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JAK Inhibitors for Atopic Dermatitis: Who's an Appropriate Patient?

Announcer:
You're listening to *DermConsult* on ReachMD, and this episode is sponsored by Pfizer. And now, here's your host, Dr. Raj Chovatiya.

Dr. Chovatiya:
Welcome to *DermConsult* on ReachMD. I'm Dr. Raj Chovatiya. I'm a Clinical Associate Professor at the Rosalind Franklin University Chicago Medical School and Founder and Director of the Center for Medical Dermatology and Immunology Research in Chicago, and today I'm joined by none other than Dr. Jason Hawkes to discuss how we can select appropriate patients with atopic dermatitis for JAK inhibitor therapy. Dr. Hawkes is a board-certified dermatologist and Co-Owner, Chief Scientific Officer and Investigator at Oregon Medical Research Center in beautiful Portland. Dr. Hawkes, thanks for joining us.

Dr. Hawkes:
Thanks for having me, Raj.

Dr. Chovatiya:
So before we dive into some of the specifics behind your views on patient selection, can you tell us how JAK inhibitors play a role in atopic dermatitis management in today's day and age?

Dr. Hawkes:
Yeah, I think this is really in contrast to where we've been. We've had these broad-acting immunosuppressants, like methotrexate and cyclosporine, and we had this rapid advancement with these targeted "snipers" of the immune response hitting key cytokines. But those cytokines are working through these cells by activating an intracellular signaling process through the JAK-STAT pathway. And what's interesting is that this is a pathway that's really redundant, meaning that it has overlapped a lot of the more than 50 cytokines that are really working through the same intracellular pathway. So blocking one of these enzymes—JAK 1 or JAK 2 for example—has a much broader impact on the immune response than some of the biologic therapies. And so this is really central to the immune response as it's going to mediate a lot of the cytokines. So blocking this pathway is going to have a broad impact. Particularly with the JAK 1, 2, and 3 inhibitors, we're seeing a broad impact on TH1, TH2, and some other cytokines, but not so much the Type 17 pathway we see with TYK2. These are going to be broad-acting medications in terms of inhibiting the immune response, so it makes sense why we see their benefits in a lot of diseases such as alopecia areata.

Dr. Chovatiya:
Yeah, it's amazing how far we've come in such a short period of time when thinking about how broadly and off target we really had to suppress our patients to get a reasonable response versus now. We can actually be broad but very specific at the same time. And with that in mind, what types of factors do you take into consideration when thinking about who the right patient is for JAK inhibitor therapy?

Dr. Hawkes:
I think when we talk about a lot of our patients who are straightforward and who have uncomplicated disease—whether it's skin disease or alopecia areata, for example. —those patients that are straightforward have a lot of options. And we know that there's multiple therapies that can effectively achieve the same thing, which is to calm down the immune response that is driving the clinical features. These can be used appropriately as monotherapy, right because they do the action, which is taking away the dysregulated immune response to restore that balance back, letting the skin get better and letting the hair start to regrow.

But I think there's another advantage for this class. And you know as well as I do that we see these patients who don't fit nicely into a bucket, or they have multiple diseases. And some of the targeted therapies miss the target, where they work for one component, but

they're not really holistically treating the patient. So one of the real advantages to this class is that because they have broad impact, we have different endotypes or subgroups of patients that don't have a predominant cytokine but might have multiple cytokines driving disease. And for more of these diseases that are more complex, they have multiple pathways; with one medication, we can block multiple pathways. So I think about this class in particular having an advantage for the messier patient or the one who is a little more clinically ambiguous, in addition to being able to work well. And for the monotherapy, they're very straightforward textbook cases.

Dr. Chovatiya:
Yeah, it's this idea of trying to figure out the right patients that has been a challenge for a lot of folks. And let me point out a couple of common patient archetypes that we've seen some data for with JAK inhibitors, and I'd love to get your thoughts. Two that come to mind are, of course, patients that have prior treatment failures on other therapies, and thinking about a more recently described class of patients, these folks with more itch-dominant disease in the atopic dermatitis world, where the severity of their itch may be out of proportion to their clinical skin involvement on exam.

Dr. Hawkes:
When we start talking about the speed of onset, that's really one of the main value props of this class of medications. One, it's convenient for patients who don't want an injection, but two, they have this rapid onset, this fast action. And certainly, we have those patients where they don't even want to move on to an injectable therapy. They'll say things like, "Oh, I'm not that bad. I don't need an injection yet." So the pill, to many of them, feels like that transition into, "I'm not bad enough for injection, but I can get on a therapy that can work quickly." And each will respond well in a lot of these patients. It does work with some of the targeted agents. But again, the advantage here is that we are having a more complete suppression of the immune response without being broadly immunosuppressant. So, not surprising, we can hit some of these other pathways that drive itch, so it may not be that canonical driver of the skin component.

Dr. Chovatiya:
And really doubling down on this idea of challenging clinical situations, you talked about this idea of patients with comorbidities. Can you tell me a little bit more about that, and is that something that the average dermatologist should be aware of when it comes to thinking about therapeutic selection? How often is this something you see, and how does that really play into your choice of therapeutic selection for the atopic dermatitis patient?

Dr. Hawkes:
The issue we're really talking about in selection of therapy is that, if you're talking about one disease, there's multiple options in terms of therapies. That's not true with every disease—we have some that have just a limited number of medications that are approved, but for patients, we're trying to simplify their lives.

So treating two or three diseases independently with different medications doesn't help the patient. It's expensive, it's complicated, they miss pills, or they mix things up. So if we can look at therapies where we can give one medicine that can hit multiple pathways and potentially has benefit for multiple diseases, this is one of the advantages of this class over some of the biologic therapies because some of the biologic therapies work well for some of these type 2 comorbidities, but not all of them. And I think a good example is I just had a patient recently that had atopic dermatitis, vitiligo, and alopecia areata. The targeted therapies that would work for the skin disease probably aren't going to work for those other conditions, and so here's a class where now it makes sense. We talked about type 1 inflammation also being mixed with type 2 inflammation—that with the JAK1, JAK 1/2 inhibitors, we're going to see benefit. So we get the advantage of having a little bit more versatility in managing these comorbidities, which are actually more common than not.

Dr. Chovatiya:
For those just joining us, this is *DermConsult* on ReachMD. I'm Dr. Raj Chovatiya, and I'm speaking with Dr. Jason Hawkes about his experience in selecting appropriate candidates for JAK inhibitors to manage atopic dermatitis.

So Jason, once you identify an appropriate patient for this particular therapeutic approach—you're going to go all-in on a JAK inhibitor—what are some of the key strategies that you employ in your real-world clinical practice when it comes to thinking about how to start therapy and maybe more chronically manage therapy?

Dr. Hawkes:
I like to start with triaging the patient. So is this a patient who's had annoying, longstanding chronic disease that's not in the severe acute flares, where they just want relief, they want to move on from topicals, or they're frustrated with the inconvenience of phototherapy, for example? Those are patients where we don't have an urgency; they just want to get something that's going to work well and get relief. So there, we don't have the timetable working against us, and so we have that conversation. It's perfectly reasonable there to start low and see how you get a response. We're going to know quickly; again, the advantage of this class is its fast onset of action. Once they get better, then we can hold that dose, or we have the ability to up-dose. We can increase the dosing for them to see if we can get more

adequate response if they've had an incomplete response. We also have that ability to say, “We can do the opposite. We could get you better very quickly with a higher dose and then back down.” There's been this idea that maybe some of these patients could be on therapy intermittently—that we use it for a short period of time, then stop it.

I think that's a little hard because it's counterintuitive to our patients; we're telling them, “You have a chronic disease, but you don’t need to treat it all the time.” So I don’t tend to employ that approach. Patients do ask, though, “How long do I have to be on the medication?” And I mention that you can stop the medication at any time, but your disease is very likely going to come back. So that's the downside there.

So I like to triage; is this is someone who I need to get better very quickly, who I need to keep out of the hospital or ER, or they’ve had a severe flare? Is this someone who’s had multiple infections, such as secondary skin infections? Or is this a patient who’s just looking for a therapy that's going to work, and we know that they're going to get better for the most part? The probability that people clear with this class of medication in multiple diseases is actually very high. So I like to set the tone that we're going to see a fast response and we have the ability to turn up the dial if we need to. We can back off if we need to, a little bit, if you’re doing well on a lower dose. But really, we want to manage this long-term chronic disease because that's most likely what you’re dealing with.

We then move into the next phase of management, which is, “Now what?” So we’re talking about those patients that, again, are older and higher risk; maybe they've had a history of herpes infections or shingles. When I think of the most recent AEs that I've seen here with our patients, they’ve actually been our older patients who’ve had pretty severe shingles or zoster. So we want to have that conversation, right? We want to prep them before getting the live vaccinations, getting other medications in place and stable before we start. It’s a little bit different from our younger group. But again, we’re looking at comorbidities and risk factors.

Obviously, with pregnancy and lactation, we're having that conversation. We're talking about cholesterol, and we're talking about watching for infections, which is obviously the main risk with this group. Blood clots, right? We're triaging to say, are these appropriate patients? But we're also making sure that we're monitoring some of these other components of their health just so that they understand that while this medication has a broad-acting impact, it comes with some strings attached. They’re lower-risk overall. We’ve seen good data showing that, but we still need to pay attention. So it moves them, and I try to not throw too much of that up front because I think it overwhelms them. We get them clear, we get them seeing the benefit of the medication, and then we start watching the long-term management and maintenance. And that's the way I try to walk patients through the part 1 and part 2.

Dr. Chovatiya:
So as we approach the end of our program, Dr. Hawkes, how have you seen JAK inhibitors truly impact your patient's quality of life?

Dr. Hawkes:
We have these patients who have suffered for years, and some therapies for them have either been inconvenient or just been inadequate, right? They’ve had a significant improvement, but not enough to take away the impact of the disease. So what we've seen with the JAK inhibitor class is that it worked for those patients where things just didn't seem to follow the typical rules or fall in the regular buckets; they were more ambiguous clinically. We've been able to clear those patients when other therapies didn't work. We’ve been able to give patients really rapid relief. Contrary to a lot of what our specialty talks about, there are still a lot of patients who prefer oral pills, so this is giving patients options for therapies that fit their lifestyle or their preference. And we're now really picking up diseases that, through my training as a resident, medical student, and even early career faculty, we didn't have good options. So it's great to talk to these patients that come in that have these conditions that we can offer a therapy for and make sense as to why it would work. And so I think this has brought hope to the community in general.

Dr. Chovatiya:
Thanks so much for sharing your experience and I truly want to thank you, Dr. Hawkes, for talking about your perspective on how you select the right patients for JAK inhibitors when managing atopic dermatitis. It was so great having you on the program.

Dr. Hawkes:
Yeah. Thanks for having me. It’s always a pleasure.

Announcer:
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