Novel Pathways in Psoriasis - An Immunological and Pathogenic Perspective (Sponsored by Bristol Myers Squibb)

Bruce Strober, MD, PhD, FAAD, interviewed by Flavia Fedeles, MD, FAAD

FLAVIA FEDELES, MD, FAAD: Hello, everybody. Welcome to another episode of Dialogues in Dermatology podcast. My name is Flavia Fedeles. I'm an instructor in dermatology at Harvard Medical School and clinical dermatologist in the Department of Dermatology, Massachusetts General Hospital in Boston, Massachusetts. Today, I have the privilege of welcoming Dr. Bruce Strober to the podcast. Dr. Bruce Strober is a clinical professor of dermatology at Yale University School of Medicine, practices and does clinical research at Central Connecticut Dermatology in Connecticut, and is a nationally and internationally recognized expert in psoriasis and clinical trials. He's also scientific co-director of the CorEvitas Psoriasis Registry, the treasurer of the International Psoriasis Council, and the editor-in-chief of the Journal of Psoriasis and Psoriatic Arthritis. His research interests center around therapeutics for inflammatory skin diseases such as psoriasis and atopic dermatitis, and his goal in clinical practice is to help improve the care of difficult- to-treat patients.

--The topic of today, we're going to be talking about Novel Pathways in Psoriasis: An Immunological and Pathogenic Perspective. Thank you so, so much for joining me, Dr. Strober. This is a very interesting topic, and I'm very excited about our conversation today. Let's start by briefly talking a little bit about what we know so far, so our current understanding of the pathogenesis, the immunological mechanisms involved in psoriasis, so that we can talk about the novel pathways after that.

BRUCE STROBER, MD, PhD, FAAD: Right. Psoriasis, over the last 10 years, has been identified as pretty much dependent on two major cytokines that are more or less interrelated, IL-23, interleukin-23, and interleukin-17, and it's more or less believed that interleukin-23 initiates a differentiation pathway of T-cells down what's called a Th17 program. Th17 differentiated T-cells

elaborate IL-17, and IL-17, thereafter, in essence forms a link between the immune system and the changes we see in patients with psoriasis in the epidermis.

--In other words, what I always thought when I was a resident, well, what's the link between the immune system and acanthosis, for example, and neutrophil migration into tissues with psoriasis? And the link is IL-17. It sets off keratinocyte pathways that, in essence, feed back on immunologic pathways and cause a perpetual loop of inflammation, which essentially doesn't turn off, but you need IL-23, more or less, for most forms of psoriasis. And so, if you inhibit IL-23 in an effective manner, you shut down psoriasis in most patients. And, similarly, because IL-17 is the downstream effect of IL-23-induced T-cell differentiation, if you block IL-17, you also shut down psoriasis.

--It's a double linchpin. There's not one linchpin molecule. You can actually target two molecules and effectively turn off psoriasis. And, just in case anyone is wondering, we used to know of another molecule, TNF, and blocking TNF, of course, shuts down psoriasis, but we believe TNF is a more broadly acting inflammatory cytokine, so that while you shut down psoriasis, you probably also have less selective effects on the immune system, and therefore, perhaps more undesirable potential adverse events, like infection, with people who get TNF blockers. The advent of understanding IL-23 and IL-17 as central to the pathophysiology has allowed more targeted interventions that are as effective, or more, than our previous, and in my opinion, safer with fewer potential side effects.

FLAVIA FEDELES, MD, FAAD: Great. Thank you for that overview. Are there any more recent pathways or novel pathways or discoveries that are in the development or in the discovery pipeline?

BRUCE STROBER, MD, PhD, FAAD: It's a great question, and we have newer molecules that block newer targets, but one way or another, I think we can fit these targets into the framework I

just described. For example, we've had a PDE4 inhibitor in apremilast, and there will be perhaps follow-on PDE4 inhibitors developed for psoriasis. And, while that's a new target, we believe its benefits with regard to treating psoriasis comes still at the effect of inhibiting IL-17 ultimately. You're downregulating IL-17, perhaps TNF, perhaps IL-23. It's a broad effect that's anti-inflammatory. I wouldn't call that a new approach to psoriasis as much as a new way to plug in to a common theme.

--The other targets that are being explored, and one has been approved, is JAK kinase inhibitors. We realize now that the JAK kinase family, and there's four JAK kinases, JAK1, 2, and 3, and TYK2, mediate inflammation that is central to psoriasis, and probably some of the greatest effects there are again the effects of blocking IL-23 and perhaps IL-12 signaling. We now have a dedicated TYK2 inhibitor, which is deucravacitinib. Yes, this is a new target. It targets TYK2, but TYK2, in its inhibition, is really downregulating the pathways mediated by IL-23 and IL-12 and interferon. You could see, if you block TYK2, you're indirectly inhibiting one of the key cytokines, IL-23.

--And then there's the broadly acting JAK kinases, for example, upadacitinib, abrocitinib, tofacitinib, which hit JAK2 and JAK3 variably, and TYK2. They're less specific in their inhibition, but they're actually also effective medications for psoriasis, and they've been shown to be so in multiple different clinical trials. And, while none of them is approved for psoriasis on-label by the Food and Drug Administration, off-label, broadly-acting JAK inhibitors treat psoriasis, again, because they're targeting these key pathways that I just described. One way or another, drug development now is somewhat always putting the focus on IL-17 and IL-23, one or the other, either directly or indirectly, because it appears to be the most sensible way to get the most efficacy, the most predictable way to get the most efficacy, and by the way, not only in psoriasis, but also psoriasis comorbidities like psoriatic arthritis.

FLAVIA FEDELES, MD, FAAD: That's great, yeah. It sounds a little bit like, like with the TNF inhibitors, JAK inhibitors are upstream and perhaps have a more broader effect on the immune system, do you expect the side effect profile to be a little bit more broad as far as safety of JAK inhibitors versus IL-17 inhibitors or something that's more downstream, similar to the TNF inhibitors?

BRUCE STROBER, MD, PhD, FAAD: Yes. The nonspecific JAK inhibitors that block the catalytic domain, and therefore inhibit multiple different JAK kinases, while effective, probably create greater risk for patients along a few fronts, one of which is the risk of herpes zoster. It's much more increased in people on JAK inhibition, and therefore, patients on JAK kinase inhibitors probably should receive vaccination against shingles. I recommend that for all my patients if they haven't already done so. Now a specific TYK2 inhibitor, deucravacitinib, is different. It doesn't appear to have some of the adverse event baggage that the broadly-acting JAK inhibitors have. I would not necessarily worry about shingles in a person on deucravacitinib.

--Other issues that we worry about in JAK kinase inhibition, non-specific JAK kinase inhibition, would be issues like deep venous thrombosis, pulmonary embolism, perhaps serious infection, perhaps non-melanoma skin cancer, myocardial infarction, and stroke. All these are in the label. While they're rare, they are definitely to be considered, and I think definitely limit the patient type you want to put nonspecific JAK kinase inhibitors into, whereas the TYK2 inhibitor, deucravacitinib, and follow-on drugs that will act like deucravacitinib, again, those issues seem to be less prevalent in the clinical trials, or nonexistent at all. You don't see a signal for DVT, PE, MI, stroke, non-melanoma skin cancer.

--When we talk about JAK kinase inhibition, and it's important we talk about it, by the way, because it's here and it's effective, we need to know there's a difference between selective TYK2 inhibition

and broadly-acting JAK kinase inhibition. Your mind should think differently when using these various classes in terms of risks for the patient and patient selection.

FLAVIA FEDELES, MD, FAAD: Great. That's a wonderful point. There are more and more of the JAK inhibitors approved and they have different profiles as far as which of the JAK kinases they're inhibiting, and of course, the side effect profile probably is going to be different. How about clinical trials, or can you comment or discuss any ongoing or upcoming clinical trials?

BRUCE STROBER, MD, PhD, FAAD: Yeah. We're going to see new TYK2 inhibition. I think there are multiple companies, I know there are multiple companies, developing TYK2 inhibitors, which they believe will be more effective than deucravacitinib. Primarily, I think they're going at this by developing a drug that is more selective for TYK2, more potent against TYK2, it doesn't at all touch JAK1, 2, and 3, and therefore gets the best of that inhibition and makes it better. I think you'll see, over the next two to three years, at least two companies, if not three, try and develop better TYK2 inhibitors.

--And I mentioned PDE4. Right now, there are clearly two, if not three, companies trying to develop better, quote-unquote, PDE4 inhibitors, better apremilast molecules. The challenge there is, in my opinion, it still appears, no matter what kind of drug you're using, you can't get away from the intolerable side effects that some people experience on PDE4 inhibitors, for example, nausea, diarrhea, and headache. They seem to be always going to be in those studies, and the game in better PDE4 inhibition development is just to get better efficacy, and it's left to be seen if those will arrive for psoriasis. I do believe they could arrive for other disease states that we even have more difficulty treating, like hidradenitis suppurativa, so that's a discussion that's continuing onward.

--And, finally, there is a drug in development, which is an oral therapy that blocks the IL-23 receptor, and people really should look out for this. It may be a misnomer to call it an oral biologic,

but it is a peptide sequence. I don't know how long it is. It's a small peptide that could be taken orally, have enough bioavailability, and it specifically, and it was designed specifically, blocks the IL-23 receptor. And the Phase 2 data that were presented recently clearly demonstrate that this is a high potency anti-psoriasis medication, really achieving PASI 75, 90, and 100 levels that touch our best performing biologic therapies. We might have an oral therapy that acts as well as a biologic therapy in terms of its ability to clear psoriasis, and it might surpass any of these follow-on TYK2 inhibitors I was just discussing in terms of efficacy and maybe even tolerability and safety. And, to me, that's really a groundbreaking finding, that we could get to an oral therapy, well tolerated, maybe once a day, that essentially is like a biologic, and has the safety of an IL-23 inhibitor.

--I really feel the breakthrough mechanisms of action are not necessarily new targets, but new formulations, and formulations that are giving us better options for treating patients. I shouldn't go without saying that novel topicals have been developed, and are continuing to be developed, for people with psoriasis, which have novel targets. For example, tapinaroff targets the aryl hydrocarbon receptor as an agonist, and in so doing affects alterations in gene transcription that probably ultimately result in decreased IL-17 expression. There you have IL-17 again. You can chalk up tapinaroff's efficacy to its ability to downmodulate IL-17.

--And then you have a topical PDE4 inhibitor, which we've been also given the opportunity to use, and that's roflumilast, and that, too, has very respectable efficacy as a once daily topical that's nonsteroidal. A topical PDE4 inhibitor, a topical aryl hydrocarbon receptor agonist, which means to me new targets are being approached not only for oral therapies and biologics, but also topical creams. And every time I think that the revolution in psoriasis care is over, another year passes and another three interesting medications are introduced to us. There's still a lot of drug development going on in psoriasis, and I really believe, 10 years from now, how we treat psoriasis is going to be dramatically different.

FLAVIA FEDELES, MD, FAAD: Wow, that's wonderful. I think you pretty much answered my next question, which was about the topicals. I think, in my clinical practice, and I'm sure a lot of people have the same experience, where some patients still have that fear of using injections, and we do keep going back to the topicals, and it is nice to have extra options for those particular patients that perhaps they just really don't want to use a biologic. And I think an oral medication would be fantastic, so I'm looking forward to see the Phase 3 trial for that IL-23 receptor oral medication. I think that definitely can potentially be a game changer, just being the oral route of administration.

--We are really approaching here the end. Can you comment about maybe crossover implications for other inflammatory diseases? I think you mentioned hidradenitis, and I think there are a couple of other inflammatory conditions that are immunologically or pathogenically a little bit similar to psoriasis. Can you comment a little bit about that?

BRUCE STROBER, MD, PhD, FAAD: I can, yeah. Essentially, any broadly-acting JAK kinase inhibitor treats not only psoriasis, but also atopic dermatitis, probably HS, though maybe we need to be careful about that comment. There will be, without question, JAK inhibitors approved for hidradenitis suppurativa in the next five years, which will be amazing because we need more treatments for that disease, of course. IL-17 inhibitors will also be approved shortly for HS, because they work, and we're going to get a whole raft of various IL-17 inhibitors, so maybe varying potencies, different molecular structures.

--Psoriatic arthritis, while not typically thought of as a dermatologic disease, we should be thinking about it in patients with psoriasis. Perhaps all of these medications, to some extent, will have efficacy in psoriatic arthritis, but there'll be varying efficacy depending on the MOA, which we've already learned through past experience. And it's very exciting to see that a lot of these drugs I'm discussing may be applied not only to atopic dermatitis but to rarer disease states that

nevertheless involve inflammation of the skin. For example, and I'm probably going a little off the reservation here, it's not exactly psoriasis, but diseases like granuloma annulare, necrobiosis lipoidica, blistering diseases, urticaria, prurigo nodularis, some of these rare entities that are vexing, but I think, ultimately, some of the pathways I just discussed will be appropriate for treating these other diseases.

--I already do a lot of off-label use of JAK inhibitors for these very rare conditions and just have resounding success for many patients. The only challenge is access of the drug for those patients when it's not on-label. But, ultimately, 10 years from now, it's a good way to finish this conversation, Flavia, 10 years from now, I think all these medicines are going to just completely change how we do medical dermatology, as long as providers are willing to use them, because you see inflammatory skin disease and psoriasis is now going to be the least challenging, and we're going to bring to bear some of these same MOAs for more challenging conditions and have great confidence, and you walk into the exam room with patients who are suffering and feel just as confident in 10 years as we do now with psoriasis. And that will be actually a quite historic moment, and quite different from when I first started practicing.

FLAVIA FEDELES, MD, FAAD: Yes, that is true, and thank you for that point. Just to wrap things up, just one or two takeaway points for our listeners, what would you like them to remember about this topic?

BRUCE STROBER, MD, PhD, FAAD: Well, I think keep learning about the novel medications coming to the fore, getting approved. I really like to emphasize JAK kinase inhibition and TYK2 inhibition as something providers should really take the time to learn. There's so many different ones and indications, of course, alopecia areata, atopic dermatitis. Get to know some of the follow-on biologics that block IL-13 and IL-4 and IL-13, and then there's going to be a whole range of drugs for atopic dermatitis that I can't even discuss in this conversation.

--It's hard to keep track of all of these medications, but do your best. I think you really still should be on a steep learning curve. You're not even close to where you probably need to be to know it all because there's so much, but the more you know, the more you can help patients instead of throwing up your hands and saying, "I can't do anything for you." It's really the opposite now, as long as you know all the possibilities out there.

FLAVIA FEDELES, MD, FAAD: Thank you so, so much, Dr. Strober, for these insights into the pathogenesis of psoriasis and the novel pathways in psoriasis. Thank you so much for joining us today on Dialogues in Dermatology.

--Again, in closing, this is Dr. Flavia Fedeles interviewing Dr. Bruce Strober from Yale University School of Medicine. Thank you for listening. Thank you.

BRUCE STROBER, MD, PhD, FAAD: Thank you.