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Reviewing the Role of JAK Inhibitors in Atopic Dermatitis

Dr. Keller:

As the most common type of eczema, atopic dermatitis is a chronic inflammatory skin disorder that affects millions of people worldwide. And although it's a complex disease with no cure, the FDA recently approved 2 oral JAK-1 inhibitors for patients with mild severe symptoms. So what do we need to know about these new treatment options?

Welcome to *DermConsult* on ReachMD. I'm Dr. Matthew Keller. And joining me today is Dr. Shawn Kwatra, Associate Professor of Dermatology at Johns Hopkins University School of Medicine and Director of the Johns Hopkins Itch Center.

Dr. Kwatra, welcome to the program.

Dr. Kwatra:

Thank you so much for having me here today.

Dr. Keller:

So to start off with some background, Dr. Kwatra, can you briefly explain how atopic dermatitis affects the skin? And what are the current treatment options available?

Dr. Kwatra:

Sure, absolutely. So atopic dermatitis is a chronic inflammatory skin disorder. It affects millions of people across the United States and around the world. And what happens in atopic dermatitis is patients get these red, itchy areas on the skin, most commonly on the extremities, the trunk, but it can also affect the face. The first systemic treatment for atopic dermatitis that was FDA-approved recently was dupilumab in 2017, and before that time, we had very poor data for many of the therapies. And patients are usually managed with topical steroids locally, and dupilumab was one of the safer options, but recently, we have had 2 oral JAK inhibitors approved and also a topical JAK inhibitor approved, and so it's changed the landscape tremendously.

Dr. Keller:

Now with that background in mind, let's zero in on the new JAK-1 inhibitors. How do they work, and how are they different from other therapies?

Dr. Kwatra:

That's a great question. So what we've learned about atopic dermatitis is it has a certain portion of the immune system that is highlighted. And so eosinophils are allergic cells in your blood, and what we find is patients who have atopic dermatitis often times have more of these allergic type of cells, and they have a type of immune dysregulation. We call it the Th2 type. And so that was the basis for the monoclonal antibody dupilumab, which was first approved in 2017, is that it targeted very specifically—almost like a missile attack—some of the cytokines or inflammatory mediators that cause this disease.

Now dupilumab is an injection. It's given every couple of weeks. And these new therapies that are approved are oral JAK inhibitors, and they target the similar cytokines, but they also target other mediators that are involved in itch pathogenesis. So I'll name them—the different cytokines are IL-4, IL-13, IL-31 and IL-22. So what we're finding is that these JAK inhibitors have very rapid itch relief. In a matter of hours to days, patients start to feel better. And so they take advantage of a mechanism that we knew about, but they are able to modulate multiple pathways that are involved in atopic dermatitis pathogenesis.

Dr. Keller:

Now based on what we've learned from clinical trials, what are some of the benefits patients might experience with these JAK-1

inhibitors?

Dr. Kwatra:

So one of the benefits is it's an oral therapy. Some patients are averse to doing injection therapy. For those patients this would be a great option. There's also an advantage with itch relief. Itch relief tends to happen very quickly with oral JAK inhibitors. Dupilumab and other agents can also reduce itch, but sometimes it may take a little bit more time. Finally, oral JAK inhibitors actually are more targeted than some of the nonspecific oral agents we had been using before, such as methotrexate or cyclosporin, which were almost entirely nonspecific agents. And so they have a few things definitely going for them in their favor and I think those are the big features.

Dr. Keller:

Great. Now how do we go about determining which of our patients are good candidates for these new treatment options?

Dr. Kwatra:

That is a great question. And, actually, to tell you the truth, we don't fully know the answer. In this past week, I was in clinic, and I was trying to explain the different options in a simple manner, and I found it was actually quite challenging. But the way I like to explain this to patients is "We have to tailor your therapy based on your lifestyle, your preferences, and also your disease severity," and so when I'm explaining these therapies for a drug like dupilumab, it's an injection every 2 weeks, it has excellent safety data, no regular laboratory monitoring, and some of the side effects we see, like eye dryness, are pretty minimal overall. So patients often times know that profile, are open to it, and they are willing to try. Some patients who have tried dupilumab don't respond completely, they have ocular side effects, or they just don't like doing an injection, and I think those patients would be excellent candidates for a JAK inhibitor.

I think we also have to take into mind patients' comorbidities or other diseases that they may have. If a patient has a history of many blood clots, then I would say a monoclonal antibody, such as dupilumab or a recently approved drug, tralokinumab, may be a better option to try first, but if they're overall pretty healthy, I think that both therapies offer good options for rapid relief but it depends on, "Does the patient prefer an injection or oral therapy? Is the patient okay with having some lab monitoring, which you may need on these oral JAK inhibitors to make sure that it's not affecting any of their parameters?"

Dr. Keller:

For those just tuning in, you're listening to *DermConsult* on ReachMD. I'm Dr. Matthew Keller, and today I'm speaking with Dr. Shawn Kwatra about the recently approved JAK-1 inhibitors for atopic dermatitis.

So Dr. Kwatra, if we circle back to the data on JAK-1 inhibitors, are there any common side effects we should look out for in our patients receiving this treatment?

Dr. Kwatra:

So I think we do have some experience with some of these JAK inhibitors for much of their clinical trials. Specifically, upadacitinib has already been approved for another indication as well. Some of the side effects that we do watch out for are sometimes nausea, cough, but in general, there's not a ton of these side effects. Some patients may even have mild acne. I think what's more rare and less common that we watch out for is infections, and so patients will get a baseline tuberculosis test or hepatitis panel to make sure that they don't have any of those conditions. And I think otherwise there's not too many things that are excessively common. We'll have to see, though, the data on these patients in the real world and to see how things evolve.

Dr. Keller:

What do we really need to be counseling our patients on and thinking about when we are prescribing these JAK-1 inhibitors?

Dr. Kwatra:

It is important to realize that patients that need to be put on oral JAK inhibitors will need to have regular laboratory monitoring, and each agent is not the same. But what I would say is most of these patients we're going to have to monitor and make sure they don't have an underlying infection, so we would get a baseline tuberculosis test, a hepatitis panel. These JAK-1 inhibitors may predispose patients to having infections, so patients should be aware of that. There are other JAK inhibitors. In particular, there's one that's approved right now called tofacitinib.

But what I would say is there's a lot of difference between JAK inhibitors. You can't say because one JAK inhibitor has this side effect that this JAK inhibitor necessarily has the same side effect. And these drugs are being taken in vastly different patient populations. So tofacitinib, which blocks JAK-1 but also JAK-3, was noted to have some concern in rheumatoid arthritis patients or patients who have multiple comorbidities. There was a concern about potential thrombosis and other factors. However, when these new oral JAK inhibitors were tested in atopic dermatitis patients, there were not major signals in these categories. But what I would always say in having an abundance of caution is to always let patients know that there may be an increased risk with other agents although that might not necessarily be true for these agents in their eczema trials. And what I would say is you should ask patients, "Do you have a history

of blood clots?" That's important to get a good history for because maybe that would influence which agent you choose or your degree of monitoring. I personally would also ask patients do they have a history of smoking, are they on OCPs, anything that may make patients more likely to have a clotting disorder, also if they have a history of Factor V Leiden, which is a pro-clotting factor. I would also say that changes in kind of blood counts or for abrocitinib platelets and for upadacitinib, you'd also want to monitor some of the labs. What we would recommend is at baseline to get a complete blood count, liver function and a lipid panel and to follow that up about a month after treatment, 2 months later and then every 3 to 6 months, similar to how we do for methotrexate with the addition of a lipid panel, and I think that would be very reasonable monitoring for these patients.

Again, the safety data for these drugs in atopic dermatitis was very clean, and so what I would caution is not to lump JAK inhibitors together in terms of their side effects and to really go through the data and then be able to counsel patients on all the data that we have today.

Dr. Keller:

Now we certainly covered a lot of ground today, Dr. Kwatra, but before we close, I'd like to take a moment to look ahead to the future. From your vantage point, what does the approval of these 2 JAK-1 inhibitors mean for the future of atopic dermatitis treatment?

Dr. Kwatra:

The future of atopic dermatitis treatment is very exciting. What I would say is psoriasis had previously led the way in terms of therapies for dermatologic indications, and now for psoriasis there's about 10 different novel agents. For atopic dermatitis, these patients have been suffering for many years. Dupilumab gave them their first targeted therapy. There's these 2 oral JAK inhibitors that have heralded a new era. We also have another monoclonal antibody, tralokinumab. We have a topical JAK inhibitor that works very fast, similar to topical steroids, called topical ruxolitinib. And then we also have several new agents in development, from monoclonal antibodies, such as lebrizumab to nemolizumab, which specifically targets an itchy cytokine IL-31, and we also have other oral JAK inhibitors.

So what I would say is this is a beautiful time for me to be a provider and also for patients because for a long time these patients have been suffering without good treatments, and now we're going to have a number of options that we can tailor to patients, and if they fail a certain therapy, we can try different therapies.

For the future, one of the things that I have my eye on in some of our work that's funded by the NIH is to look at personalized medicine. So if we have a variety of therapies, are there blood tests or skin tests that can be performed that can help us predict which agent may be the most appropriate for which patient and also factor in some of their comorbidities? The other thing I would say is that atopic dermatitis, especially if it's severe, is associated with systemic inflammation in the blood. Our group showed that these patients, especially those who have sleep disturbance, have increased C-reactive protein levels and other biomarkers of cardiac disease as well, and so what I would say is there's a price to not treating. And so many of these agents can lead to reduction in overall inflammation and many of these other things like sleep disturbance, anxiety, and depression, which a lot of these patients suffer from. So overall, very exciting times.

Dr. Keller:

Those were all great insights into the new treatment options for our patients with atopic dermatitis. And I want to thank my guest, Dr. Shawn Kwatra, for sharing these updates. Dr. Kwatra, it was great having you on the program today.

Dr. Kwatra:

Thanks so much for having me today.

Dr. Keller:

For ReachMD, I'm Dr. Matthew Keller. To access this episode and others from this series, visit ReachMD.com/DermConsult, where you can Be Part of the Knowledge. Thanks for listening.