Updates on JAK Inhibitors for Alopecia Areata
(Supported by Pfizer)

Brett King, MD, PhD, FAAD, interviewed by Jacquelyn Dosal, MD, FAAD

JACQUELYN DOSAL, MD, FAAD: Welcome to *Dialogues in Dermatology*. My name is Dr. Jackie Dosal and I'm in private practice in Park City, Utah. This episode is titled "2024 Updates on JAK Inhibitors for Alopecia Areata." This episode is sponsored by Pfizer. I have the privilege of having Dr. Brett King here with me to discuss this topic, which is certainly a hot topic that everyone wants to hear about. Until recently, Brett King was Associate Professor of Dermatology at Yale University School of Medicine, but he has left academia for private practice in the town where he lives, in Fairfield, Connecticut.—

--He specializes in inflammatory skin diseases and hair loss disorders. He pioneered the use of Janus kinase or JAK inhibitors in dermatology. His work has revealed the broad utility of JAK inhibitors for the treatment of alopecia areata, vitiligo, atopic dermatitis, and other conditions. Welcome, Dr. King, it's a great pleasure to have you here.

BRETT KING, MD, PhD, FAAD: Thank you so much for the opportunity, I'm really excited.

JACQUELYN DOSAL, MD, FAAD: We were talking before and I remember listening to you speak about JAK inhibitors for alopecia areata about ten years ago. We were talking about, this is June 2014, you can expand on that. So I have this great memory of being at the AAD and listening to your work on this. So I'm thrilled to be interviewing you today and I'm thrilled to learn more, because so much has happened in ten years. It's so exciting and such a paradigm of the excitement that we have in our dermatology field. So thank you again.

BRETT KING, MD, PhD, FAAD: It really is, it's a fun story because in a really short period of time, an entire disease has changed. I think it really did begin with publication of a single patient with severe alopecia areata, who had been referred to me for treatment of his psoriasis. He had

failed a biologic or two at the time. I recognized that he also had severe alopecia areata, had almost no hair at all.—

--I was aware of a few scientific abstracts that had been published regarding JAK inhibitor treatment or prevention of disease in a mouse model of alopecia areata. I was aware of this brand-new class of medicines called JAK inhibitors, in particular tofacitinib had been approved in November of 2012 for the treatment of rheumatoid arthritis.—

--So here's this patient sitting in front of me in June or July of 2013 with psoriasis and alopecia areata. Tofacitinib was in clinical trials at the time for psoriasis. I looked at him and I said, "You know, there's a chance that this really new class of medicines might treat your psoriasis and might make your alopecia areata better. At least it makes alopecia areata better in a mouse that has your condition."—

--"So if you want to try, let's try." And he said yes and lo and behold, I think eight months later he had all of his hair. We published that as a case report in the *JID* in June of 2014, as you said. Truly within hours of a press release going out about that single case report, I was on the phone with CNN and that night, Kyle was on CNN. Truly within days, it is news around the world. Really exciting.—

--And then to think, eight years later, eight years almost to the day after that moment, baricitinib was approved, the first medicine ever approved for alopecia areata, was approved for treatment of adults with severe alopecia areata.

JACQUELYN DOSAL, MD, FAAD: It's so great.

BRETT KING, MD, PhD, FAAD: It's really amazing. And then a year after baricitinib was approved, we had approval of ritlecitinib in patients 12 years and older with severe alopecia

areata. And then just a few months ago, in July we had approval of the third agent, deuruxolitinib. And so just think about that.—

--A decade ago, nothing. And then in the last two years, three medicines truly transforming the care of these patients.

JACQUELYN DOSAL, MD, FAAD: It really speaks for the need for us to do things like this, to educate. Because so much is happening so fast that even I know I'm going to benefit from this *Dialogue*, so thank you. This may be a good moment to talk about what we had to do before the approval of these agents. Certainly you could have used some of the approved oral JAK inhibitors off-label. But I know in that time in the interim, there was a lot of talk about trying to compound topical versions of this. Could you spend a moment just talking about where that led us or how it turned out?

BRETT KING, MD, PhD, FAAD: It's a really important question, because as dermatologists we look to use topicals. We own topical medicines. It's impossible to not have a feeling "maybe I can treat this disorder topically and more easily or without systemic exposure." There have been for sure a very tiny number of case reports or small case series reported of successful reversal of alopecia areata, whether eyebrow involvement or beard involvement or a few patches on the scalp with compounded, as you said, compounded JAK inhibitors.—

--But I think what we all need to be aware of is that there has been a large phase 2A clinical trial of ruxolitinib 1.5% cream, which we now are all very familiar with for the treatment of atopic dermatitis and vitiligo. Well, that was in a clinical trial in alopecia in patients with 25 percent to 100 percent scalp hair loss.—

--I point that out because often people say, "Well, oh, it didn't work because it was only being used in the most severe patients." That clinical trial included patients with 25 percent to 100

percent scalp hair loss. In almost nobody did it grow hair. Another comment that's often made is, "Oh, well maybe it wasn't absorbed. Maybe it didn't make its way across the epidermis to the hair follicle bulb in order to suppress inflammation and reverse disease."—

--Well, while I don't have the details of all of the patients in that clinical trial, in the paper that describes those results it is said that there were measurable blood levels of ruxolitinib. So in my mind, if there are measurable blood levels, then necessarily it got across the epidermis and still, nobody grew hair or nobody grew an appreciable amount of hair.—

--So really in my mind, that plus two other smaller studies, one of (s/l galidocitinib) and one of tofacitinib, together the data for me says topical JAK inhibitors are ineffective. I think that we can say not sometimes, I think that we can say are ineffective, at least for patients with 25 percent to 100 percent scalp hair loss.

JACQUELYN DOSAL, MD, FAAD: My follow up question to that, and I don't want to spend too much time here, is for the patient with one or two patches that's mild.

BRETT KING, MD, PhD, FAAD: That's why I'm always super careful to say 25 percent to 100 percent. Because it might be that having one or two patches or having 5 percent scalp hair loss, it may be that that is just more, and in fact we know that it's more amenable to treatment. We know that trying to use intralesional triamcinolone in somebody with 50 percent scalp hair loss never works, but we know that it works in the patient with one or two patches, just as you said.—

--So it may be different for those people. But again, just as long as everybody who is using it kind of understands what the data is and what that informs us of, so that you're using these medicines judiciously.

JACQUELYN DOSAL, MD, FAAD: And maybe adjunctive, in addition to other more standard of care. So let's move on to the meat of this. So we now have the three approved medicines, JAK inhibitors for alopecia areata. They are approved for severe alopecia areata, so you hinted at this. So we need to define what severe means, because this was not something we did commonly. So could you help us with that?

BRETT KING, MD, PhD, FAAD: It's really interesting that the labels for baricitinib, ritlecitinib, and deuruxolitinib all say approved for severe alopecia areata, without any further clarification of what that means. Not a SALT score, nothing. So really what I think was in some ways intended by that was a SALT score of 50 percent or greater, meaning 50 percent or more scalp hair loss.—

--After all, the clinical trials of baricitinib, ritlecitinib, and deuruxolitinib have involved patients who had 50 to 100 percent scalp hair loss at baseline. But what I think we all need to sort of as a community recognize is that in the absence of clarification in the label of what severe means, what does severe mean to us, what does severe mean to our patients?—

--In my mind, this disease is severe at much lower SALT scores than 50. You take a patient who has five patches on their scalp but they're missing their eyebrows, I'm not sure that that's not severe. Certainly I would say it's at least moderate, if we're going to sort of adopt this way of thinking mild, moderate, and severe in terms of severity. So here, I would encourage all of us to think more holistically about alopecia areata.—

--Because as you pointed out, this is new to us. We're going to have to come around again, both individually but also as a community, to decide what is mild, moderate, and severe. I feel like we're still early enough in this where we can kind of insist as a community that severe is not just 50 to 100 percent scalp hair loss. It doesn't mean the payers are going to jump on board and say, "Well, if that's what you say as a community, then we agree with that."—

--But I think it's important for us to again kind of recognize the myriad presentations of disease and that this is not just about scalp hair loss.

JACQUELYN DOSAL, MD, FAAD: It's nice that there is some flexibility and that they didn't use a SALT score for the label, so we can have that flexibility as the provider. You wonder, do we need to include the DLQI or some measure of the way it affects their life to determine that. My follow up question that still needs to be determined, do we need to do any documentation for most insurers to cover this, other than saying it's severe? With some of the other medications, you have to document PASI or you have to make some case that it's severe.

BRETT KING, MD, PhD, FAAD: It's a great question, as we're all aware, holy cow, a payer in one state does not act like the same payer in another state. So there's a lot of variability here. But my experience has been that in general, payers are asking for a SALT score of 50 or greater, meaning 50 percent or more scalp hair loss to mean severe. However, I would just advocate here that we can use other ways of thinking about this.—

--One tool that has been put into the literature in the last year or two is the Alopecia Areata Scale, which has mild, moderate, and severe, at first anchored in the amount of scalp hair loss, so less than 20 percent, 21 to 49 percent, 50 to 100 percent to mean mild, moderate, and severe. But then we have the ability with the presence of eyebrows involvement or eyelashes involvement to take somebody who is a mild and make them moderate.—

--Or we can take, as you pointed out, the psychosocial impairment. If that's present, if we can document that in some way, then we can take somebody again who is mild and make them moderate, or moderate and make them severe. One of the things that I really love about the Alopecia Areata Scale is that it's super amenable to practice. It's not a calculation, you don't have to get out a calculator. It's simply scalp hair loss and then modified by the presence of other really important factors.

JACQUELYN DOSAL, MD, FAAD: That's great. I think you've made some excellent points there. Let's dive into the nitty-gritty of the three medicines. Before we get into that, can I just clarify for those not familiar with SALT score that it's sort of the opposite of PASI. So you want a low SALT score. Can you spend a minute on that?

BRETT KING, MD, PhD, FAAD: Actually really important. So SALT score, and again this is also new to us, there's no reason why anybody should have a familiarity with SALT score. So Severity of Alopecia Tool score simply measures amount of scalp hair loss, ranging from zero, absolutely no scalp hair loss, to 100, 100 percent scalp hair loss. Really important, the SALT score doesn't care about why there is hair loss. So again, it's simply the amount of scalp hair loss, ranging from zero, no scalp hair loss, to 100, 100 percent scalp hair loss.

JACQUELYN DOSAL, MD, FAAD: Would you just spend a moment talking about the similarity and differences between the three that are now approved JAK inhibitors for alopecia areata?

BRETT KING, MD, PhD, FAAD: Super important point, because again in a world where there is not just one but now a few, the question arises, are they all the same, are they different? Thinking very kind of broadly, baricitinib and deuruxolitinib achieve scalp hair regrowth somewhat faster than ritlecitinib does, though really importantly, approximately 45 to 50 percent of patients achieve a SALT score less than or equal to 20, between one and one and a half years of treatment, for all three medicines.—

--A little bit of difference in speed to get there but all three medicines arrive at around kind of the same ceiling, if you will. There are two doses of baricitinib, there's a single dose of ritlecitinib, and a single dose of deuruxolitinib.

JACQUELYN DOSAL, MD, FAAD: Now I want to dive into the three approved JAK inhibitors. Before we dive into the differences, could you just spend a moment talking about how these

medications were studied? Things like the SALT score, which is a little bit different than what we typically think of. And just how we can think about these medicines.

BRETT KING, MD, PhD, FAAD: Across baricitinib, ritlecitinib, and deuruxolitinib, we had clinical trials involving patients with 50 percent to 100 percent scalp hair loss. The way we measure scalp hair loss or assess scalp hair loss in clinical trials is using the Severity of Alopecia Tool, or SALT score. The SALT score ranges from zero, meaning no scalp hair loss, to 100, 100 percent scalp hair loss.—

--Again, in these clinical trials patients had a baseline SALT score of 50 to 100, or 50 to 100 percent scalp hair loss. The goal, the endpoint of clinical trials to date has been achievement of SALT score less than or equal to 20. Meaning achievement of 20 percent or less scalp hair loss.

JACQUELYN DOSAL, MD, FAAD: Now we can dive into the differences between the three medications.

BRETT KING, MD, PhD, FAAD: Super important, because we went from nothing to having one, a year later two, a year later three medicines now in our toolchest. So how do we think about the ways in which they're the same and how they're similar, and how do we think of them as being different. So baricitinib and deuruxolitinib achieve scalp hair regrowth somewhat faster than ritlecitinib, but really importantly approximately 45 to 50 percent of patients achieve 20 percent or less scalp hair loss around one to one and a half years of treatment for all three medicines.—

--So speed is a little bit different but they all get to the same place over one to one and a half years of treatment.

JACQUELYN DOSAL, MD, FAAD: You said it was about 50 percent?

BRETT KING, MD, PhD, FAAD: Yes.

JACQUELYN DOSAL, MD, FAAD: So about half of patients will really respond to get to about 80 percent of their hair--.

BRETT KING, MD, PhD, FAAD: Or better. If we had more time, we could really get into the weeds. But it's really important for everybody to understand that the vast majority of people in clinical trials who achieve a SALT score less than or equal to 20, or 20 percent or less scalp hair loss, the vast majority of them achieve 10 percent or less scalp hair loss. So it's not like people are getting to 20 percent and sitting there, they're getting down to really complete, often complete or near complete scalp hair regrowth.—

--As you pointed out, I think that that's the super important kind of highlight, is that really across all three medicines, about 50 percent of people achieve this really great result. Really important also is that this is with monotherapy. This is clinical trials, super clean. We're not adding intralesional triamcinolone. We're not adding topical corticosteroids to those kind of resistant patches. We're not adding oral minoxidil. So this is monotherapy data.—

--Thinking about the other things that are sort of the same or similar and different, there are two doses of baricitinib. There is a single dose of ritlecitinib and a single dose of deuruxolitinib. Baricitinib is approved not only for alopecia areata but also for rheumatoid arthritis, atopic dermatitis in patients ages 2 and older outside the U.S., juvenile idiopathic arthritis in patients ages 2 and older outside the U.S. So again, sometimes people like that kinds of give them a feeling of like, "Oh, okay, wait a second." Age is often a proxy for safety and so I think it's helpful for people to know that.—

--Ritlecitinib is in phase 3 clinical trials for vitiligo, so if you haven't heard about or read some of that data, we're going to be hearing more about that, hopefully a lot more in the future. When we

think about laboratory monitoring across the three medicines, largely similar but a little bit different in that ritlecitinib does not require lipid monitoring. Lipid monitoring is a pain and so it's kind of nice, in some ways I think of laboratory monitoring across all JAK inhibitors as being kind of one-size-fits all.—

--But here, ritlecitinib does stand out as not requiring lipid monitoring. Lastly in terms of labs, prior to treatment with deuruxolitinib, CYP2C9 genotyping is recommended. So that again is just something that's different. So again, just similarities and differences.

JACQUELYN DOSAL, MD, FAAD: Because of interactions potentially--?

BRETT KING, MD, PhD, FAAD: Because of interactions and because of theoretically, certain CYP2C9 genotypes may lead to having more deuruxolitinib present than we otherwise think there would be by virtue of that 8 mg dose, which could change the adverse event profile.

JACQUELYN DOSAL, MD, FAAD: So they're not metabolizing it as well, okay. Could you also review the labs that you check, just for our listeners who maybe haven't used a JAK before, which there are still a lot out there? So what are you checking for them?

BRETT KING, MD, PhD, FAAD: I think it's a really good question and just to be clear, this is what I do but I think this is based on the labels. Like this is not like lab checks, per Brett King. It really is the labels across JAK inhibitors say that everybody should have tuberculosis check prior to treatment and annually. Hepatitis B and hepatitis C should be screened for prior to somebody taking these medicines.—

--Beyond that, really think kind of AST, ALT, CBC with differential prior to starting somebody. Again, fasting lipids prior to starting, except in the case of ritlecitinib. And then really if you try to kind of wrap all of them together, including abrocitinib and upadacitinib for AD, then

approximately four weeks after starting we would recheck fasting lipids, CBC with differential, AST, ALT.—

--And then what's really great about this, and I think this is a really important thing for listeners, the labels for JAK inhibitors say lab monitoring per routine. That is not prescriptive. That is not language that tells us that we should be fearful of laboratory abnormalities. So for those of us who are sort of less familiar with this or kind of starting to get our feet wet with using these medicines, really they're quite straightforward to use.—

--They're not onerous. I think with tofacitinib, the label said every three months. That feels like other things that we have done in the past, cyclosporin, methotrexate, azathioprine, mycophenolate. That was tofacitinib and I think it was just because it was the first one for treatment of inflammatory disease. Now we have labels that make these medicines really quite convenient to use and really should give us some reassurance that they're not dangerous medicines.

JACQUELYN DOSAL, MD, FAAD: Whenever I've interviewed quite a few experts in JAK inhibitors and you all say the same thing, that we really shouldn't be scared of them, use them, we'll be impressed by them. We do have to respect them but they're just great medicines and great tools, so thank you. So we talked about the safety profile and efficacy of these medicines. But besides growing hair, what else have the clinical trials of these medicines taught us about alopecia areata?

BRETT KING, MD, PhD, FAAD: This is such a fun aspect of this. That we're coming from a time when everything that we knew or thought we knew about alopecia areata was something that was handed down. It was somebody's opinion, which sometimes equals knowledge. But it was handed down from one generation to another. It was put in a textbook.—

--We're going to have to unlearn some of the things that we have grown up with. The first is that every textbook chapter says alopecia areata is a waxing and waning and reversible hair loss disorder. Well, we now know from clinical trials, clinical trials of people who have 50 to 100 percent scalp hair loss, when you look at the placebo rates over up to 36 weeks, very few people spontaneously grow hair.—

--So it's not waxing and waning when you have more severe disease, it's chronic disease. The idea of reversibility is something else that we have to unlearn. Because the clinical trial data is, in fact this was really clear even in the first 60-some patients that we treated in an open-label clinical trial of tofacitinib, that as your episode of severe loss, so not how long you've had alopecia areata but your episode of severe loss, most easily thought of as how long have you not had hair at this moment in time.—

--As you march out towards ten years, your opportunity to regrow hair with tofacitinib started to diminish. And out past ten years, your chances of regrowing hair became very small. Now we have again three clinical trials of baricitinib, ritlecitinib, and deuruxolitinib that all confirm this, that undergoing treatment in the first three to four years of current episode of severe disease, efficacy is markedly better than if we treat you in the fourth, fifth, sixth, seventh, or eighth year of severe loss.

JACQUELYN DOSAL, MD, FAAD: That's excellent. You answered one of my questions, which was what was that other 50 percent of patients, the nonresponders, were all of them over ten years or over five years? Could it all be attributed to the duration or were there other factors you could figure out?

BRETT KING, MD, PhD, FAAD: Because of that very earliest data with tofacitinib, the companies that have developed medicines in this space have limited the duration of current episode that a patient could have and enroll in a clinical trial. So sometimes it was eight years,

sometimes it was ten years. But your question is super astute and gets at that idea that a lot of those nonresponders are people with longer duration of current episode.—

--Also people who started, meaning underwent treatment with no hair versus those who had some hair. So patients say with 50 percent to 90 percent scalp hair loss, that really is much more amenable to treatment than having 95 to 100 percent scalp hair loss. So there are some really important points that emerge from that, and that is when a patient is sitting in front of us we need to say, “How long have you not had hair?”—

--If they say six years and they say, “And you know, I’m not sure I want to do this,” it’s obviously it’s their decision. But they came to us for information and so it’s paramount that we say, “You can elect not to undergo treatment but I just need you to know that at this moment in time, every year that you do not treat, you are getting closer to not having an opportunity to grow hair.”—

--While maybe this is unfair, it’s one thing for an adult to make that decision, a 30-year-old, a 40-year-old, but what do we do with the 12-year-old who hasn’t had hair in six years?

JACQUELYN DOSAL, MD, FAAD: And whose parents are afraid of something.

BRETT KING, MD, PhD, FAAD: It is in some ways, if listeners of this podcast took away nothing more than that, we have learned this is not always a reversible form of hair loss. And we don’t want the 8-year-old to never have an opportunity to have hair. We don’t want the 12-year-old to never have the opportunity to have hair.—

--That means that we might have to get out of our comfort zone and have sometimes kind of awkward conversations with parents and be really encouraging of something that we might not otherwise be encouraging of. But just knowing that there’s a clock ticking and there’s an opportunity that’s going to pass. And my guess is we wouldn’t want that for our own children. So let’s be considerate of that when we’re sitting with another family in our office.—

--And even if we don't want to undertake treatment because they're 10 and again it's off-label, so now what are we going to do? That's okay if you don't want to but maybe find somebody who will, somebody who is comfortable having that conversation, comfortable doing that. Because again, we've all taken the task to take care of people, to give them good information, and we don't want people to make decisions that they can never take back. And if they do, we want them to know that they made it with full disclosure of the data.

JACQUELYN DOSAL, MD, FAAD: That was a great lesson. That taught us a lot, those clinical trials.

BRETT KING, MD, PhD, FAAD: I think it's been really amazing, because now we can sit in front of patients and say what we know. Not what I believe, not what I learned from somebody who gave a talk once and they said. But rather, we can sit in front of people and we can talk amongst ourselves with knowledge and less opinion. I think that that's critical. That's the world that we want to live in always, is one of knowledge and data and less of opinion. And we're getting there, we're getting there, slowly but surely we're getting there in alopecia areata.

JACQUELYN DOSAL, MD, FAAD: So let's look ahead. What do you think is next for dermatologists and their patients with alopecia areata? What do we have to look forward to?

BRETT KING, MD, PhD, FAAD: As exciting as it is how far we've come in so short a time, the future is just so bright. There are multiple clinical trials happening in alopecia areata and one of the really fun things is that they're not all JAK inhibitor clinical trials. Upadacitinib is in clinical trials, that's exciting. We're waiting to hear results of a clinical trial of deucravacitinib, that sort of different JAK inhibitor in alopecia areata.—

--There have been other clinical trials of again different medicines for which we're waiting to hear the results of. And then things that we're looking forward to hearing about in the next six

months, a year, an IL-7 receptor antibody. The OX40 agent, amlitelimab, is in clinical trials. We've heard some data in atopic dermatitis, it seems really promising there.—

--What I want everybody to hear is it's like as far as we've come, we have so far to go. Truly, I think that we are going to be having this podcast with somebody in three years or five years and it's going to be, you're going to need twice as much time. It's going to be we have five things approved, we have six things approved. How do we think about the treatment of patients with all of these different kinds of agents? So it's really fun.

JACQUELYN DOSAL, MD, FAAD: Yeah, we never stop learning, that's the best part of dermatology, it's super fun. So thank you so much. This has been a fantastic *Dialogue*. I thank you for your expertise and your dedication to the field. Really, I learned so much from this so thank you again, Dr. King, for being here. Again, I am Dr. Jackie Dosal. This is *Dialogues in Dermatology*. And this is your 2024 Update for JAK Inhibitors in Alopecia Areata. Thanks for being here.