Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/dermconsult/a-look-at-the-evolving-therapeutic-landscape-for-vitiligo/14415/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

A Look at the Evolving Therapeutic Landscape for Vitiligo

Announcer:
You're listening to *DermConsult* on ReachMD. 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 evolving therapeutic landscape for 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 we get the time to chat with each other today.

Dr. Turck:
So, Dr. Chovatiya, let's begin by taking a look at some of these novel approaches. Starting with microRNA-based therapeutics, would you tell us how they work to treat vitiligo?

Dr. Chovatiya:
Sure. So I just want to say that there is no microRNA therapy for vitiligo currently available, but what we're going to be talking about is some really cool research into an area of science we're just beginning to understand that hopefully is not only going to change the way that we could treat vitiligo, but many other diseases. So let's just get to the basics. MicroRNAs are really short pieces of noncoding RNA, so about 19 to 25 nucleotides. And they're really important for gene expression and regulation. We didn't really know much about their existence for a long time, but we've learned a lot over the past decade. Now they're really important when it comes to post-transcriptional regulation and at the translational level as well. So you can basically allow finetuning for degradation of mRNA, or repression of actual translation. There's a bunch of microRNAs that can attack one mRNA molecule, or one mRNA can find multiple different microRNAs; it's very cool in the way that they can mix and match. So there's a lot of different studies that have kind of looked at the role that microRNAs play in cell survival, immune cells, and melanocytes, and you can imagine based on some of the words I'm saying how this might be interesting for vitiligo where we know that there's really important roles that the immune cells play in terms of autoimmune reactivity, melanogenesis, differentiation, and oxidative stress. And so really, the big idea here is if we could actually understand and unleash how these microRNAs work, we might be able to modulate these areas that are either inappropriately activated or overactivated in the case of vitiligo.

Additionally, there's some cool research showing that different types of microRNAs might actually be really good biomarkers to understand disease severity and disease progression. So really, there's a couple of strategies in which therapy is centered on. One strategy is directed towards gain-of-function type mutations. And in this way, you can basically inhibit pathogenic microRNAs by using microRNA antagonists, such as anti-microRNAs. There's another strategy where you're basically replacing a microRNA where you'd want to actually have more of something to actually modulate gene expression as well. This technique actually has been able to be shown previously to alter melanocyte migration in some studies. So I think this one you should pay attention to because you may actually see some progress as a vitiligo therapeutic in the future.

Dr. Turck:
How about adoptive Treg cell therapy? What do we need to know about that area of research?

Dr. Chovatiya:
I love it, we're really digging deep on the immunology today. And this is another one of those really exciting areas that if you asked me

10 to 20 years ago, I wouldn't have much to say, but we really learned a lot about how regulatory T cells modulate—that's the key word here, modulate—elements of activity in the immune system. So taking a step back and just reframing things, when you think about autoimmune disease, chronic infection, and transplant rejection, basically, there's something similar happening in all these states, right? The immune system is responding inappropriately to self-antigens or really doesn't stop reacting even though something has been removed. And so we oftentimes use immunosuppressants to reduce inflammation or targeted biologic therapies or small molecule therapies. But really, we have to keep using these over the long run to try and modulate that activity. What if we could have a longer-lasting response to actually modulate that overactivity of the immune system? This is kind of where regulatory T cells come in. They basically allow you to maintain a healthy immune response and suppress inappropriate activation. And in recent years, we've actually been turning to Tregs for adoptive cellular therapies, where you can actually reintroduce or add specific Tregs to modulate some type of immune activity that you really want to damp down.

Now these are overall pretty rare cells in the body, only about 5 percent of circulating CD for positive T cells or Tregs. But basically, once Tregs are activated by their cognate antigen, they suppress the immune response in a few different ways. They can release inhibitory cytokines, they can express certain suppressor cell surface molecules like CTLA or PD-1, which we've learned a lot through oncology, and they can also actually deprive nutrients needed for T cell activation. So as of now, there's sort of three therapeutic areas in which people are looking at Tregs. There is adoptive cell therapy for polyclonal T regulatory cells that respond to a lot of different things but lacks sort of much specificity, but these are oftentimes derived from an individual's own blood. There's antigen-specific Tregs that can be proliferated ex vivo utilizing donor antigen presenting cells. These are rare and hard to come by, but you can actually end up with a lot more specificity, and then chimeric antigen receptor Tregs or CAR T cell therapy. This has been an area that's shown a lot of growth in oncology and now moving into the autoimmune disease regulation space.

Now in terms of what we know about vitiligo, we know that there's low numbers of Treg cells in vitiligo skin, which makes sense because we're having extra immune activity. And we know that when you transfer Tregs or signals that cause recruitment of Tregs, you can actually improve depigmentation. So I think this is where we're going to start seeing if we can actually harness what we know into one of these therapeutic modalities that I just discussed.

Dr. Turck:
Now if we look at one more emerging therapy, Dr. Chovatiya, what do we need to know about JAK inhibitors?

Dr. Chovatiya:
Sure, so JAK inhibitors have really been the hot-button word in dermatology and a lot of medicine in the last couple years. And let me frame this one in terms of the overall organization of the immune system so it makes sense why we're thinking about this as a target too. So in the immune system, you have a number of inflammatory mediators, soluble signals that bind to different receptors on the outside of cells. But the cool way in which evolution works is that nature waste not, want not; you utilize actually very similar signaling machinery for a lot of different types of signals. And this is where the JAK-STAT pathway comes in. JAK literally stands for Janus kinase. So it's a family of four proteins, JAK 1, 2, 3, and TYK2 that occur in pairs. And these actually bind to the intracellular portion of a number of different cytokine receptors. This is how you can take a signal on the outside of the cell, transmit it to something on the inside of the cell, and then cause activation of the stack proteins, signal transducers, and activators of transcription. These can directly go to the nucleus and modulate transcription. And then you actually end up getting transcribed mRNA and then translation of protein. So in this way, when the immune system is overactive, you're seeing a lot of signaling through this pathway and a lot of production of downstream pro-inflammatory mediators. So this is kind of where the revolution in medicine part comes in, where there's been a lot of different disease states, including vitiligo, where there's been extremely promising results by using small molecule inhibitors of that JAK protein activation to really cut down on inflammatory signaling.

Now in the case of vitiligo, we know that there's a really important loop of activity between CD8-positive T cells and melanocytes that cause their destruction. So we know that there's a lot of interferon gamma that's produced by T cells themselves; that gamma binds to downstream cells, causing immune activation and destruction. We also know there's a lot of chemokine, like CX 09 or even 10 produced, and these actually bind directly to T cells. Both of these signals utilize that JAK-STAT signaling pathway. So this is really where you can almost start to see the translation of what I just mentioned in basic immunology to a disease-specific state. And for this reason, that's why earlier this year, we actually saw approval of topical ruxolitinib cream, a JAK 1 2 inhibitor that actually met primary endpoints for looking at facial vitiligo resolution and repigmentation but also other areas of the body as well. Now there are other JAK inhibitors currently in research and development, probably one of the furthest ones along is ritlecitinib. This is a mixed JAK 3 and TEC inhibitor. And there's been older studies looking at two JAK inhibitors; you might be familiar with tofacitinib and brepocitinib as well. But I've also demonstrated that really targeting JAK proteins can be an effective way to work against 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 the changing therapeutic landscape for vitiligo.

So Dr. Chovatiya, if we look beyond these emerging therapies for just a moment, how do we create individualized treatment plans for our patients with vitiligo?

Dr. Chovatiya:
So I think this is going to be a stepwise process because compared to maybe where we've gone in terms of psoriasis or eczema where we've learned about some of the more finetuned aspects of the actual activation and disease, we're really beginning to unlock some of those mysteries in vitiligo. And in the case of this disease, we haven't had that many treatment choices. So in many ways, we haven't been able to modify and personalize our treatment strategies. But now as we develop more and more therapeutics—in addition to conventional topical anti-inflammatory agents like steroids, topical calcineurin inhibitors, phototherapy, oral immunosuppressive agents, and potentially maybe one day biologics, oral JAK inhibitors, topical JAK inhibitors, and then some of those cooler emerging immunological technologies I talked about—different combinations of these approaches may actually be able to result in more targeted repigmentation for our patients. And the ultimate goal which we have across inflammatory skin diseases and vitiligo is no different is if we can have a patient come into the office, learn a few things about them, and maybe even have a point-of-care test, we can really understand how we match the right therapy with the right patient.

Dr. Turck:
Now we've certainly covered a lot of ground today Dr. Chovatiya. Before we close, do you have any final thoughts on these novel approaches to treating vitiligo?

Dr. Chovatiya:
Yeah, I want everyone to stay excited. I mean, for as much as I can sit here and say that, you know, these things are perhaps far off very nebulously, the case in which we've seen development go from the actual bench to the bedside has been incredible. And really, even a few years ago, we weren't even talking about JAK inhibitors in vitiligo, and we have an approved therapy as of this year, and that is an astronomical pace. So I want everyone to stay motivated knowing that we have new therapies and more are coming. And really a disease that folks may have not necessarily been thought about in a medical sense really should be thinking about vitiligo as a chronic burdensome autoimmune condition, that we now have the ability to treat, stop in terms of depigmentation, and repigment for our patients. It's a really exciting time to be practicing medicine and, in particular, dermatology.

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 emerging treatment options for vitiligo and other key considerations for patient management. Dr. Chovatiya, it was great to have you on the program.

Dr. Chovatiya:
Thanks so much. Always a pleasure working with you.

Announcer:
To access this and other episodes in the *Derm Consult* series, visit ReachMD.com/Derm Consult, where you can Be Part of the Knowledge. Thanks for listening!