Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/practical-dermatology-il-17-journal-club/mechanisms-of-action-for-il-17-inhibition-in-treating-psoriasis-and-hidradenitis-suppurativa/48808/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Mechanisms of Action for IL-17 Inhibition in Treating Psoriasis and Hidradenitis Suppurativa

Neal Bhatia:
Hi, I'm Dr. Neal Bhatia. I'm Chief Medical Editor of Practical Dermatology. I'm here with my best of friends, Dr. Jason Hawkes. Jason from Portlandia, who's doing excellent research and translates immunology to English, which is a skill. This will actually be a good fun one for both of us. So this is talking about the IL-17 Journal Club, by the way, which is a good installment. Tell us why psoriasis drugs should work for hidradenitis suppurativa, just in a nutshell.

Jason Hawkes:
Yeah. I mean, this has been really an advance. I think when we looked at what happened with HS over time pathogenically, I think we start thinking, is this occlusion? Is it the hair follicle? Is it something to do with the glands? I think we see early on there's this perifollicular inflammation and clearly there's very early stages, this hyperproliferation of keratinocytes. And for me, that's the easiest link, is that you see that epidermis going down around the hair follicles, obviously one of the potent drivers of keratinocyte hyperproliferation, that IL-17 signaling. So of course it makes sense. It's inflammatory. It helps recruit neutrophils, which obviously contribute to pustules and abscesses. So I think this idea of the very early phases being somewhat IL-17 dependent with that keratinocyte response can certainly help recruit in a lot of the other immune cells that can lead to some of the destructive components. And obviously once we get the fistulas and the scarring, then I think we shift that immune response. And I think that's the overlap.

Neal Bhatia:
Which is why we were going after TNF blockers before, because they were helping with the tissue destruction and all the necrosis. There was a regulation of inflammation around TNF that we understood. But somewhere in there, we figured out 17, whether it be promoting epidermal turnover, promoting other cytokines in the game, all of that became a target. And now we see A and F with that just the same way. We're seeing a few drugs in motion with that. And then down the road, we're going to see BTK with that. But is there a master player in the game? Is there a queen bee of both psoriasis and HS? I think it's an interesting topic.

Jason Hawkes:
Yeah. And this is kind of looking into the crystal ball a little bit, but if I had to sort of hedge my bet, I think this is going to be a disease that's not immunologically as simple as psoriasis, right? Plaque disease for psoriasis patients is pretty straightforward. You hit one key pathway, you do it really well. Most patients, vast majority, like we're getting eight, nine out of 10 patients 100% clear over periods of time. That's remarkable. We're way off in HS. And I think part of that is because there are probably multiple immune pathways contributing. And I think IL-17, A and F obviously expanded our treatment option. TNF, not a very good inhibitor of the 17 pathway. We know that in psoriasis and broad acting, at least the number of issues. But as we get to the targeted component, I think we're teasing out that T-cell innate component in the skin, but it's still not getting us where we need to be in terms of HS. And I think part of that's going to likely lead to combination therapies.

Neal Bhatia:
Yeah.

Jason Hawkes:
But as we get these individual targeted therapies, we're going to start to say, "Well, does that cell type or this pathway contribute?" And I think that's going to open up a whole host of R&D options as we start looking at bispecifics and co-formulations.

Neal Bhatia:

Oh, absolutely.

Jason Hawkes:
So I think we're just barely cracking into our ability to knock off most disease in the majority of patients, but we're still not getting them. We're not talking a lot about high score 100.

Neal Bhatia:
No, of course not.

Jason Hawkes:
Right, but we're getting there.

Neal Bhatia:
But it is enlightening to think how far we've come from antibiotics and intralesional steroids and-

Jason Hawkes:
Absolutely.

Neal Bhatia:
... all the things that HS patients had to go through to get now to the point where we can say, "All right, we can take 90% of your disease or at least 75% of it and knock it way down." But I think, again, the therapeutic choices that we understand, they're still confusing to Average Joe dermatologists to say, "These are psoriasis drugs. Why am I using it for this?" And to your point about neutrophils, how do we put IL-17 in the same sandbox with neutrophils? It's tricky.

Jason Hawkes:
Yeah. I mean, the way I think about that is that when you up-regulate IL-17, you get this very potent keratinocyte response. They up-regulate the receptor for IL-17, but they also become metabolically active. They make signals like IL-36 and IL-19, and those are chemo attractants for neutrophils.

Neal Bhatia:
Of course.

Jason Hawkes:
The real question, is HS a neutrophilic dermatosis or do neutrophils show up to the party that already started because you've activated the immune response? And I think that's a really important question. Where IL-17 A and F added to our therapeutic algorithm is that we didn't see dramatic improvement in a lot of patients with TNF. Moving to 17A blockade, it was kind of a lateral move, if not maybe a little drop-off. It didn't add much, but there was clearly the synergy between IL-17, A and F together. And I think, again, that gets back to the complexity of the immune response. We're thinking about one pathway, but we need to be thinking about what are the potential multiple pathways working together to drive this messy inflammatory response that's not as clean as the diseases that we see in the T-cell mediated conditions.

Neal Bhatia:
No, completely. And again, just think of the history of HS. I mean, again, a lot of it's pattern recognition, getting to the source. Antibiotics and steroids may have been great before, but now we have disease modifying and even really majestic outcomes with some of these. We just have to get out of our own way as dermatologists, but we have to get patients on board to think, "Let's think about the process, not just the results."

Jason Hawkes:
Yeah. They need to think about their own disease as being more than just the skin-deep component, but all of the other inflammatory aspects, hormonal component. And we need to push our colleagues into actually using these systemic agents.

Neal Bhatia:
Absolutely. And the good news, like you said, the pipeline is rich. We just need to optimize them and put them into motion. So it's good. Well, thank you, Jason. This was good. A bunch of eggheads reviewing immunology, that's what we do best. And this is another installment of the IO-17 Journal Club, and we'll see you next time.