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From Pathophysiology to Therapeutic Progress: TYK2's Significance in Plaque Psoriasis

Dr. Chovatiya:
Tyrosine kinase 2, or TYK2, plays a central role in the pathophysiology of psoriasis, and a new therapy called deucravacitinib is now available for patients with moderate to severe plaque psoriasis. So the big question is: What should we know about the safety and efficacy of this treatment?

Welcome to *DermConsult* on ReachMD. I'm Dr. Raj Chovatiya coming to you from Chicago, Illinois. And joining me today to discuss this treatment for patients with moderate to severe plaque psoriasis is Dr. George Han. He's an Associate Professor in the Department of Dermatology at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell in Uniondale, New York.

Dr. Han, welcome to the program.

Dr. Han:
Thanks for having me.

Dr. Chovatiya:
So to start us off, could you explain the role of TYK2 in psoriasis?

Dr. Han:
Yeah. I mean, it's so interesting because we've learned a lot about psoriasis in the past 20 years or so, and most of it has come around thinking about what are the immune mechanisms behind psoriasis. And actually, interestingly, we had gotten a couple of things wrong, not majorly, but among them TYK2 was actually discovered quite some time ago, well over 10 years ago, and I don't think we fully understood the impact of this important molecule—an interesting one also—in the pathogenesis of psoriasis. And it was around here that we found that IL-12 and 23 seem to be kind of the central role in psoriasis in terms of just propagating the rest of the inflammatory cascade, and by signaling through the Th17 cell and producing IL-17, that's how we get psoriasis, and that's usually how we think about it.

But a couple of nuances have developed in the past decade or so, which is, number one, it seems like IL-23 really is the central mediator. IL-12 actually doesn't have so much to do with it. But in terms of looking at what actually happens in the Th17 cell, that's where a lot of interest has been because we have mechanisms that we can target—for example, the free-floating antibodies—and there's different ways that we look at blockade of these different mechanisms. Right? So we have antibodies such as the biologics—as I mentioned, kind of free-floating antibodies targeting cytokines—but then you have other mechanisms like TYK2, which are involved in signal transduction. So when you think about where TYK2 falls in, I think the best way to think about it is it is the signaling mechanism whereby both IL-12 and 23 signal through the Th17 cell to create more IL-17, so I think that's probably the simplest way to look at it, but it's a little more complex because TYK2 belongs to the Janus kinase family. And of course, we know there's JAK1, 2, and 3, and also TYK2. One of the interesting things about this general family is that a lot of cytokines signal through some combination of these Janus kinases. Right? So they can actually heterodimerize or homodimerize, meaning they actually have to always function in pairs, but they can combine in different pairs, and based on this, that's where you get the signaling through the STAT pathway and subsequent gene expression.

Now what's interesting about TYK2 is that contrary to the Janus kinases JAK1, 2 and 3, you actually only have a very narrow spectrum of signaling through TYK2, meaning there's about at least 60 or 70 known cytokines that signal through this family of kinases, but for TYK2, really it seems to be very narrowly focused on a few immune mechanisms, and so that's the IL-12/23, but it's also type 1

interferons, or interferon-alpha, beta are the most kind of commonly and well-understood ones in that family. But when it comes down to it, the TYK2 kind of sits on the cell surface, and it propagates that signaling from either IL-12 or 23 to then activate the signal transduction of IL-17.

So it's kind of interesting because if you look at any of these pathway figures of psoriasis, you'll have IL-23 with an arrow to the Th17 cell, with an arrow to IL-17, but underneath the hood in that Th17 cell has always been kind of a black box until now. And so this pathway of TYK2 has been developed, and it's really interesting that the FDA was able to allow this to be a completely new mechanism and thereby distancing a little bit from the traditional JAK inhibitors that we know of and I think it's important that that distinction is made both mechanistically and in terms of how we actually target TYK2.

Dr. Chovatiya:
That sort of leads us to deucravacitinib, our first approved TYK2 inhibitor that we have available to us in the clinic, and this one's approved for moderate to severe plaque psoriasis. We've had it for a little while now. Maybe you could just kind of review safety and efficacy to start with for me.

Dr. Han:
Yeah. So deucravacitinib has really been kind of the leader in this realm because it's our first TYK2 inhibitor. It's available as an oral small molecule. And I think there's a couple of important things. Thinking about TYK2 inhibition as a mechanism into immune-mediated diseases I think is really important. And so, the idea then is that you have to very narrowly target the specific mechanism because if you have a medicine that targets TYK2 but also has off-target effects on like other Janus kinases, then we really haven't accomplished very much because we have this narrow pathway now; but if we're still blocking these mechanisms that are important in producing red blood cells, platelets in lipid metabolism, then you haven't really accomplished very much, so I think that's where this specific mechanism of deucravacitinib is really interesting.

What's really unique about deucravacitinib is that it's an allosteric inhibitor, so rather than functioning as a competitive inhibitor at the ATP binding site, you're actually binding to the regulatory domain, and those binding sites are actually very different among each kinase. So you have this allosteric inhibitor that they're actually able to design much more selectivity for just TYK2, and then that changes the confirmation of the ATP binding site. I know this is like kind of very heavy basic chemistry, but I think it's a concept that we hopefully all remember to some degree. So when you attach the allosteric inhibitor, I think the key here really is that on the regulatory domain, this binding site is actually quite different among all the different kinases, and that really, I think, drives home the point that deucravacitinib on any assay that's ever been tested—you're talking about either in vitro, whole blood IC50 values, you're looking at plasma concentrations over time in an in vivo model—you're actually way below any threshold that you would actually be significantly blocking JAK1 or 3 and even farther below anywhere where you'd be JAK—blocking JAK2, which is actually kind of the one that we're all a little more scared of, if anything.

But, of course, we need to know about the safety. Right? And I think that's where also I think so far everything has been mostly reassuring. When you look at the adverse event rate versus placebo, there's nothing that really we don't expect from any of our immune-mediated mechanisms. In general, all of our treatments for psoriasis carry the small increases in nasopharyngitis and upper respiratory tract infection, so these kinds of minor infections, and here it's within par for the course, meaning we are within a few percent of placebo so not really a strong signal there. But one of the interesting things about an oral molecule is that we have to make sure it's well tolerated. It's a little different in that sense from the biologic, for example, where the name of the game is like injection-site reactions. In terms of tolerability here, we want to see low rates of diarrhea, nausea, things that might make our patients not want to take the medicines, and here, actually the rates are very low, similar to placebo, and actually a little lower in some cases, so not really much jumping out at us in terms of any adverse events that we really need to be concerned about.

The longer-term data looking at one year and beyond so far looks very good. The lab parameters for the most part stayed within normal but has a lot of promise in our treatment arsenal for psoriasis.

Dr. Chovatiya:
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. George Han about a recently approved drug for patients with moderate to severe psoriasis.

Now, Dr. Han, could you tell me a little bit more about how you think we could work better with our psoriasis patients to choose the best treatment option now that we have another entrant, this time an oral one, into our already very deep armamentarium for psoriasis?

Dr. Han:
I think we're in a really good time for treatment of psoriasis for patients because we have so many choices, but it also becomes a little confusing and sometimes takes a lot of time to go through all of the options. You know, not only do we have newer topical medicines,

new mechanism in that realm, we have so many biologics, and we have new oral options. We're talking about very modest efficacy rates for medicines like apremilast. But with the coming of deucravacitinib, I really feel like being able to offer this to my patients and giving them good confidence that they can achieve high levels of clearance has really made an impact.

And, you know, I tend to always go through kind of the whole spiel in some way, and I've been surprised how many people just say, "Let me start with the oral medicine." And I think they just think of it as less invasive, as something they're more used to, and as such they're more comfortable with it. And I think from a mechanistic standpoint also, when you think about one of the things that happens normally with our psoriasis patients, is they kind of stop wanting to inject themselves, or you start to think about antidrug antibodies. That really doesn't happen with small molecules. So if patients forget to follow up and they run out of medicines and the psoriasis starts coming back, it's actually less of a theoretical concern for me to put them back on an oral small molecule than, for example, biologics, so I think there are a lot of strengths that are capitalized upon in an effective oral molecule like deucravacitinib.

Dr. Chovatiya:
Well in the last moment, maybe you can tell me, looking to the future, is there anything specifically that you are really excited for your psoriasis patients when it comes to moderate to severe disease?

Dr. Han:
I think there's still a lot of interest and a lot of research happening in psoriasis. You know, we've got more biologics coming, more oral small molecules, but I think the biggest impacts are going to come probably in two areas. One is we need more effective medicines in psoriatic arthritis. And the second one is really targeting and thinking about the comorbidities of psoriasis and figuring out what our treatments have to do with our patients' other domains of health. Right? We know that our psoriasis patients are at higher risk of many things that are involved in metabolic syndrome, cardiovascular events, and negative outcomes, and that has to do with the severity of psoriasis too. So what can we do for our patients that really can help them not just with their psoriasis but live a healthier life?

Dr. Chovatiya:
Well as those are the final thoughts, that brings us to the end of today's program. I really want to thank my guest, Dr. George Han, for sharing his valuable insights on new treatment for psoriasis patients. Dr. Han, thanks so much for joining me today.

Dr. Han:
Thanks for having me.

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.