved for palmar plantar or pustular psoriasis, would you have used that first? And yes, absolutely. I will tell you that this pustular, especially palmar plantar, is so difficult to treat. Even though in the clinical trials, palmar plantar did not do as well as generalized pustular, I would still go for it because the patient definitely needs some relief, and you're kind of just out there grabbing at things trying to get them relief as soon as possible.

So, let me just say thank you for everyone for attending. Remember, it's important to complete your program evaluations for each presentation. They are necessary for you to get your CME certificate, and behalf of Practicing Clinician Exchange and Clinical Care Options, thank you for attending this program.

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