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A New Era in Plaque Psoriasis Care: Examining Topical Nonsteroidal Therapies

Dr. Chovatiya:
According to the National Psoriasis Foundation, more than 8 million Americans and 125 million people worldwide are affected by psoriasis; but perhaps what's even more staggering is that about 80–90 percent of these patients experience plaque psoriasis. So what are the best topical treatment options for this type of psoriasis?

You're listening to *DermConsult* on ReachMD. I'm Dr. Raj Chovatiya coming to you from Chicago, and joining me today is Dr. Jason Hawkes, 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:
Let's zero in on a couple of new treatment options that we have for our patients. Let's start with roflumilast. What do we know about its safety and efficacy, and what is it?

Dr. Hawkes:
When we talk about the new therapies, we really only have two new therapies, and with roflumilast, what we're really looking at is an iteration of a medication that we have had in the oral form. So when we talk about apremilast, we're talking about a PDE4 antagonist, so we're talking about a small molecule that blocks the function of PDE4. And without getting into the complicated immunology of the phosphodiesterase enzymes, and specifically enzyme 4, which is most prominent in the immune cells in the skin, we have a topical therapy that can effectively do what apremilast did in oral form, but it has the ability to do it with a much higher efficacy and potency. And so when we talk about roflumilast, we're talking about disrupting the proinflammatory pathway but doing it with a topical that has the ability to really knock down a number of cytokines in the skin that contribute to psoriasis. And this has one of the advantages of sort of being broad, like a topical steroid which hits many immune pathways, but doesn't have the collateral damage of hitting nonimmune pathways that lead to some of the side effects, like the skin atrophy, and so this really falls under something that we've known about in an oral form that had some drawbacks, primarily GI side effects, like diarrhea or constipation. So now we have an oral form that we have now translated into a topical form to potentially benefit patients who, again, may not require oral systemic therapy.

Dr. Chovatiya:
And another cream, actually, that has come to market is tapinarof, a totally different molecule, totally different biology. Maybe you can tell us a little bit more about this treatment option as well.

Dr. Hawkes:
Yeah. And one other point on roflumilast that's going to tie into this other molecule here is that we traditionally use topical steroids, and most topicals as twice-daily application, and what we get at is that patients are trying to use the topical steroids twice a day, but they get into this topical fatigue where it's actually really hard with all of our busy lives to do something twice a day, and so compliance starts to drop. So I think that for many of our patients who are treated with topicals, effectively they're probably only using most of these medications once a day, which is the advantage of these topicals. We're looking at this new therapy, different mechanism, tapinarof, which also has the added benefit of once a day, so I wanted to get that point out there.

So when we're talking about tapinarof, we're talking about a completely separate mechanism of action. We're still talking about a small molecule, but here what we're talking about is a medication which impacts the aryl hydrocarbon receptor, and this is a receptor that has been involved in multiple pathways, but it's prominent in a number of immune cells, including keratinocytes and melanocytes, and it's widely expressed in immune cells, so basically antigen-presenting cells like T-lymphocytes and fibroblasts, for example. And we know this pathway is important for modulating the differentiation of type 17 cells or type 22 cells and also helps balance regulatory T-cells, so this makes sense why it's going to be useful in a number of inflammatory diseases, probably atopic dermatitis as well as psoriasis, but because of the predominance of the type 17 and type 22 pathway, this is a mechanism that makes sense for trying to target it. And we know that when we activate this aryl hydrocarbon receptor, it shuts off that proinflammatory response, so a little bit different than we kind of think of an on switch and turning it off. Here we're turning something on that's going to result in sort of an off switch of the immune system, and that's going to primarily work through the keratinocytes on the skin but also in helping to move down into some of the other immune cells that are populated in both the epidermis and the dermis, so again, targeting primarily type 17 and 22 cells in both the keratinocytes and the infiltrative immune cells.

Dr. Chovatiya:
Yeah, I think about tapinarof as a molecule that really modulates an important part of the pathway we think about for barrier homeostasis, right? There's a reason why aryl hydrocarbon receptor holds important roles, whether it be the gut, the skin, potentially the lungs and others, and so I think of it as another way to try to get the skin kind of back to normal. And it's really exciting that we have a couple of new options and a lot more progress to be made in terms of figuring out how they're going to fit into our armamentarium.

And for those of you just tuning in, you're listening to *DermConsult* on ReachMD. I'm Dr. Raj Chovatiya, and I'm speaking with Dr. Jason Hawkes about topical nonsteroidals in patients with plaque psoriasis.

So, Dr. Hawkes, how do you know which patients are going to benefit the most from these therapies? What are some of the benefits or pitfalls to using them? How do they really fit into your real-world clinical practice?

Dr. Hawkes:
Yeah. So unfortunately, for any therapy, whether it's topical, oral, or injectable medication, what we don't have in psoriasis is a consistent test or predictor assay that tells us that this patient sitting there in the clinic is going to respond to X therapy. Now that's something that we need, and it's maybe the golden nugget of our specialty with regards to the treatment of inflammatory conditions, but I think number one is that we really are still in a trial-and-error basis of medicine with regards to the treatment of inflammatory diseases. So I can't tell which patients are going to respond consistently to any medication, and yet, there are some that have a higher probability of getting patients clear, and so we tend to use that sort of overall probability from these big studies, these phase III, sometimes phase IV studies, so I think that's an important point. It highlights an unmet need in psoriasis.

But the way that we would incorporate topical therapies as we mentioned is looking at the need of the patient. Now the advantages we already kind of highlighted is that they tend to potentiate that immune response without having the collateral damage of the topical steroids, and they also have the benefit of being used once daily. They can be used in really critical areas that might push our likelihood of more aggressive therapies—so, for example, genital involvement, facial involvement, ears are very common area affected in our patients. And so the ability to use these therapies once a day increases compliance and gives us options in these sensitive areas where patients might be a little hesitant or concerned, and I think it also has the potential—while we don't have approval—it has the potential benefit of maybe comforting parents who might be treating pediatric patients, for example, so I think that's going to be an important area. And in contrast to the limited disease, we're talking about the benefit of having incorporation of topicals to work complementary to our systemic agents because we know mostly systemic therapies don't always get a person 100 percent clear. So the other way I would use these medications as being a supplement: again, increased compliance, use in these troublesome areas, a high efficacy.

The primary downside though I think practically is that these medications are going to be harder to get. Insurance and payers are going to make more obstacles to get these medications, which are going to be more expensive than topical steroids, so that obviously presents a practical challenge and an administrative burden to practices, and so that has to be balanced there. But that would be the way that I would view these novel medications as relative to the old school topical steroids that we still use a lot and to these new systemic therapies.

Dr. Chovatiya:
I love it. I think I might even throw another one out there in the sense that both of these newer topicals seem to have some very interesting data for long-term maintenance therapy that suggests that they may even do a better job potentially than topical corticosteroids do in terms of trying to achieve long-term control, which is something that we struggle with no matter what the extent of psoriasis is, so I think a lot of really exciting analysis and further development to happen in this space.

Dr. Hawkes:
I think one important point is that there's this idea that these therapies may shut off some of these long-lived cells in the skin, and while that's been suggested, we really don't have the experiments that really prove that. And I think this is going to be a really important aspect for all therapies moving forward is that how do we not just treat symptoms for a short period of time, but how do we actually modify disease and maybe even potentially shut it off permanently. And while we're starting to dabble in these mechanisms around these long-lived resident memory T-cells, we really don't know if that's how these topicals are working, but they do appear to keep disease shut down for longer periods of time—not permanently. And I think the research leading into the biological mechanisms driving that longer response might mean that we can improve all sorts of therapies into keeping disease at bay longer, so maybe we get to therapies eventually where rather than injection once a month or every two or three months, maybe we can get to therapies where it's a pill, you know, once every six months or an injection once a year, for example. And these therapies, both topical and systemic, that would be a really important thing to move forward to try to eliminate the burden for these patients, so something that we need to keep working towards.

Dr. Chovatiya:
I couldn't agree more, and thanks so much for those closing thoughts. I really want to thank my guest, Dr. Jason Hawkes, for sharing his insights on these treatment options for plaque psoriasis. Dr. Hawkes, thanks so much for joining us today.

Dr. Hawkes:
Yeah, thanks for having me. It's always great to be here.

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