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Practical Dermatology Roundtable: Generalized Pustular Psoriasis, Ch. 4

Dr. Neal Bhatia:
Just before we get into therapy a little bit, Laura, you're one of the authors on the consensus paper from the National Psoriasis Foundation. But tell us a little bit about what your group kind of came through with the findings, as well as some of the recommendations.

Dr. Laura Ferris:
Yeah. So what drove that was, if you look at the last set of US guidelines for GPP treatment and evaluation, it was written pre really having options that target the IL-36 pathway. So a lot of that was the discussion and sort of the recommendations in there were one, that this is a serious life-threatening disease. Two, that it is a distinct disease from plaque type psoriasis III, the importance of very rapid treatment. That was actually a big point of discussion.

So how do you rapidly initiate treatment? Access to dermatologists, critical. But once you have a dermatologist on board, do you order TB testing? Wait several days? Do you get a skin biopsy? Wait for that to be read out? And really, one of the big points in this paper in our discussion was that you don't need a skin biopsy to make this diagnosis. This is a clinical diagnosis by a trained professional who takes a good history, performs a good physical exam, rules out other causes. And then, two, you do not need to wait for the results of screening. You do want to ask patients, you want to make sure somebody doesn't have active TB. You do want to do sort of a screening based on history, but this is not something where we need to wait for lab testing to come back.

And then, three, when you have FDA-approved drugs that you know are validated in rigorous clinical trials to show that they work for this disease, that's what we should be using to treat this disease. Not trying to repurpose drugs that were designed and are used to treat for plaque-type psoriasis, and basing that on a couple of case series, or case reports, and going there first. We really owe our patients to go to sort of the proven therapies first.

Dr. Neal Bhatia:
Yeah. Well, it's a perfect example of ... The risks of not treating are really more significant than the risks of treating, especially in this case. And the mitigation of the flare, stopping the process in its tracks is really very critical to the outcomes for a lot of these patients too.

Jason, you touched on the 36 pathway before, and now we have spesolimab, which we'll talk about for a second. The first FDA-approved treatment for us. It's mainly, again, it's a receptor antagonist not working on the cells, not working on the cytokines themselves, and working mainly to prevent the dimerization of the 36 and one receptor on the membrane, as well as kind of prevent the 36 cytokine from binding. Getting to some of the weeds on how that works from there, and why it's important to recognize how that pathway is critical over again, the traditional 17 and 23 blockade.

Dr. Jason Hawkes:
So I like to break it out in my mind, that when you look at plaque psoriasis, you're talking about a T-cell-mediated disease, really the adaptive immune response. So these are predominantly signals from the dendritic cells and the T-cells driving disease in plaque psoriasis.

Totally different when we talk about GPP, because we're really looking at the primary cell type really being the keratinocyte, because you're looking at the keratinocyte as being, really, a predominant source of IL-36, and that's going to trigger that hyperproliferation, the inflammation. And then as Laura touched on, IL-36 is a very strong attractant or chemo attractant for other cell types, particularly the neutrophils. And then once IL-36 is upregulated, it's going to then activate some of the T-cells, but the T-cells are not really driving that

process. So when we focus in on the keratinocyte, we're talking about alpha, beta, gamma, of IL-36. These are, you can think of it simply like the gas of that receptor. So any of these receptor, any of these isoforms can activate the receptor. IL-36 gamma is really probably the prominent driver in the skin of inflammation in the keratinocyte. So those are going to activate that pathway, obviously through the IL-36 receptor.

And then that same system has a break. So the IL-36 receptor antagonist can obviously stop that signaling. So the beauty of the spesolimab really blocking the IL-36 receptor, right? It's really functioning as that receptor antagonist. So it works in the two situations, that some of these patients don't have a mutation that makes the IL-36 receptor protein dysfunctional, right? They have a normal functioning break, but their gas is up high. And then you have these patients that don't have the functioning break. So by blocking the receptor, you actually sort of take care of both situations here, right?

And that's really going to be helpful in, basically we want to block that upregulated unopposed signaling of IL-36 in the skin. So I think for clinicians, if they can think about this as really starting in the skin. Having high IL-36, or a broken break that doesn't oppose when IL-36 gets activated, then that's going to be the link. And obviously neutrophils with IL-36, those two are going to come hand in hand.

So we're basically just giving a replacement, where we're adding in and reinforcing the break of the system so we can shut off that feed-forward mechanism between the keratinocytes, IL-36, and then the adaptive immune response, which is going to contribute. Because we know that IL-17, for example, has a very potent response on the keratinocytes, which can then reactivate these keratinocytes to hyperproliferate, make more proteins. And now we have this cycle that can be difficult to shut off.