Advances in Understanding of Alopecia Areata Pathogenesis (Sponsored by Eli Lilly and Company)

Jerry Shapiro, MD, FAAD, interviewed by Jules Lipoff, MD, FAAD

JULES LIPOFF, MD, FAAD: Welcome to *Dialogues in Dermatology*. I am Dr. Jules Lipoff. I am an Adjunct Clinical Associate Professor at Temple University. My esteemed guest today is Dr. Jerry Shapiro, who is a Professor in the Ronald Perelman Department of Dermatology at the NYU Grossman School of Medicine. Today, we are going to be talking about the fascinating developments and pathophysiology in alopecia areata that have come to the fore in recent years. Dr. Shapiro, thank you so much for joining me.

JERRY SHAPIRO, MD, FAAD: My pleasure, thank you for asking.

JULES LIPOFF, MD, FAAD: So I want to get right into it. When it comes to alopecia areata, how has our understanding of it changed over time? What do we think was the pathogenesis and what is now believed to be the case?

JERRY SHAPIRO, MD, FAAD: If you go to old medieval records of alopecia, they thought it was some kind of infection and people who had alopecia areata had infection and all this. This is a long time ago, we're talking about several hundreds of years ago. But as we've gone into the 20th century and we feel more that it's an autoimmune disease, and now we have confirmatory evidence that it's an autoimmune disease, so most people understand this as a dermatologic autoimmune condition against anagen hairs.

JULES LIPOFF, MD, FAAD: When did that conception come together? And how has that evolved, even within that conception of it as being an autoimmune disease?

JERRY SHAPIRO, MD, FAAD: It's been kind of understood that it was an autoimmune disease, because we see all these lymphocytes around the hair follicle. And so the hair follicle was being attacked by lymphocytes and making the hair fall out. So we figured these "swarm of bees" that

we get around a hair follicle, the bees being the lymphocytes, make the hair fall out and cause some kind of dysfunction in the hair cycle.—

--And so what we have is a complete disruption of the cycling of the hair. And we don't have destruction of the hair, we have more kind of puts things on pause to some extent, that I always tell patients that their hair is sleeping. That it's not dead, the stem cells are still intact. The inflammation is at the bottom or at the bulb, not bulge, the bulb, at the bottom near the dermal papilla. And that's where the warm of bees are.—

--The stem cells are higher up. So you're not getting a scarring hair loss, you're just getting a temporary, now the temporary may go on for years and years, we like to think it's temporary, of the hair cycle being totally disrupted. And that's why we feel it's an autoimmune condition.

JULES LIPOFF, MD, FAAD: Can you tell me, why do you think we see this distinctive pattern with alopecia areata? It's so unusual to have these round patches of hair loss. The only other thing that seems remotely like it is trichotillomania. Why do we see that?

JERRY SHAPIRO, MD, FAAD: We don't understand why. There may be something that starts in an area of the scalp that kind of radiates outward. So radially, you get a change of things going on and that's why they're round. But they're not always round. You can also get acute, diffuse, total alopecia or alopecia areata incognito. And sometimes the lesions can be linear, as well. So it's not always round, but most of the time it is round and we think it has something to do with some trigger that occurred somewhere in the scalp that kind of grows radially around that trigger.

JULES LIPOFF, MD, FAAD: Interesting. So as far as our understanding, what misconceptions do you think dermatologists may have about alopecia areata? And how about the public, how does the public misunderstand this disease?

JERRY SHAPIRO, MD, FAAD: The public really doesn't understand. They kind of think, "Oh, the person has been on chemotherapy." Or they feel that the person is very sick, when they're not really sick at all, 99.9 percent of people who have this problem are perfectly healthy and they can live to 120. It's just specifically against the hair. And so that's the misconception is that other people in the public think that these people are ill, but they're not, except for the hair. But general medical health usually is good.—

--Now, in terms of what doctors' misconception, dermatologists know what it is. I don't think there's too many misconceptions there. It's an easy diagnosis to make. And regular primary care physicians may not know. They may think it's a fungus or some other maybe autoimmune condition. They don't necessarily have a clear idea of what it is. But every dermatologist in their residency program was taught how to recognize alopecia areata.

JULES LIPOFF, MD, FAAD: As an expert, I thought you would be more likely to come across common issues, misunderstandings. But I guess one thing I see with patients is they see the word "alopecia" itself as a distinctive diagnosis like, "Oh, I have alopecia," as if that's something very specific, where in reality it's a whole umbrella of all sorts of diagnoses. I want to ask a little more about associations. What do you think are the most important associations or comorbidities that dermatologists should be aware of? And what are they likely to overlook?

JERRY SHAPIRO, MD, FAAD: Most people are perfectly healthy. Now, there are some comorbidities that have come up with respect to cardiac issues. We were one of the first to publish cardiac issues in animal models who had alopecia areata. There's a question whether that can translate to humans. So that's one comorbidity. Another one that's more common is atopy. Whether the eczema, hay fever, asthma, these kinds of things are associated with some people who have alopecia areata.—

--There's certain ethnic groups, for instance Asians have a higher chance of atopy. And when you have atopy, there is a higher chance of getting alopecia areata. And if you have alopecia areata and you're in the Asian population, we always ask anyway whether there's hay fever, asthma, eczema, or anything else in the family.

JULES LIPOFF, MD, FAAD: I want to transition to treatment. I think that was the impetus for this conversation actually. How has your thinking about alopecia areata treatment evolved over time?

JERRY SHAPIRO, MD, FAAD: I've been doing this for 35 years and I never thought we'd have anything actually that was that reliable for alopecia universalis or totalis. In the past, we used topical immunotherapy with diphencyprone or squaric acid dibutylester. Of course, for more limited disease we use cortisone injections. We've developed an algorithm that was published in the *Journal of the American Academy of Dermatology*, also on the National Alopecia Areata Foundation website, that goes through how we treat children, how we treat adults.—

--But the big change, the big game changer is the JAK inhibitors. And the JAK inhibitors have really changed how we want to approach someone who has severe alopecia areata that is affecting more than 50 percent of the scalp.

JULES LIPOFF, MD, FAAD: So when you see a patient with severe alopecia areata or alopecia universalis, what are generally their treatment goals? Are they expecting to get all of their hair back? Or are they not thinking treatment, they just want to know what's out there? Or is there some middle ground, they just want selective hair growth? What do you generally find?

JERRY SHAPIRO, MD, FAAD: Everybody's different. Some people just want eyebrows and eyelashes back, because it can be very difficult for them to function without that. Even nasal hairs can cause a problem, as well. So some people just want selected areas. Others want their

hair back, they want it all back. And we have finally something that works in 40 percent of people, giving them 80 percent coverage of the scalp when they had so little hair before, they had very severe alopecia areata.—

--And this is a big breakthrough for alopecia areata in that we finally have something that works in a significant number with severe alopecia areata. Like I said, we did have DPCP before but the chances of success may not have been as high. And for universalis, totalis, it was extremely low. So finally for universalis and totalis, there is a pill that we can give people that is FDA approved, that has a reasonable chance of working.—

--So I think that's been the big game changer. It's been a paradigm shift in terms of how we treat someone who comes in with universalis or totalis. I won't bother going to topical immunotherapy anymore for universalis or totalis. I'll go right away to the approved JAK inhibitor.

JULES LIPOFF, MD, FAAD: So as far as your therapeutic ladder, you mentioned that you've published on this in the *JAAD* and on the National Alopecia Areata Foundation website, but are you using systemic corticosteroids, methotrexate, cyclosporin at all anymore?

JERRY SHAPIRO, MD, FAAD: I don't feel cyclosporin is that good. I used it 20 years ago. We did study it and we published it. We pulsed initially with cortisone and then gave them the cyclosporin. It only worked in let's say two out of eight people and they had serious side effects from it. So I don't really like using cyclosporin. Methotrexate I've used but it hasn't really worked that well. It's nothing compared to a JAK inhibitor.—

--So some people have had success with methotrexate. I've gotten good eyebrow and eyelash growth with methotrexate but I haven't gotten good scalp growth with methotrexate. So why

bother with that now? Yes, I've used them in the past, they did help a little bit, but really patient satisfaction was so low.

JULES LIPOFF, MD, FAAD: That seems reasonable, especially when you have a JAK inhibitor approved by the FDA. How do you weigh the benefits and risks of the JAK inhibitors? How do you explain it to patients?

JERRY SHAPIRO, MD, FAAD: I tell them, the one for instance that is presently approved by the FDA, baricitinib, that has already been used in rheumatoid arthritis for many years already. So we have data on that and how safe it is. Yes, there are potential problems but the study done on alopecia areata on over 1,000 patients showed the side effect profile was very low. There were, of course, no deaths, and there was no intestinal perforations. There was nothing that was serious in any of these people.—

--So we feel that it's a fairly safe medication. Nothing is 100 percent. And I go through all the side effects at length with the patient and we just say that the chances are low and most people want to go on it.

JULES LIPOFF, MD, FAAD: Just to be a little devil's advocate, I think some people might say should we treat conditions that some might call cosmetic with treatments that could have potential significant systemic side effects or even increased mortality risk? How would you answer that?

JERRY SHAPIRO, MD, FAAD: First of all, it isn't just a cosmetic disease, it's a medical disease. And we've published this already. Peoples' total self-esteem is affected by this. So to call it a cosmetic disease, it's not really appropriate. And peoples' lives are changed by this. People are even suicidal over this, especially teenagers. And so we can't just consider it

cosmetic. And you have to weigh the risks and the benefits. The benefits far outweigh the risks.—

--For instance, if a member of my family had a totalis or universalis, I would put them on a JAK inhibitor. Because life will be so much more pleasurable for them. Their self-esteem, their quality of life. There is already data out there on SKINDEX, as well as anxiety scores and all this, when people get treated how the scores change, how much happier they are.

JULES LIPOFF, MD, FAAD: I think we have this with a lot of diseases in dermatology. We see really increased quality of life indices when we treat aggressively and that can't be overlooked. But when we hear things about embolic diseases or septic shock, maybe these things are uncommon, but it makes some hesitate.

JERRY SHAPIRO, MD, FAAD: I tell patients this. If you want no risk, stay home, don't even go to a doctor. Everything has a risk. Coming here had a risk. Going to the doctor, you could have made an accident and something bad could have happened. The chances of somebody getting a thromboembolic phenomenon, the chances of someone having some kind of serious cardiac event is so low that you have to weigh the risks and the benefits. If you want no risk, stay home, don't do anything, nobody dies of alopecia areata.

JULES LIPOFF, MD, FAAD: Specifically about the JAK inhibitors, I know baricitinib is the one that's approved. But do you use others, like tofacitinib, or how do you choose amongst the ones that are on the market, on-label or off-label?

JERRY SHAPIRO, MD, FAAD: Before baricitinib, I was just using tofacitinib. The problem with tofacitinib, it wasn't covered, and so we'd have a lot of trouble trying to get it covered. The company that makes tofacitinib, they tried to help certain patients, if they had a certain economic condition. When I say economic, I say hold this and I'll have to change that. The

company that makes tofacitinib would try to help people who were financially disadvantaged, so they could get it.—

--The ones that were not financially disadvantaged, it would be more difficult. I used to get it from Canada actually. There was a pharmacy there that we were able to get it at a cheaper price. Because it can be quite expensive if people have to pay out of pocket for tofacitinib. So what I would do would be we'd fill out all the forms necessary to try to get the drug company to get some kind of help. If they couldn't and it was refused, then I would prescribe it either in Canada or patients would go to other countries, like Turkey, and really get it much cheaper there.—

--So that's the tofacitinib. To me, they work almost equivalently. I can't say one is better than the other, baricitinib versus tofacitinib. I'm not sure, there are no head-to-head studies that show that one is better than the other. But now that bari is available, then I would just say let's get going on this one, it's going to be covered by your insurance company. There may be a little co-pay or whatever. There are some forms we have to fill out, but we can get it covered.—

--Now, if they're already on tofa and it is being covered because they have rheumatoid arthritis or they have some other disease where it is covered, I don't change them. They're already on tofa, let them stay on tofa as long as the insurance pays for it. But if the insurance isn't paying for it, for most people it's very expensive, and so I will transition them to baricitinib.

JULES LIPOFF, MD, FAAD: It certainly changes the playing field once it's approved by the FDA. That should increase coverage. It does seem that Dr. Brett King has been a pioneer particularly in publishing studies and exploring with different diseases, so I want to give him a shout out. As far as when you start a JAK inhibitor, what is the timeline that it is effective? When do you start seeing hair growth? Will there be maintenance of hair if you were to stop the JAK inhibitor or would you lose all of it? Tell me about that.

JERRY SHAPIRO, MD, FAAD: Usually we start seeing growth sometimes early, even 8 to 12 weeks. But the studies where you can get cosmetically-acceptable regrowth, covering 80 percent of the scalp, that may take 36 weeks to get that kind of coverage. In the studies with baricitinib has shown that if you continue for 52 weeks, they will continue to grow even more hair. But when the onset of the hair growth, may start as early as two months and then you get more and more coverage, cosmetically-acceptable coverage.—

--So that's when you start seeing some kind of response. But even if you don't see anything at two months, it doesn't mean you should stop it. No, you should still continue it for I would say really at least 36 weeks, if not 52 weeks. If it doesn't work after 52 weeks, probably it isn't going to work that well. It doesn't work in everybody.

JULES LIPOFF, MD, FAAD: Are you likely to lose all of that hair if you stop the medicine? Or is it just dependent on being on it?

JERRY SHAPIRO, MD, FAAD: A lot of it is dependent on being on it. However, there are studies that show that people will keep their hair for quite a while and then it falls out. But it's not a cure, there is no cure for alopecia areata. There is data though that if you go from 4 mg of baricitinib and then you go to 2 mg after they have a full head of hair, let's say or almost a full head of hair, that the 2 mg does work. So once you've given them the 4, you can start the 2, because it comes in two different doses, the 4 or the 2. So if I do see that all the hair has re-grown, we may go to 2.

JULES LIPOFF, MD, FAAD: So I'm going to start winding down our interview, I really appreciate your time. As far as the horizon, what do you see as the landscape of treatments for alopecia areata? Are there new things, new JAK inhibitors, other classes of medications you anticipate becoming available or being studied?

JERRY SHAPIRO, MD, FAAD: First of all, there are definitely going to be new JAK inhibitors. Next year, another one will probably be FDA approved or maybe even two, by two other pharmaceutical companies. And I see more and more JAK inhibitors coming out, so I think that's maybe the route to go. But there may be other classes of medications that may help, as well, that somehow affect the immune system and block the pathway that causes alopecia.—

--There are studies with dupilumab, for instance, that show some success with dupilumab, although it's certainly not as dramatic and works as fast as a JAK inhibitor. So there are other drugs that are on the horizon that will be studied, but I think right now the big focus is on the JAK inhibitors.

JULES LIPOFF, MD, FAAD: Do you see any barriers to access? You commented on the insurance coverage and the difficulty getting around getting patients what you want to give them before, but do you think there are, for instance, any groups of patients more marginalized groups that are having more difficult access to treatments they need? And if so, how do you suggest addressing that?

JERRY SHAPIRO, MD, FAAD: I think now that it's FDA approved, I don't think there's any marginalized group at all. All we need to do is fill out the forms. We have a team at NYU that helps get the coverage for these people. I may have to write a letter of medical necessity stating the SALT score, the percent of scalp involvement, it has to be over 50 percent for certain insurance companies. So all I do is write some letters. We haven't had anyone really refused at this point, since it became available. We may have to fill out more letters but it usually is not as cumbersome as it was with tofacitinib.

JULES LIPOFF, MD, FAAD: As far as rounding this interview up, I again appreciate your time, what are the key practice points? What are the take home messages you want listeners, dermatologists looking to enhance their treatment of this disease?

JERRY SHAPIRO, MD, FAAD: Well, there's an algorithm. If it's very limited disease, we've been using intralesional corticosteroids. I've published even the concentration of what we use in terms of triamcinolone acetonide, the volumes and all this. So that's for limited disease. But the take home message here is for over 50 percent scalp involvement, JAK inhibitors must seriously be considered. And if you don't, I think you're doing a patient an injustice.—

--You should consider it. You should present all the facts to the patient. Go through the risks and benefits. And then you and the patient can decide whether this is the best treatment for them. And for people definitely with universalis, totalis, it's really the way to go, I go directly toward. I don't do systemic steroids. I may combine baricitinib with let's say minoxidil, we're using now more oral minoxidil. Brett King has combined the two with Rodney Sinclair, they're showing some better results.—

--Or we might use intralesional corticosteroids for the eyebrows. But if somebody has total alopecia totalis, universalis, you've got to think of going right away to the JAK inhibitors. It's FDA approved. And we now know the right dose. We know what to give the patient. We kind of know what to expect. And it's the way to go. And I never thought I would see this in my professional lifetime when I started 35 years ago that we would have something like this.

JULES LIPOFF, MD, FAAD: It sounds like you're very much an advocate and you've been involved with some of those studies, as well, and worked with the companies. So I think everyone definitely, it would behoove them to learn about the JAK inhibitors and be familiar and consider whether they're appropriate for your patients. Thank you so much for giving us your time this morning. It's been a pleasure learning more about alopecia areata. So again, Dr. Jerry Shapiro, thank you for your time. And this is Dr. Jules Lipoff. Thanks again and see you next time.

JERRY SHAPIRO, MD, FAAD: Thank you very much. Bye.