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New Approaches to Treating Vitiligo: The Emerging Role of JAK Inhibitors

Announcer:
You're listening to *DermConsult* on ReachMD, and this episode is sponsored by Incyte. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *DermConsult* on ReachMD. I'm Dr. Charles Turck, and joining me to examine the emerging role of JAK inhibitors in the treatment of vitiligo is Dr. Raj Chovatiya, who's an Assistant Professor of Dermatology and Director for the Center of Eczema and Itch at the Northwestern University Feinberg School of Medicine. Dr. Chovatiya, thank you for being here today.

Dr. Chovatiya:
Thanks so much for having me. I'm really excited to talk about some of the big progress we've made with vitiligo.

Dr. Turck:
Well to start, Dr. Chovatiya, would you give us an overview of the current treatment options available for vitiligo?

Dr. Chovatiya:
Sure, that's a great question, and I think that the first thing I really want to emphasize is that there's a common misconception that vitiligo is a superficial, or even some say cosmetic, condition and that's the first thing I really want to clarify. It's not a cosmetic condition; it's a chronic, inflammatory disease with very important autoimmune mechanisms, and we have safe and effective treatments for the disease. Obviously, we're in need of more, but there's a variety of different treatment options that exist right now. So many of the first-line treatments are oftentimes topical anti-inflammatory therapies. Topical corticosteroids and topical calcineurin inhibitors are two common ones. Largely these are pretty broadly acting, so they're not specifically targeted, and so thus, they do have some issues in terms of long-term efficacy and durability in terms of response. Phototherapy, particularly narrow band UVB-based phototherapy, is another very common one that's oftentimes combined with topical therapies, and a theme that you hear a lot in vitiligo therapy is combination approaches. Most people are doing multiple things at once, highlighting some of the difficulty in actually treating the disease with current options that we have right now. There are oral immunosuppressive agents that can be used in certain contexts, particularly in terms of rapidly spreading disease, so there's many pulses of oral steroids that are used. There's some data for more traditional oral immunosuppressive medications, as well. And finally, there's surgical techniques out there, where oftentimes people can do various types of grafting with this tissue, like melanocyte transfer. It's not available everywhere; it's a bit labor intensive.

And then, finally for folks who have quite a bit of body surface area in terms of vitiligo, there is actually an FDA-approved treatment for depigmentation. This is not repigmentation, but this is rather to make the smaller amount of remaining skin match the rest of depigmented skin, and so this is monobenzone or monobenzyl ether. And then of course, there's a variety of cosmetic camouflage options as well that are out there. But bottom line, by highlighting what the landscape looks like and what the really big needs are, I think we really need a much more straightforward treatment regimen.

Dr. Turck:
Well as a quick follow-up to that, where do gaps in the vitiligo treatment landscape exist?

Dr. Chovatiya:
So another really good question, and one I'm glad we're talking about now because we've been doing a variety of different treatments for vitiligo over a lot of years. For instance, topical corticosteroids, which are our first-line treatment, we've been using these for 50-plus years. But there's really no specific guidance in general on optimal regimen, frequency, or duration. If you go back in the literature, you're not going to find very many trials, specifically randomized, controlled, phase 3 trials, for topical corticosteroids. In addition to

these limited trials, we know that there's a lot of heterogenous study designs so it's really hard to compare efficacy of one treatment to another treatment. Additionally, there's always been a historical issue with diversity in our populations for studies, and vitiligo is no exception. And we know that the psychosocial burden of vitiligo affects certain patient populations more than others. If I really had to think about the big buckets regarding innovation and improvement with vitiligo therapy, you want something that's going to be durable and to keep working. You want something that's going to work fairly quickly, so you can really put a dent into rapidly spreading disease. You want something that's going to be safe, so you feel comfortable using it in the long run. You obviously want something that's going to stop depigmentation. That's step one. And then, step two is stimulating repigmentation. If I'm going to be greedy, I want high levels of repigmentation. That's really what our patients want as well. And then there's the other aspects, like balancing something that gives you good cost. You have access to something that's feasible. And I think all of that together, in my mind, is the perfect vitiligo therapy, and that summarizes a lot of the gaps that are out there as far as care goes.

Dr. Turck:
With that background in mind, let's zero in on JAK inhibitors. What are they, and how do they work to treat vitiligo?

Dr. Chovatiya:
Great question, and one that sort of gets more complicated the deeper you dig, but let's try to break this down into the simplest terms. And I think that we can take a bigger step back and talk about the general pathogenesis of vitiligo itself, and then I think it becomes really clear of the important role that JAK inhibition may play. So when we think about the inflammation and autoimmunity that's going on beneath the surface in vitiligo, there's multiple nodes of activity that are involved. We know that there's some intrinsic defects in melanocytes, the pigment-producing cells. They tolerate oxidative stress a little differently. They don't necessarily connect correctly; they're not lined up in the right way. We know that there's some genetic predilection with the disease as well. So there's family history that can increase risk. There's a number of gene loci that have come out of GWAS studies that have shown some degree of association. And we know that there's different mutations in certain genes related to the stress response and immune response, as well. When it comes to oxidative stress, we know that there's reactive oxygen species that are released from the melanocytes themselves and this causes an imbalance within pro and anti-accident mechanisms, and all of this together leads to an increased stress state. And finally, we know that there's an immune process going on here, both activation of the innate arm of the immune system, and then most importantly in this disease, the adaptive arm of the immune system. And so there appears to be a loop between cells that are in the skin and CD8 positive T-cells. These CD8 positive T-cells seem to recognize melanocyte antigens, ones they really shouldn't be recognizing. And so some of the words that you hear thrown around in the literature are gp100, Melan-A and MART-1, and tyrosinase; these are all proteins found in melanocytes, and these are all things recognized by your own T-cells. And we know that these T-cells are a really important source of interferon gamma production.

We also know that cells in the skin produce quite a bit of chemokines, another type of inflammatory signal. CXCL9 is an important one for the recruitment of immune cells, and CXCL10 is an important one for the localization of immune cells. And so there's this loop going on between cells in the skin and immune cells, so a production of each of these different signals. Now the bigger question is, how do these signals transmit their information to the inside of the cell to cause changes in transcription and translation of pro-inflammatory factors? This is where the JAK-STAT pathway comes in. So JAK literally stands for Janus kinase; STAT stands for signal transducers and activator of transcription. You can think of the JAK-STAT pathway as this little relay race or intermediary system that translates the signal from the outside of the cell into information that's recognized on the inside of the cell that causes downstream effects in transcription and translation. So the JAK proteins typically associate in pairs on the intracellular portion of different receptors for signals like interferon gamma, CXCL9, and CXCL10. JAK1 and 2 are two important JAK proteins that are involved in a lot of this signaling. So you could imagine that if you were to actually inhibit the activity of JAK proteins, you could stop this signaling process very early on, and stop it across multiple different signals that are important in vitiligo. In this way, JAK inhibition represents a huge evolutionary leap forward into how we can specifically and broadly attack inflammation when it comes to a disease like vitiligo.

Dr. Turck:
For those just tuning in, you're listening to DermConsult on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Raj Chovatiya about JAK inhibitors for the treatment of vitiligo.

Switching gears here a bit, Dr. Chovatiya, how do we know which of our patients with vitiligo may benefit from a JAK inhibitor?

Dr. Chovatiya:
I think one of the places I like to start is thinking about what are JAK inhibitor therapeutic options for our patients with vitiligo and thinking about the indications in the way that they were studied. And so there's one JAK inhibitor currently that's approved for the treatment and repigmentation of nonsegmental vitiligo. This is topical ruxolitinib cream, which was recently approved, and the indication for this particular drug is the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older. So I think this highlights a couple of important points. So somebody who's 12 and up might be a very good candidate, along with somebody who has

nonsegmental vitiligo. So let me explain that concept for a bit. Vitiligo historically has been characterized in two major buckets. There's nonsegmental, which is 80 to 90 percent of vitiligo, and then 10 percent or smaller is the segmental variant. Segmental vitiligo seems to occur much more rapidly and oftentimes in a unilateral or even people say dermatomal distribution. I've seen a bit more refractive therapy, and it probably has different underlying mechanisms. And potentially the way it's involved has something to do with the initial migration of melanocytes in the skin. Nonsegmental vitiligo, or oftentimes just what's called vitiligo, is the more common type that we're used to seeing across different mucosal surfaces like the lips, fingertips, and the face in generalized patterns. And so this is the one that's been much better studied in the case of JAK inhibition. So that's usually the type of vitiligo you're thinking about.

Dr. Turck:
Now once an appropriate patient begins treatment, what are some of the most common adverse events they may experience, and how might we monitor for them?

Dr. Chovatiya:
I think that when it comes to thinking about treatment, efficacy is always important, but you can't forget that safety is the other half of that coin and the one that probably matters to our patients, sometimes as much or even more. So in the case of topical ruxolitinib, which does have phase 3 data available that led to its approval as a treatment for vitiligo, the most common adverse reactions that occurred were acne in about 6 percent of patients, application site pruritis or itching in about 5 percent of patients, and then it goes back down to 4, 3, 2, and 1 percent for nasopharyngitis, headache, urinary tract infection, a little bit of redness around the application site, and then pyrexia as well. So bottom line, it was a pretty favorable treatment profile overall in terms of the most common things that were observed. Now when it comes to JAK inhibitors in general, no matter whether it's an oral JAK inhibitor or a topical JAK inhibitor, the entire class has a class-wide boxed warning mandated by the FDA. And this boxed warning contains warning that talks about serious infections, mortality, cancer, major adverse cardiovascular events, and thrombosis. And so a question that oftentimes comes up in those clinician-patient discussions is, what is this boxed warning and where did it come from? Is it something I should be worried about? So it's important to think about the context of where this warning comes from and how that relates to the therapeutic option that you're considering. So a lot of the warning inside this boxed warning comes from a very long-term, 10-year, phase 4, post-marketing study looking at a different JAK inhibitor – one of the earlier, broader acting ones called tofacitinib - in the context of rheumatoid arthritis patients who were over the age of 50 and who had at least one cardiovascular risk factor. And they followed these folks to understand whether or not there was an increased signal in some of these areas. And so, these areas that are spelled out in the boxed warning are all ones where it seems like there might have been sort of a slightly higher rate of these in patients treated with that JAK inhibitor versus standard of care with a TNF-alpha biologic agent.

Dr. Turck:
Well, as those final thoughts bring us to the end of today's program, I want to thank my guest, Dr. Raj Chovatiya, for joining me to discuss JAK inhibitors for the treatment of vitiligo. Dr. Chovatiya, it was great having you on the program.

Dr. Chovatiya:
Thanks so much for having me. My pleasure.

Announcer:
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