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JAK Inhibitors for Moderate-to-Severe Atopic Dermatitis: Examining Efficacy and Safety

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:
This is *DermConsult* on ReachMD, and I'm Dr. Raj Chovatiya, a dermatologist based out of the beautiful, cold Chicagoland area. But most importantly, joining me today to discuss the efficacy and safety of JAK inhibitors for atopic dermatitis, is none other than Dr. Adam Friedman. He's a Professor and Chair of Dermatology—the chair of my heart as well—and the Residency Program Director, Director of Translational Research, and Director of the Supportive Oncodermatology Program at the George Washington University School of Medicine and Health Sciences in Washington, DC. Dr. Friedman, thanks so much for being here today.

Dr. Friedman:
The feeling is mutual. Thanks so much for having me.

Dr. Chovatiya:
So let's just get right to it. What are JAK inhibitors, Dr. Friedman? And how can they help manage moderate to severe atopic dermatitis?

Dr. Friedman:
So when we think about the JAK-STAT pathway, which is really what we're referring when we are trying to inhibit inflammatory communication, let's go ahead and go through the steps through which this actually occurs. So importantly, when we think about drugs and their targets, it's important to divide up broad categories. So we think about biologics, multiple antibodies, these are going to work outside the cell, whether binding to a signal or to receiver. And that's step one: you have a ligand, and in this case, when we're thinking about atopic dermatitis, it's probably a cytokine. It's going to bind to its receptor, which will then result in cross linking of the receptor. This dimerization occurs, a signal goes into the cell, and right beneath the surface, that's where your JAKs live. And that's where the JAKs will transphosphorylate and activate one another. And these activated JAKs will then phosphorylate the receptor tail, so it's kind of sticking out, waving in the breeze, for a STAT protein to then be recruited to the receptor tail and then be phosphorylated or activated by the JAKs. That phosphorylated STAT will kick off and it will then dimerize. And that dimerized STAT will then move to the nucleus and regulate gene transcription. But then in the setting of atopic dermatitis, it's going to be the production of inflammatory mediators. So it is a very linear way of thinking about things, even though nothing is linear in biology.

So then, when you think about inhibition, you are going to stop those JAKs from enabling the phosphorylation or activation of STATs. And so it's cutting the cord on communication inflammation. And of course, when we think about atopic dermatitis, the second most common inflammatory skin disease, T2-driven inflammation—by inhibiting those JAKs, you are in essence blocking the downstream effect of, for example, interleukin-4 and interleukin-13 signaling.

Dr. Chovatiya:
What should we know about that mechanism in terms of the way that JAK inhibitors work across multiple cytokines? And then how do we think about the efficacy of our currently approved JAK inhibitors, of which we have a couple of oral options, and then a topical option as well?

Dr. Friedman:
While, yes, we have these selective JAK inhibitors, which really means that they have varying binding affinity, they all bind to all three JAKs—1, 2, and 3. And so because of that, even though there may be some selectivity, you are getting a broader effect. Not to mention

you have to consider that when you are using a protein to mop up too much signal or block maybe too many receptors, there's a rate limiting step there. You can only give so much protein. And these are pretty big molecules.

Now, moving into maybe some of the unique clinical impacts as we start to think about a broader impact across different inflammatory mediators, size certainly matters. Something to consider is also onset of action. We know that any of these FDA approved medications for moderate to severe atopic dermatitis are going to be, to some degree, effective, right? A certain number of patients in the clinical trials have to meet the primary outcome, all of which are pretty onerous when you think about it from a clinical translation. But that rapid onset of action is what those 80 patients really want. They don't want to hear, “Oh, you're going to be doing so much better 16 weeks from now,” when we know even with biologics in atopic dermatitis, there is a nice earlier onset of action. But we have a need for speed, especially with certain patient types, and we do see this rapid onset of action and impact on itch. And I'll talk about that in a moment, with both the topical as well as the oral JAK inhibitors.

Now with itch, impeding inflammation, which can be driving some of that neuronal sensitization and driving some that itch, is certainly important. But we also know that JAK plays a significant role in the function regulation of sensory neurons. And so it's not just about inhibiting inflammation, but also, inhibiting JAKs can actually influence the transduction of nerve signaling, which is probably also why we are seeing rapid onset of itch reduction. One study was looking at a matter of minutes to hours, which we would never have thought of or done before when it comes to thinking about any topical or systemic. But certainly, even with the oral JAK inhibitors in the clinical trials looking at that early onset of itch reduction when it comes to AD—that itch that feels insanely good but you hate to scratch—cutting that down very quickly is going to be very important for disease control and, of course, maintenance.

Dr. Chovatiya:
What are some of the real common adverse events we think about associated with JAK inhibitors? And let's maybe think more broadly about some of that safety baggage without making this a sort of heavy conversation about, how do you contextualize everything we just talked about with what we should think about with safety?

Dr. Friedman:
What are the known, most common side effects of using oral JAK inhibitors in atopic dermatitis? Headache, GI upset, nausea, and what has lovingly been called JAKne, which looks like acne—though, I am convinced it's not true acne, but rather, it's like the eruption we see with EGFR inhibitors. And then also herpes zoster—increased risk for that—and maybe some signal with elevated creatinine and kinase. But those are really the ones to think about and expect.

And also, I will say that the rates of these do vary from JAK to JAK, but those are the things we need to think about and talk to our patients about. Ask about vaccination status for zoster and consider age-appropriate vaccination. I know that there is not a general consensus on whether you should vaccinate every single patient going on a JAK for zoster before you start; if you ask 10 people, you'll get 10 different answers. But these are the things I really want people to think about.

Now, in the world of atopic dermatitis, what wasn't really seen in subsequent studies since the FDA approval of two JAK inhibitors for moderate to severe AD on the same day—which was, I think, somewhat groundbreaking—we did not see an increased risk for serious infections, venous thromboembolism, cardiovascular complications, malignancy, or nominal skin cancers. So in this cohort, we are not seeing that.

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. Adam Friedman about the role of JAK inhibitors in managing atopic dermatitis.

How do you get someone ready to start on a JAK inhibitor? Are there certain monitoring protocols you follow to make sure that you're capturing the right patient, or if you want to make sure that you're not necessarily missing anything that may happen once you start therapy?

Dr. Friedman:
There are a lot of different patient types for which a JAK inhibitor would be appropriate for moderate to severe atopic dermatitis. But at that day zero, I'm getting a CBC. I want to know how their bone marrow is working. I'm getting a comprehensive metabolic panel. I'm looking at their lipid panel because we know that the JAK-STAT pathway plays a role in lipid metabolism and homeostasis. I'm screening for Hepatitis B and C. In the right setting, I might screen for HIV or maybe an RPR, but that rarely comes up. But usually it's really just going to be hep B and C, and then I'm going to do a screen for tuberculosis. And then I will check, at a month, a CBC and the liver function. I tend not to check lipids at a month. I tend to check that at three months, and that's why I'll check a CBC and a hepatic panel. And then if everything's kosher, I will start checking maybe every six months. Now, there are some cases I don't check everything until three months, but in general, it's the one, three, and every six months thereafter.

Dr. Chovatiya:
To bring us to the end of our program, Dr. Friedman, do you have any final thoughts on JAK inhibitors and their now and future role in atopic dermatitis management?

Dr. Friedman:
I think we are in an incredible time to have so many options to really personalize our approach for an incredibly common, yet only recently paid-attention-to chronic inflammatory disease. So I think there's a huge role for them. And I think where we're going to see things headed is a combination role, in terms of whether it be using a JAK inhibitor, maybe transitioning to biologic, or vice versa. Certainly, the long-term safety data we have thus far, and even head-to-head data, is really giving us a lot of confidence and comfort, whether you're selecting this as a first line or as your next step up after your first line does not cut it.

But I think the future is going to be very bright for JAK inhibitors in AD and well beyond, both on label and off label too—one of my favorite things in dermatology is being creative with therapeutics that may not be so narrow focused to address disease needs that really have nothing. So I think it's really important to throw your name into the hat, so to speak, and get comfortable utilizing these because they can make a tremendous difference in someone's life.

Dr. Chovatiya:
As those final comments bring us to the end of today's program, I want to sincerely thank my guest, Dr. Adam Friedman, for joining me to discuss the efficacy and safety of JAK inhibitors for atopic dermatitis. Dr. Friedman, as always, it was great having you on the program.

Dr. Friedman:
Thank you for having me.

Announcer:
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