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Journal Club: What's New in Pathogenesis and Treatment of Atopic Dermatitis

Dr. Neal Bhatia:
Hi, I'm Dr. Neal Bhatia. I'm Chief Medical Editor of Practical Dermatology, and with me is Dr. Jason Hawks, Medical Dermatologist from Sacramento, California. And this is an episode of the Practical Dermatology Atopic Dermatitis Journal Club, where we discussed some of the new articles as well as some of the new findings. And Dr. Hawks is one of my favorite experts of all these subjects. We were talking a little bit about just updates on the pathogenesis of atopic dermatitis and some new articles that explain the flow in the cytokines, everything involved. Give us a little rundown of what you've seen in some of the description.

Dr. Jason Hawks:
Yeah, this is a nice to have another T-cell mediated disease where we see that same feed-forward inflammation. So we've got a primary T-cell disease, it's type two inflammation rather than type one or type three. So really looking at the atopic allergic type cytokines. So IL-4, IL-13, IL-5 we really see that activation early on, T-cells, dendritic cells, and then we have a really rapid response in the skin. So we start to see that epidermal proliferation, the scaling, the erythema, the itching, and then we see the epidermis become very immunologically active feeding back to the beginning. So we get this really vicious cycle in patients. And what's been nice to see over the last few years, we've started to tease out there's more than just this predominant Th2 or type two inflammatory pathway that we're starting to pick up signals that are coming from the keratinocytes, like TSLP, for example, and some of the dendritic cells signals.

We're starting to see new targets on both the T-cell, but also the dendritic cells like OX40, for example, has been interesting. And so I think we're starting to tease out some of these cellular targets, the different compartments, the immune system. But then we started moving into some of these intracellular mechanisms as well. So the JAK/STAT pathway obviously has a lot of interest. We're starting to see the movement into IL-31 with the itch cytokine. So we're now starting to tease out the little pieces, and I think this is going to be great for a disease, which we talk about it's a clean bucket, but there's a lot of heterogeneous subtypes. So I think trying to tease out which therapy is going to be the best for these patients, these specific subtexts, I think is really exciting.

Dr. Neal Bhatia:
Yeah. I like the way you phrase about targets because everything we see as a potential actor in the game could be a potential target for therapy. And like you also mentioned about Th2 being the predominant cell type. We do see a lot of Th1 coming in later on, a lot of lichen simplex has Th17 built in IL-22 with epidermal hyperplasia, all the other potential actors in the game. They're all contributing both early and late. But with that, what are you seeing now in terms of the pipeline? Where are we focusing our efforts? We've had IL-4 and 13, we've got Janus kinase inhibitors that are working very well. What are we seeing in the future in the crystal ball?

Dr. Jason Hawks:
Yeah. I use the analogy of a target like shooting practice where we started off with these big bombs that just blew up everything, cyclosporine, methotrexate, prednisone, these not ideal therapies. And then we moved really quickly to the snipers, so these really targeted selective biologics, one or two cytokines. But the problem is we have disease that's messier. So people say, "Well, maybe we've made a step backwards with a JAK/STAT pathway," But I don't really think of it that way. I think about some disease when you just hit a single cytokine or a single pathway, there's other aspects of disease that's not well controlled.

So backing up a little bit, not having the big bomb, but maybe a shotgun would be in between where we can hit these other pathways. It's more than one pathway. So a patient, a lot of the atopic disease patients different from our psoriasis patients have a lot of comorbidities. So backing up a little bit can be helpful where one therapy can hit multiple disease types. So I think what we're working on is those simple, straightforward eczema patients, they respond really well to monotherapy. But we have these patients with more

complex, more severe disease, other comorbidities that some of these other small molecules or other targets might do a better job at hitting certain aspects of disease. And finding those subtypes, that's been the exciting part that we're starting to see really develop.

Dr. Neal Bhatia:
Yeah, because you think about the potential asthmatic or the patient with seasonal allergies on top of eczema, and then you think, are we treating the whole picture and treating what's under the hood, not just what they come in with? But at the same time, you have the 2% to 5% BSA patients who we could probably just treat topically, but we have to think about how are they doing with their itch? Are they sleeping? Are they able to concentrate at work? I think about all these eczema patients who they're driving and they're begging for a stoplight, they just want to start scratching. So with that, are we focusing enough on itch or is it really just more about inflammation first?

Dr. Jason Hawks:
Well, I think we need to shift back to the patient. One of the downsides to BSA is that people use it as this hard cutoff. So you're talking about patients that traditionally would've said, "Oh, they have less than 10% body surface area. Let's not go on systemic." But we've seen a shift. Psoriasis did this really well where it was like patients with localized disease who didn't respond to topical therapies, they were good candidates for systemic therapies. And I think we need to be less concerned of these hard and fast rules and more on what's working for the patient. If somebody comes in and they're like, "I've tried every topical and nothing works," then there's no point in reinventing that wheel.

Dr. Neal Bhatia:
Absolutely.

Dr. Jason Hawks:
Let's move on. So we're looking at systemic therapies, and I think the real advantage of systemic therapies is that we're treating more than the skin. So we're really getting at that level of shutting down the systemic inflammation, which we know has some chronic negative effects long-term.

Dr. Neal Bhatia:
Absolutely.

Dr. Jason Hawks:
So I think we're trying to get out of the therapy idea of putting it nicely in these firm categories of severity and more saying, "This patient's recalcitrant or failed or intolerant." Or let's just be honest, nobody wants to put on a cream twice a day for a chronic disease that they're going to have for the next 30 or 40 years.

Dr. Neal Bhatia:
That's where we end up chasing things. You and I are big proponents of getting dermatologists off the ledge for that reason. We're in a specialty where we have all of these options, and yet still, we have so many of our colleagues who sit there and say, "I'm not comfortable. I don't want to write these drugs. I'm worried about box warnings." How do we get through to these people and say, "Look, the percentages of the adverse events that actually happened in the trials don't even sit forward with a box warning"?

Dr. Jason Hawks:
Yeah, our specialty has to be honest. It's not about safety. Let's just forget about that because we're using medications like how many dermatologists are writing prednisone, oral prednisone, methotrexate, cyclosporine? These are far more dangerous medications than any of the newer systemic therapies that we have. So we have to have a realistic conversation. So we're actually doing our patients a disservice by using these explosive medications that hit everything in the immune response and pretending that it's safety. Now the admin stuff is real. The clinical, the extra work for a biologic or systemic therapy that's imposed on practice, that's real. But that shouldn't be the reason that we don't choose the best therapy for our patients.

Dr. Neal Bhatia:
Exactly. And a lot of our colleagues too, they hide behind cost. They're worried about cost to the system. But let's not forget the cost of not treating patients. What happens to those patients who are sitting at home scratching, they can't concentrate at work, at school? How do we address those concerns about let's actually get to the heart of treating patients correctly?

Dr. Jason Hawks:
Well, I think that's why we come to these conferences. These are discussions about if you're having trouble getting to particular therapies, we can help you with that. We've all been there. We've learned some of the tricks, things that get to therapy, but we need to look at the data holistically. These patients are having better outcomes, they're doing better. The top goals are helping with the

superficial aspects of disease, but they're not really having an impact on that systemic inflammation. And we start to see the development of these comorbidities, like psoriasis I think led in that space. But eczema's catching up, we're starting to see the chronic effects of systemic inflammation.

So we are moving towards systemic therapies, and I think there's this idea now that one, if we can more completely suppress inflammation, maybe acting earlier, maybe we can shut off some of this atopic march or the development, some of these things that happen in kids who have disease that don't have disease X, Y, and Z, that maybe more effective therapies early on, maybe it really can be disease modifying.

Dr. Neal Bhatia:
Exactly.

Dr. Jason Hawks:
I think that's really going to be the next push where we're saying, "We're trying to treat the patient to shut off what might come down the road." And that's something that I think we can really explore now.

Dr. Neal Bhatia:
Yeah. Just like we used to talk about with rheumatoid arthritis and psoriasis and all the others, but if we had to take a practical approach to the atopic dermatitis patient, we still want to treat top down. We still want to treat inside out to get all the other components of itch and other things that are going along with the disease state, but optimally, what would be in your treasure chest? If we could pick out the best things for itching without mentioning any names of products, if you had to really choose what's your recipe? Aside from daily cleansing and moisturizing something for itch, something to work top down for breakthrough, something for shots and pills, what would be your ideal recipe?

Dr. Jason Hawks:
Yeah, I try to have the conversation with patients that first and foremost, your disease is driven by your immune response. I always say, "You know what? Your thermostat should be at a two or a three, but yours is out of 10." So it gets us around this idea of immunosuppress. It's like, "Well, yes, we are trying to do that, but we don't want to take it to zero. We want to bring it from 10 to three. We want to bring it back to normal." So I try to start there of this is the underlying cause, and that's not the same thing as saying, "Pet dander triggered your disease." It's that your immune system's activated. But then I like to go to the secondary points. There are things that we know are going to be better. If there's obviously clear triggers, things that are activating the skin, want to try to avoid those. We know that barrier repair, we know there's a strong epidermal component. So I always say moisturizers aren't going to take away the inflammation, but when your skin's good, it can help it stay good.

Dr. Neal Bhatia:
Well, that's the key. And we're going to keep them away. Just like I tell my kids, both of them have eczema I try to tell them like, "Look, let's stay on top of moisturizing so we can stay away from having a flare-up because..." And you think about all the patients, their two biggest phobias are steroids and antibiotics. If we can minimize exposure to those, I think we can at least gain some trust from the atopic dermatitis patients.

Dr. Jason Hawks:
Yeah, I think the goal is we want to keep people clear, but this disease has flares, and so I think we need to have a clear plan of preventative maintenance and then acute therapies. We don't want to be mixing those categories because the things that work for maintenance don't work for acute inflammation.

Dr. Neal Bhatia:
No, exactly.

Dr. Jason Hawks:
So patients need to understand what happens when X, like you get a big flare of your disease? Are you going to use your topical cream, the moisturizer? No, you're going to move to your medicine. And then when you get clear, you're going to go back. So that dynamic's really important for patients to understand because then you can really give them a good plan. Here's what you're going to use on your daily. If this isn't working, you got this back up.

Dr. Neal Bhatia:
Exactly.

Dr. Jason Hawks:
And if these aren't working, we're going to move you down this path.

Dr. Neal Bhatia:
Yeah. Well, we have to remind them to play all four quarters, right?

Dr. Jason Hawks:
Exactly.

Dr. Neal Bhatia:
That's just the key. Well, Jason, thank you. That was a really nice synopsis of everything, and thanks for watching another episode of the Atopic Dermatitis Journal Club, and we'll see you next time.