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Beyond Plaques: Treatment Challenges and Strategies in Palmoplantar Psoriasis

ReachMD Announcer:
You're listening to *On the Frontlines of Psoriasis* on ReachMD. And now, here's your host, Dr. Gates Colbert.

Dr. Colbert:
Welcome to *On the Frontlines of Psoriasis* on ReachMD. I'm Dr. Gates Colbert, and joining me to discuss challenges in treating palmoplantar psoriasis is Dr. James Song, who's the Director of Clinical Research and Co-Chief Medical Officer at Frontier Dermatology in Mill Creek, Washington. Dr. Song, thanks for being here today.

Dr. Song:
Thank you for having me.

Dr. Colbert:
To start us off, Dr. Song, could you briefly define palmoplantar psoriasis and how it differs in presentation than classic plaque psoriasis?

Dr. Song:
Palmoplantar psoriasis is not the same as plaque psoriasis. We typically think about these as two distinct entities. What I will say is that about a quarter of patients with plaque psoriasis can have palmoplantar involvement, but then about 20 percent of patients who have predominantly palmoplantar psoriasis can also have some plaque involvement. And what's interesting is that when you look at the incidence of patients who get just predominantly palmoplantar psoriasis, they tend to be females and they tend to be smokers as well, so these do seem to be risk factors for this particular type of psoriasis.

When we think about palmoplantar psoriasis, we like to think of it in four distinct subtypes. So there are patients who can get the hyperkeratotic type, so the skin is much thicker; there are those who get more of a pustular type; and then there are some that could get a mixed hyperkeratotic and pustular type, as well as those who could have psoriasis in other places as well. Now, the key thing about palmoplantar psoriasis is that given its anatomical location, it's under a lot of mechanical stress and trauma. The areas tend to be much more thick and scaly—hyperkeratotic—but also fissured, and it's that fissuring that causes an immense amount of pain, which then takes me to this next point: even if the body surface area that's affected is fairly limited, the potential functional burden that this can have on patients is a lot, right? So this is what we consider to be a high-impact area because the impact and quality of life is outsized compared to the relatively low body surface area. And what this means for us is that if you have a patient with palmoplantar psoriasis that doesn't respond to a topical therapy, we probably should consider escalating those patients to a systemic therapy fairly early on.

Dr. Colbert:
Now, what do we know about the underlying immunopathology of palmoplantar psoriasis, particularly when it comes to cytokine drivers and immune cell activity?

Dr. Song:
We know, based on a number of different molecular profiling studies, that there are some similarities with plaque psoriasis and palmoplantar psoriasis. Specifically, there are higher levels of what we call these Th17 cytokines, like IL-17A and F and IL-22, but there are also some key differences. For example, there does seem to be even greater levels of IL-17 signaling in the palmoplantar type. We also start to see some contributions from interferon gamma signaling. And in the pustular types of palmoplantar psoriasis, we now start to see some of the innate immune system playing a role as well, particularly IL-36. And because of the constant mechanical stress and

trauma, we do see more of this koebnerization phenomenon where damage to the skin leads to more psoriasis, so we see a lot of these cytokines that are amplifiers for this Th1 and Th17 axis. And then because of the location as well, we do seem to see a higher preponderance of secondary dermatitis, so irritant or allergic contact dermatitis happens on top of your palmoplantar psoriasis. And I think intuitively, we all know this because we have therapies, specifically biologic therapies, that are highly effective for just regular plaque psoriasis, where 80–90 percent of the time we're going to get people to clear or almost clear. With palmoplantar psoriasis, we are not getting anywhere close to that effect. Maybe a third of the time these biologics are going to work, so this does tell us that even immunologically, palmoplantar psoriasis is a distinct subtype from just plaque psoriasis.

Dr. Colbert:
For those just tuning in, you're listening to *On the Frontlines of Psoriasis* on ReachMD. I'm Dr. Gates Colbert, and I'm speaking with Dr. James Song about palmoplantar psoriasis and what distinguishes it from plaque psoriasis.

Dr. Song, why does palmoplantar psoriasis tend to be more resistant to treatment than plaque psoriasis?

Dr. Song:
Part of the challenge is the anatomy of the palms and soles. These areas are much thicker, and that's by design because of the friction and trauma, and so it is harder for our topicals to penetrate that thickened skin. And I said this before, but it's the constant mechanical stress and that repetitive trauma that perpetuates this inflammation and does damage and ultimately the pathology. And then also, it's the heterogeneity of these patients, not just clinically, but we talked about how hyperkeratotic and pustular types are different, and they also respond differently to treatments, and there's also the molecular heterogeneity. And we talked about how the highly selective biologics, although very effective for plaque psoriasis, are not consistently effective for palmoplantar psoriasis, which tells us that there's a lot of different endotypes for palmoplantar psoriasis.

Now, anecdotally, what we've seen is that patients who have more of this pustular subtype of disease, they respond very well to what we call antineutrophilic therapy—so acitretin, which is a retinoid, as well as dapsone—whereas patients who have more of this hyperkeratotic or eczematous overlap tend to do better with broader-acting immunosuppressant agents, like systemic steroids, which we try to limit, such as methotrexate and cyclosporine. But now probably the best experience that we've had has been the JAK inhibitors, and we'll talk maybe a little bit about that later.

One thing I will say about the palms and soles is that it takes longer for it to heal, and so while our traditional primary endpoints in psoriasis studies are done at 16 weeks, what I would say is that you need at least 24 weeks to really decide whether this treatment is going to work. And I've had a number of patients that may have not been considered a responder in a clinical trial at 16 weeks, but we kept them on therapy long enough and by that one-year mark, they are now a responder, so this area just takes longer to respond.

Dr. Colbert:
And are there certain therapies that have shown better efficacy in palmoplantar psoriasis compared to plaque psoriasis?

Dr. Song:
Pretty much every single biologic class has been studied in palmoplantar psoriasis, whether it's TNF-alpha, IL-12/23, pure IL-23 inhibitors, or even IL-17 inhibitors. And what we've seen fairly consistently is that they all work maybe about a third to 40 percent of the time, so there's no clear winners here—although, anecdotally, I do think the IL-17 inhibitors work marginally better for this population.

I do want to clarify something though. When you look at the pivotal phase III studies for psoriasis and then you do subgroup analyses based on the location of involvement, drugs that generally work well for psoriasis will work well for all of these different areas, like the palms and soles. So if a drug has a very high PASI 100 score, it does well seemingly in the palms and soles. But the problem is that patients who have bad psoriasis elsewhere and also have palmoplantar involvement is different than patients who have just plaque psoriasis on the palms and soles. They don't respond the same way, so I always caution people when you're looking at clinical trial data to not take post-hoc analyses of these large, moderate-to-severe plaque psoriasis studies. You need to look at dedicated studies that were designed and powered to show that this drug works in this particular subset of patients.

Now, as I mentioned, for pustular psoriasis, acitretin or dapsone works well. If you're a more hyperkeratotic or mixed subtype, while I used to use cyclosporine and methotrexate, now the JAK inhibitors are by far the most effective therapy. I mean, we've cleared patients who failed every single therapy for years, and within a matter of a couple of weeks, their skin is completely clear, so JAK inhibitors are the winners. We have multiple different JAK inhibitors that we can use ranging from pan-JAK inhibitors, which target over 50 different cytokines, to much more selective JAK inhibitors that are really going to be targeting much more of the JAK1 pathway.

We also have some other oral small molecule inhibitors that have shown some promise; specifically, PDE4 inhibitors like Apremilast seem to do actually decent in this cohort as well as some of our newer Tyk2 inhibitors. And so Tyk2 is part of the JAK family, but it is

one of four members that signals IL-12/23 and type-I interferon. And what we've seen with these selective mechanisms is that they do quite well in the palms and soles as well. There's one that's currently approved called deucravacitinib, but we have two other next-generation Tyk2 inhibitors that are under study. One's called ESK-001; the other is called Zasositinib. So those are going to be, I think, the next ones to really study in this group.

And lastly, there is a pan-JAK inhibitor topically that is currently approved for chronic hand eczema. This is called delgocitinib. It is now being studied for palmoplantar pustulosis, which is a subtype of palmoplantar psoriasis in a phase II study. So that is what's to come.

Dr. Colbert:
Before we wrap up, Dr. Song, do you have any final thoughts you'd like to share on how our treatment approach should differ between these two types of psoriasis?

Dr. Song:
We are at a point in 2025 that if you have plaque psoriasis, you probably can't go wrong with one of our newer biologic therapies. They're all very effective. You can't expect the same level of efficacy in patients who have predominantly palmoplantar psoriasis, and sometimes it is going to just be trial and error to see which ones they respond to, but we should be patient with these patients and wait a minimum of six months to see if they're going to respond. If they don't respond to one class of biologic, it's not unreasonable to switch to another class, but I have a pretty low threshold to switch to a JAK inhibitor in these patients if they don't respond to my first therapy as long as they don't have any other comorbidities that would preclude them from going on a JAK inhibitor.

Lastly, we should think about palmoplantar psoriasis as a high-impact area irrespective of the body surface area that's affected. Because it has such a high functional burden, if a patient doesn't respond to a topical therapy, they should be eligible to move on to a systemic therapy fairly quickly as well.

Dr. Colbert:
That's a great way to round out our conversation. And I want to thank my guest, Dr. James Song, for joining me to discuss how we should approach palmoplantar psoriasis differently from plaque psoriasis. Dr. Song, it was great having you on the program.

Dr. Song:
Likewise. Thank you for having me.

ReachMD Announcer:
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