Current Therapies and New Approaches in Alopecia Areata
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Brett King, MD, interviewed by Steven Chen, MD, MPH, FAAD

STEVEN CHEN, MD, MPH, FAAD: Welcome, everyone, to another episode of *Dialogues in Dermatology*. This is Steven Chen. And I am thrilled to be joined by Dr. Brett King, who is an Associate Professor of Dermatology at the Yale School of Medicine. Today, we are talking about Current and New Therapies for Alopecia Areata. Let's dive right in. First of all, welcome, Brett, to *Dialogues*.

BRETT KING, MD: Thank you so much, Steven, it's really a pleasure to be here.

STEVEN CHEN, MD, MPH, FAAD: We're talking about alopecia areata today. As we think about areata, I think as dermatologists we all conjure up this image of those telltale nonscarring patches that we're accustomed to seeing. Also, there's clearly a spectrum: there's people that come in with a patch here or there, we treat them, they get better. But then there's those folks who really have the universalis or the totalis picture, there's quite a spectrum. But before we start talking about how we treat our patients, could you just remind us of what's happening pathophysiologically in alopecia areata?

BRETT KING, MD: It's really fun. This whole conversation is going to be fun because I think it really is sort of an amazing story of coming from a time when we knew nothing, and therefore we had nothing, into a time when we now understood or are beginning to understand pathophysiology, which then gives way to targeted therapies and the possibility of reliably effective treatment.—

--So just a brief walk through history. We all heard as residents that alopecia areata was caused by stress and anxiety and depression. And this is an idea that we're still having a hard time shaking and I think it's going to take us a long time to shake that idea. But in 2014, we had this

landmark paper by Angela Christiano and Raphael Clynes that showed us in a mouse model of disease that interferon gamma and IL-15, or interleukin-15, are really important cytokines that drive this disease.—

--And what's so amazing about that sort of knowledge or that advancement is that IL-15 and interferon gamma signal through the JAK/STAT pathway, which is a pathway that we, obviously as dermatologists we're clinicians, we're not immunologists, we're not accustomed to thinking about signaling pathways. But what's so cool about the JAK/STAT pathway is that it's one in which we can intervene with a new class of medicines called JAK inhibitors.—

--And so we have in this learning that interferon gamma and IL-15 are important drivers of disease the possibility of treatment in a way that was previously really I think impossible.

STEVEN CHEN, MD, MPH, FAAD: Absolutely. Obviously, we've learned so much about areata in the last few years. I think for our residents' sake and maybe even for the rare medical student who might be listening to *Dialogues*, can you remind us again about where that inflammation is around the follicle? And why is it that alopecia areata is nonscarring versus scarring? And what is it about our treatments that make it reversible versus other processes that might cause hair loss?

BRETT KING, MD: Again, kind of going back in history, it was in 1982 that we learned that there was this lymphocytic infiltrate around the hair follicle bulb or the deepest aspect of the hair follicle in the skin, the "swarm of bees" that we see on pathology when we biopsy these patients. What happens in this dance, if you will, between the immune cells and the hair follicle is, as you point out, it's nonscarring, in a sense a dystrophic event of the hair follicle.—

--It doesn't chew up the hair follicle. It doesn't destroy it. It literally just goes into sort of senescent state that we can rescue it from, as you point out. In limited alopecia areata, this

sometimes happens spontaneously. But in more severe disease, I would say that we are able now, more than ever before, to rescue that hair follicle from in a sense its sort of sleeping state under attack and bring it back to life, so that it does what it's born to do, and that is grow a hair.

STEVEN CHEN, MD, MPH, FAAD: Thank you for that. I always want to make sure that we get to some of the basic information, knowing that our audience is pretty broad. And so thinking about the title of our episode, you might gather that what I'd love to really chat about is the treatment landscape that's rapidly changing with alopecia areata. Before we start talking about the new stuff that's coming, can you just remind our listeners what are the current treatments that exist at our disposal?

BRETT KING, MD: Here we have the things that we use for limited hair loss or think of mild alopecia areata. Topical and injectable steroids. Topical immunotherapy or topical irritants. And then for more severe disease, when the amount of hair loss gets to a point where we just can't reasonably inject it anymore. We're talking about 30, 40, 50, 60, 70, 80 needle pokes, it just becomes sort of untenable, almost barbaric, then we're going to reach for systemic therapies.—

--And, not surprising here, this is the same list that we draw from in the past for treatment of any disease: psoriasis, atopic dermatitis, that merited systemic therapy, corticosteroids, methotrexate, cyclosporin. And it's just so important in this conversation to recognize and acknowledge, there's very little data and there's certainly no high quality data to support use of any of these systemic therapies for the treatment of alopecia areata. And so really, we're coming from a time of enormous unmet need in alopecia areata for effective therapies.

STEVEN CHEN, MD, MPH, FAAD: Right, absolutely. I think it's interesting, I feel like we're transitioning from that phase of treatment for this disease that we're so used to in dermatology, where we don't have a lot of evidence, and we're extrapolating from other disease types, and we're trying our best, and it's a lot of expert opinion or case reports and case series that we're

using, to a time where now, as you mentioned before, we're getting to pathophysiologic mechanisms and targeted therapy, which is really exciting.—

--Not to mention, a lot of the stuff that we're talking about from before, the ILK, the longterm systemic steroids, those are things that carry a lot of concerning adverse effects. So it's great to turn our attention to something that's new. So in that vein, could you tell us what's coming down the pike for treatment of alopecia areata?

BRETT KING, MD: This is unbelievably exciting stuff. Last June 2022, almost eight years to the day after we published a case report of a patient with severe alopecia areata who re-grew his hair taking a relatively new medicine at the time, tofacitinib, a JAK inhibitor. Almost eight years to the day after that publication, baricitinib, another JAK inhibitor, was FDA approved for severe alopecia areata in adults.—

--This was truly historic. Making headlines around the world. An incredible milestone for patients with this disease and those of us in dermatology who take care of these patients. It was the first time that we've had in our toolbox a medicine with high quality data, 1,200 patients between two clinical trials of baricitinib in adults with 50 percent or more scalp hair loss.—

--Just an incredible moment for all of us. And to think there's more coming. It's like this moment was huge and truly, I mean the headlines around the world, the amount of media attention given this was really spectacular. Which just tells you, I think one, it tells you how exciting it is to see a head that has no hair covered in hair, 24, 36, 52 weeks later. It's something, it doesn't matter who you are, it doesn't matter what you do, those two images side by side just touch something in all of us that just makes us think, wow, like what happened?—

--And we're able to do that now. Baricitinib has ushered in a new era in dermatology in which we can say with a fair amount of confidence when we see a patient, "Oh, I can help you get to that

new place." It's just sort of exceptional. And again, there's more coming. There are two more JAK inhibitors: ritlecitinib and deuruxolitinib that are in late phase 3 clinical trials.—

--I'm hopeful that in the next months ahead, three months, six months, nine months, twelve months, we'll see FDA approval of both of these JAK inhibitors. And what's really neat is each one offers something really special. It's not just like oh, geez, we have one and now we'll have three. Ritlecitinib clinical trials, we're down to age 12. And alopecia areata frequently affects children. And so having an agent that we can use down to age 12 would be a huge advance for us.—

--And then deuruxolitinib seems to be pushing efficacy in a really interesting way. And so even that, considering the short amount of time that we're talking about, even that would be yet another really important advancement for us in dermatology and for patients with this disease. So it's just really exciting.

STEVEN CHEN, MD, MPH, FAAD: That's amazing. I have to be selfish for a second and think about my own patients who have had longstanding alopecia areata. We've had that conversation about baricitinib being kind of an agent that would be of choice, at least at this moment in time. I'm curious, for people who have lost their hair and they've kind of come to terms with it and they've decided to live without hair and now that there's an approval for a JAK inhibitor for this, what's your way of counseling? Do you tell them, "Listen, it's been a while so the chances of this really working are different," does it matter how long they've kind of gone and let the alopecia areata just go? Or do you expect everyone to improve?

BRETT KING, MD: Now Steven, it's a really important question. And for everybody tuning in, this is a super important point about treatment of patients with severe alopecia areata. Again, here we're talking about people who have for a period of years had complete or near complete

scalp hair loss, the data is really clear. And that is the longer this goes on, the prognosis, the chance of regrowth diminishes.—

--So what that looks like, if you look now across data sets, this is true for baricitinib, this is true for ritlecitinib, this is true for deuruxolitinib. This was apparent even some years ago in the first 90 patients that I treated with tofacitinib. It was clear that the longer this goes on, the less likely somebody is to achieve regrowth of scalp hair in particular with treatment.—

--So the clinical trials of baricitinib included patients with current episode of severe disease. So now the how long you've had alopecia areata, but how long have you had complete or near-complete scalp hair loss. The limitation in enrollment was seven years or less. Now, in the ritlecitinib and deuruxolitinib clinical trials, they've made it ten years or less.—

--But no matter how we look at that number, if you take patients who have had current episode of severe disease less than three and a half or four years versus greater than three and a half or four years, you see a quite significant increase in efficacy for the patients who have had current episode for shorter periods of time.—

--Again in that sort of three and a half to four year cutoff. Now, this does not mean that patients with longer standing current episode do poorly, it's just making the point that we need to get to these patients sooner rather than later. There's actually a really important implication here in how we talk to our patients. When somebody comes to us and it's five years, six years, seven years since they last had a full head of hair, we need to sort of impart a sense of urgency to that patient that if they think they want to get their hair back again, the treatment sooner, in fact maybe even treatment now is really important.—

--Because if this goes on for 10, 11, 12 years, at some point it may not be possible to do it. And so it's really, that is a really, really important message for all of us to hear and understand. We

want to get to these patients sooner rather than later. Again, we can undertake treatment of the patient who has had no hair on their head for 10, 11, 12 years, there's nothing that says that we can't do that.—

--But it's really important, one to set expectations for the patient, help them understand what they're getting into. But also it's helpful to set expectations for ourselves. Because we don't want the first three patients that we treat to be patients who are unlikely to succeed, then leaving us with the impression that this doesn't work. Because it does work. Patient selection, if done right, it actually works 40 or 50 percent of the time, without even adding anything else.—

--So probably the most important question you could have asked is that one. And we really need listeners to catch that point.

STEVEN CHEN, MD, MPH, FAAD: That's such a helpful, helpful clinical pearl for us as we counsel our patients, thinking about this. And so I will just say that I am anxiously awaiting for you and your team to figure out how to grow hair for folks who have lost it for over ten years. And I can't wait to see those studies in the future. JAK inhibitors, obviously all over the news for us in dermatology. There's sessions at the AAD about it. We've been talking about it for a little bit of time now. It's really exciting. But I'm curious, what else? What else, other than JAK inhibitors, might we expect or are we starting to look at for alopecia areata?

BRETT KING, MD: I know I like to answer every question with "this is really fun, this is amazing." But it really is. I think there's so much wrapped up in the conversation about alopecia areata, like multiple things that really are fun and amazing. And this is another one. You go back ten years, people weren't really talking about alopecia areata. It was obviously we own the disease in dermatology, there are book chapters about it. But it wasn't like a thing.—

--You go to the AAD just a couple weeks ago, right now a symposium on alopecia areata. And multiple talks about alopecia areata. It's really fun. It's really exciting. It's a disease that affects a lot of people. And again with these advancements in our understanding, we're able to really think about treatment in really interesting ways.—

--Obviously, JAK inhibitors are hugely important and advanced all of this dramatically. But what's cool is there are now clinical trials of other medicines to treat the disease. One treatment is deucravacitinib, a TYK2 inhibitor. A TYK2 inhibitor is a JAK inhibitor but it's a slightly different flavor of JAK inhibitor. There's now a clinical trial happening with that.—

--There is a clinical trial of a PD-1 agent, rosnilimab, in alopecia areata. There's a clinical trial happening with an agent called daxdilimab, which is a medicine that affects plasmacytoid dendritic cells. The idea here is truly like we're bringing all sorts of interesting immunomodulatory therapies to bear on an autoimmune disease. It makes perfect sense.—

--But again, what's so fun is that it's happening when ten years ago, we weren't even talking about it. So really the future is just every six months, it brings sort of new data and I think just kind of continues to build the excitement around this disease.

STEVEN CHEN, MD, MPH, FAAD: That's great. Obviously, those other treatments that are in clinical trials, we're not quite at the point where we can use those yet. So if it's okay I'd love to ask, thinking about JAK inhibitors, because that's really the newest thing for all of us that we can reach for right now, are there safety concerns that we should be thinking about? I think we've all heard the stories about tofacitinib in *New England Journal* and all the signal there, but that's in a different population, a different specialty. So I'm curious when you see a patient, we talked about the time piece, but who are the patients that you feel are perfect for JAK inhibitors? And what are you doing in terms of counseling about warning them about potential adverse events,

about lab monitoring, if you don't mind taking me through how you approach that for maybe a new start of a JAK inhibitor for this?

BRETT KING, MD: So this is a critically important topic. We can't talk about JAK inhibitors without talking about the boxed warning. And as much excitement as there has been around JAK inhibitors and their potential across a multitude of dermatologic diseases, there has also been a lot of attention to the boxed warning. Which it's a new boxed warning for us. It includes malignancy, infection. We've got those down, right? We learned how to have that conversation internally and with our patients with the TNF-alpha inhibitors.

STEVEN CHEN, MD, MPH, FAAD: Like everything else we use.

BRETT KING, MD: Exactly, and everything else, exactly. But in addition, we have in the boxed warning thrombosis or blood clots. Cardiovascular events, so myocardial infarction, stroke. And even sudden death. And this, we're not accustomed to talking about these things. For those of us who use say the oral contraceptive pill for the treatment of acne in young women, maybe we're kind of used to having the conversation about blood clots.—

--But again, this is sort of uncharted territory for us. So it's important for us to understand the safety. Understand where that warning, the boxed warning came from. And then as you point out, understand, kind of have an idea for how to communicate that with patients. So right, we could have a whole episode on this.—

--But in short, the idea is that the box warning for JAK inhibitors, for all JAK inhibitors regardless of disease state, came from a longterm safety study of tofacitinib for the treatment of moderate to severe rheumatoid arthritis in patients 50 years of age and older, importantly with at least one additional cardiovascular risk factor.—

--So the idea is that when tofacitinib was originally approved in 2012 for rheumatoid arthritis, there may have been a malignancy signal, not sure but there may have been a malignancy signal. And about a third of patients had some mild elevation in lipids: total cholesterol, LDL, HDL.—

--And so the FDA tasked Pfizer with doing a longterm safety study to help understand the risk of cardiovascular disease and malignancy. And so what happened subsequently was that study was undertaken. It was a study of tofacitinib versus TNF-alpha inhibitors.—

--And the idea is that it wasn't like there was a marked signal. In fact, really in the original tofacitinib clinical trials in RA, there was no signal for MI or stroke. And so what did Pfizer do? They enriched a clinical trial in a population of people more at risk than everybody else: patients 50 years of age and older, with at least one additional cardiovascular risk factor.—

--So these are patients with hypertension, hyperlipidemia, a personal or family history of cardiovascular disease. They randomized them to tofacitinib or to TNF-alpha inhibitor and they watched them over a long period of time. And over the next four to five years, they say that about 4 percent, roughly about 4 percent of patients in the tofacitinib arms developed a heart attack or stroke.—

--About 4 percent of patients in the tofacitinib arms developed a malignancy. Versus 3 percent of patients in the TNF-alpha inhibitor arms. And so it's that 4 percent over 3 percent that then says, oh, there's a possible risk of heart attack or stroke, there's a possible risk of malignancy with tofacitinib.—

--And so that warning then gets extrapolated to all JAK inhibitors, including, and I think that this is really kind of the extraordinary thing that everybody needs to understand, that message gets

extrapolated to topical JAK inhibitors for the treatment of atopic dermatitis and vitiligo. Really and truly folks.—

--And by the way, my point here is not to dismiss the risk of JAK inhibitors. No, no, you will never see me dismiss the risk or this side effect profile of JAK inhibitors. But it's really important for us to understand, when we say there's a boxed warning, there may be risk of these events, we're talking about risk that has been extrapolated from patients for whom the mean age in those tofacitinib RA, that tofacitinib RA clinical trial, was 60s, patients in their 60s.—

--The average BMI was 30. One hundred percent of patients are taking methotrexate, 57 percent of patients are taking prednisone. And even under those circumstances, you have 4 percent versus 3 percent in TNF-alpha inhibitor-treated patients. So for me, it's important for us to recognize, gosh, this is a really small risk, even when the risk is optimized.—

--And so how do I think about that in my 20-year-old, 30-year-old, 40-year-old, 50-year-old patient who is otherwise healthy, with alopecia areata? Or otherwise healthy with atopic dermatitis? I think we have to be thoughtful of this. We can't just say there is a boxed warning, therefore no way, I don't understand those risks. No, we can understand those risks. We can understand where the risks are observed most.—

--And then with patients, I think that we communicate. We communicate that in a real simple story. Again, we're not going to spend 20 minutes talking about the oral surveillance study with everybody. But we just say, "I just need you to understand there may be risk. But even when that risk is optimized, we saw these events very uncommonly.—

--And so in you, an otherwise healthy 20-year-old, an otherwise healthy 40-year-old, an otherwise healthy 50-year-old with alopecia areata, personally I say I have to believe that those

risks are even less than in that oral surveillance study." And with that knowledge, I want the patient to make a good decision for himself or herself.

STEVEN CHEN, MD, MPH, FAAD: I think it's really highlighting the importance of going to the primary literature and actually seeing how that study is done. So thank you so much, Brett, for breaking it down for us because I think that's so critical for us to have that information as we counsel our patients. Before we sign off though, thank you so much for what a whirlwind of a conversation about the landscape of alopecia areata, the treatments. And if anything, I think the thing that our listeners will take away is your passion for this area and how excited you are for this disease state and how much is changing in it. Anything brief that you want to add before we sign off?

BRETT KING, MD: I think for me, what I want everybody to sort of hear and to do is just do it. It's really fun. You're going to change lives by doing this. The patient that goes from no hair or very little hair to regrowth will be the happiest patient that you've ever treated. And to think that we can be a part of this journey, that we can facilitate this for patients, it's just extraordinary. And so just dive in and have fun doing it, changing lives.

STEVEN CHEN, MD, MPH, FAAD: Amazing. And I will just say on behalf of the dermatology community, thanks for everything that you do to give us that opportunity, so that we can have that, be a part of that journey for our patients. This has been another episode of *Dialogues*. I just want to say thank you again to Dr. Brett King for joining us today. And thank you to all of our listeners for tuning in on our discussion about current and future therapeutics for areata. Thanks again, Brett, for joining.

BRETT KING, MD: Thank you so much, Steve, I really appreciate the opportunity.