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Unlocking the Potential of TYK2 Inhibitors in Plaque Psoriasis

Announcer:
You're listening to *On the Frontlines of Psoriasis* on ReachMD. And now, here's your host, Ryan Quigley.

Ryan:
This is *On the Frontlines of Psoriasis* on ReachMD. I'm Ryan Quigley, and today I'm joined by Dr. Christopher Bunick to explore the evolving role of TYK2 inhibitors in treating moderate-to-severe plaque psoriasis. Dr. Bunick is an Associate Professor of Dermatology and Translational Biomedicine at Yale University School of Medicine.

Dr. Bunick, thank you so much for doing this. Really appreciate it.

Dr. Bunick:
It's a pleasure to be here. Thank you for having me.

Ryan:
So, Dr. Bunick, for some background, how do oral therapies currently fit into the treatment landscape for patients with moderate-to-severe plaque psoriasis?

Dr. Bunick:
Well, we've generally thought about or classified psoriasis patients into a mild, moderate, or severe category. However, there's a shift in dermatology to how we think about psoriasis patients as a whole towards topical eligible or systemic eligible, with systemic eligible meaning a body surface area greater than 10 percent involvement or involvement of high-impact areas, which could be the scalp, the palms, the soles, or the genitals, or having failed topicals. And actually, just recently, in 2025, we had the International Psoriasis Council come out and tell us its definition of what topical failure is, and they defined it as two consecutive four-week periods of using a topical therapy for psoriasis but not achieving clear or almost clear skin.

So this is really helpful for practitioners trying to decide, "Do I want to go to a systemic therapy? Is my patient eligible for systemic therapy?" And the ultimate answer is that any systemic-eligible patient is eligible or could benefit from an oral therapy. And overall, they generally have a little bit lower efficacy than our biologic therapies, and this has limited their use right now towards milder phenotypes of psoriasis, those who prefer orals, or those who have some contraindication to the injectable biologics.

Ryan:
Thank you for that. And the TYK2 inhibitors, like deucravacitinib, and the investigational agent, zasocitinib, are generating a lot of interest. What should we know about this class?

Dr. Bunick:
I'm going to walk you through four key areas that I think are important to know, and the first is just understanding the basic signaling pathway that the TYK2 inhibitors are working in. We hear so much about the IL-23/IL-17 axis in psoriasis, and the reality is that IL-23 signals outside the cell by binding the IL-23 receptor, and then there are signals that cross the membrane into the cell, and then machinery in the cell propagate that signal to impact transcriptional programs in the cell. And the TYK2 protein, which happens to be a phosphorylating kinase, sits inside the cell. And much like what we hear about in atopic dermatitis where the biologics are working outside the cell, either targeting the receptor or the cytokine, and the JAK inhibitors are working inside the cell targeting the signaling machinery inside the cell, the same thing happens for TYK2 inhibitors in psoriasis. They are a JAK family protein, and therefore, they are working inside the cell, and that impacts how rapidly they can work and potentially how they can shut down multiple signaling

pathways.

And I think that is one of the key differentiating factors of TYK2 inhibitors. Not only can they hit the IL-23 pathway, like all the IL-23 biologics, but they also have the ability to hit IL-12 signaling. And that is really important for some patients who have a lot of innate drivers of their psoriasis through this IL-23 independent signaling. So being able to hit multiple pathways is one key differentiating factor or important factor for the pathophysiology of the TYK2 inhibitory mechanism.

The second, when we think about inhibition of TYK2 inhibitors, is the allosteric nature in which they work. When we think of JAK1/2/3 and TYK2, they all work by having a kinase domain, which can phosphorylate, and next to that is an allosteric or regulatory domain. And what differentiates TYK2 inhibitors from the current JAK inhibitors in dermatology and elsewhere in immunology, rheumatology, et cetera is the fact that they work by hitting the regulatory allosteric domain. This gives them more precision and selectivity.

And that's the third key point: selectivity. What really makes zasocitinib unique is that it is selective for this allosteric or regulatory domain of TYK2 much greater than the JAK1 regulatory domain, and it's over one million-fold more selective for that TYK2 regulatory domain over the JAK1 compared to deucravacitinib. And that is the difference between the first-generation deucravacitinib and the next-generation zasocitinib TYK2 inhibitor.

So the fourth and final key point that I want to emphasize is the differences in the pharmacokinetics properties of TYK2 inhibitors. We generally think about IC50, or what's known as the half-maximal inhibitory concentration, so that concentration to inhibit the enzyme at a 50 percent level. When we think about zasocitinib, one 30 mg dose over 24 hours completely maintains a concentration above the IC50 level for all 24 hours of a day. This compares to only six hours for deucravacitinib. So what does this mean clinically if you're going to talk to a patient? Think about it in terms of the percent of total daily inhibition of your TYK2 enzyme. And the reality is that zasocitinib can inhibit TYK2—about 91 percent of all TYK2 inhibition throughout a 24-hour period—whereas deucravacitinib can only do 23 percent based on these pharmacokinetic properties.

Ryan:
And compared to other treatment options, how do these TYK2 inhibitors perform in terms of PASI response, onset of action, and long-term durability?

Dr. Bunick:
Let's first start with deucravacitinib, and I'm going to focus on week 16 data, which was the primary endpoint in these phase 3 trials for deucravacitinib, apremilast and zasocitinib, the three oral therapies that we're going to talk about. At week 16, deucravacitinib, around 34 percent of patients achieved PASI 90, and over a course of going out to a year, it increased to around 50 percent. What about PASI 100? Well, at that week 16 time point, the deucravacitinib was able to achieve in about 12 percent of patients that PASI 100 level, which increased to around 20 percent by the end of a year. Compared to apremilast, well, it turns out apremilast was only able to achieve PASI 90 in about 20 percent of patients at week 16.

In the case of zasocitinib, in terms of its phase 3 efficacy, over 50 percent of patients achieved PASI 90 at week 16. That positioned zasocitinib for potentially best in oral therapy in psoriasis. And almost 30 percent of patients achieved PASI 100 at week 16. So that's better data than deucravacitinib and apremilast, and it's basically right on par exactly with, if not slightly ahead of, the oral IL-23 receptor peptide inhibitor that is being developed as well, so these are very exciting developments in the oral space. Now, how would that compare to potentially a biologic? Well, just to provide some comparison to the week 16 data to risankizumab, 75 percent of patients achieved PASI 90 around week 16, whereas in about 47 percent of patients achieved PASI 100.

So I think that, yes, we're dealing with two different entities here, oral therapies and biologics, but what we're seeing is a great improvement in what oral therapies can do in psoriasis.

Ryan:
For those just tuning in, you're listening to *On the Frontlines of Psoriasis* on ReachMD. I'm Ryan Quigley, and I'm speaking with Dr. Christopher Bunick about how TYK2 inhibitors can play a role in moderate to severe plaque psoriasis management.

Now, Dr. Bunick, how might TYK2 inhibitors align with patient preferences?

Dr. Bunick:
Well, this is one of the wonderful things about caring for other people—you realize no two people are the same, and people have very different preferences for different reasons. We've heard over the last two or three years a lot of reemergence of the concept of shared decision making, and I think that that's a fancy modern way of just saying good doctoring—just being that doctor who cares for your patient and listens to the patient and makes decisions with the patient.

And when it comes to some of the preferences that I've seen in my clinic in psoriasis, there's definitely a subset of patients that want an

easy-to-use pill, and the reality is having a pill once daily, especially if there's no laboratory monitoring and no significant side effects, works very quickly and deeply in terms of relieving the plaque psoriasis. The easy-to-use pill is a big one. Patients want strong efficacy and strong safety, and I think that the oral therapeutic space in plaque psoriasis is headed that way. It's taking a leap with zasocitinib, and I think that that is something patients are going to welcome.

And the last point I want to make on this question is patients want therapies that make them healthier, and what I mean by that is it's not always just about the skin. So there are going to be patients, as well as potentially providers, who say, "Why do I want to inhibit TYK2? Is it potentially dangerous to inhibit TYK2 in my patient?" This is one of the rare targets for therapeutics in psoriasis where there is a natural mutation in part of the population. So a certain percentage of the world population carries a mutation in TYK2. It's a proline to alanine amino acid substitution. And it actually decreases TYK2 activity by 70 to 80 percent. And what do we find in these patients? They're healthier. It actually decreases autoimmunity. It decreases inflammation in these patients. They have lower risk of psoriasis, psoriatic arthritis, and other diseases, including multiple sclerosis, lupus, and many others.

Ryan:
Dr. Bunick, what practical considerations should clinicians keep in mind with these agents?

Dr. Bunick:
For me, the single biggest important thing is if you're going to use an oral therapy, you have to stress compliance, and that is because when you inject someone and you can not think about it for three months, that medicine's working in them. That's in part due to the long half-life of the biologics, which can be around four weeks, for example, such as for risankizumab, whereas the half-lives for a lot of the oral therapies, such as deucravacitinib or apremilast, is around 10 hours. And I think zasocitinib's half-life is projected somewhere around 20 to 24 hours. So with those shorter half-lives, if you miss a dose, that drug's out of your system because of the way the half-life is and the elimination of the drug from the body.

As part of my counseling to patients, I would be very cautious to make sure I emphasize compliance, that this is a drug you do need to take. The advantage is it's just once a day, not twice a day, but at the same time, if you don't take your medicine, there is a good chance that the psoriasis could flare.

Ryan:
Now, Dr. Bunick, before we close, I'd like to look ahead for a moment. What should clinicians be watching for as the treatment landscape for moderate to severe plaque psoriasis continues to evolve?

Dr. Bunick:
For me, one of the most important areas in psoriasis—and this is really true for a lot of inflammatory skin diseases, including atopic dermatitis—is the overlap with systemic inflammation and the fact that plaque psoriasis is not just about the skin. It is also about other ways in which the systemic inflammation of psoriasis is affecting other tissues. So for example, when I see a patient, I'm not just thinking, "Oh, they have plaque psoriasis; I'm only going to treat the skin." And I think this is one of the reasons I think topical therapy alone for the vast majority of psoriasis patients is not adequate—it's not going to address the systemic inflammation. So I'm asking patients about their joints. Are they having joint pain? Is there psoriatic arthritis? And I'm also asking them about other things, like cardiovascular risk factors and metabolic risk factors.

One of the things that we know now scientifically is there's a significant overlap between the psoriasis genes and atherosclerosis genes. So the overlap between psoriasis and atherosclerosis genes really links psoriasis and cardiovascular disease and the mechanisms behind them. And we're finding with newer studies that come out that there's actually also increases in atherosclerotic risk in, for example, moderate-to-severe atopic dermatitis. And to me, that is where I think the landscape for future treatment needs to evolve. Are we as dermatologists going to have to play more of an internal medicine-type role in managing the overall cardiovascular atherosclerotic risk of our patients?

And I think that this is a very important concept to pay attention to because, at least for me, when I practice medicine, I'm not just trying to treat the patient's skin and forget about the rest of them. I'm really trying to do what's best for the whole patient, because imagine you're the patient and you have a doctor in front of you—do you want the doctor to dismiss all the inside stuff that they know could be going on and that they could help benefit you by addressing?

So I think that this is an evolving area, and I'm very excited to see where the treatment landscape goes and where our understanding of systemic inflammation goes in diseases like psoriasis.

Ryan:
That's an excellent point, and I think that's something that just about any clinician can utilize as they care for their own patients, so thank

you very much for that, Dr. Bunick.

And as we come to the end of today's program, I do want to thank my guest, Dr. Christopher Bunick, for joining me to share his perspective on TYK2 inhibitors for moderate to severe plaque psoriasis. Dr. Bunick, this was wonderful. Thank you so much for doing this. Really appreciate it.

Dr. Bunick:
Thank you for having me. It's been a pleasure.

Announcer:
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