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## JAK Inhibitors in Vitiligo Treatment

### Ted Lain, MD:

Hi, I am Dr. Ted Lain. I'm a board-certified dermatologist living in Austin, Texas. I am excited about the promise of JAK inhibitors for vitiligo. Of course, we have one currently FDA-approved topical JAK inhibitor called Opzelura or topical ruxolitinib 1.5%. This is really exciting for our patients because prior to topical ruxolitinib, we haven't had anything FDA-approved for vitiligo. Of course, Opzelura is applied twice daily. It does take time for us to see results and unfortunately, as with any JAK inhibitor, whether topical or systemic, the timeline to response varies by patient. And so oftentimes, we have to be individual cheerleaders for our patient if they just don't see results in the first 12 to 24 weeks, they may see results after that. And so it's really important for us to ensure that our patients understand at the very beginning that they have the correct expectations in terms of treatment response, just like we would expect for excimer laser, for example, or narrowband, which can again, take quite a while for more pigment to appear within these vitiliginous areas.

The mechanism of action of JAK inhibitors, we believe, is of course, acting through that Type 1 interferon pathway, reducing the effect of interferon gamma, reducing the production of chemokines that cause the recruitment of helper T cells and other inflammatory cells that will lead to the release of inflammatory cytokines that can then lead to melanocyte death. If we're able to stop that melanocyte destruction, stop that pathway, at least, reduce that pathway, we're able to do a couple of things. We're able to both allow stem cells in that melanocyte bulge within that follicle to differentiate into adult melanocytes, which can then, of course, produce melanin and do what they do, and we start seeing those islands of repigmentation that we're so used to seeing within our vitiliginous areas that then coalesce, right? Or you can get marginal repigmentation, which is the slow crawl of those melanocytes from the unaffected margins of those patches that slowly cause the reduction in size of those patches, and oftentimes, those occur simultaneously.

I'm using JAK inhibitors, primarily the topical JAK that I mentioned, but not as monotherapy. Quite frankly, even though this is off label, I oftentimes will use it in conjunction with excimer. I might do pulse steroids as well, if we're having a flare and or use the topical Opzelura Monday through Sunday, and then maybe add a strong topical steroid Saturday and Sunday. So it depends on the patient, depends on the history. And then we may in addition, start using oral JAKs or systemic JAKs off-label. Of course, there are systemic JAKs that are going through clinical trials, including phase 3 clinical trials, so I believe in the next three to five years, we're going to have more options within the JAK inhibitor family that are systemic in nature versus topical, which I'm excited about because I do think that will help those patients who are having current flares or having spread of their vitiligo.

And I should mention, we're primarily discussing non-segmental vitiligo versus segmental vitiligo, right? Segmental vitiligo is that which occurs in a younger patient, usually. It tends to be on one side in one segment or dermatome even. It tends to come on quickly and burn itself out quickly and is pretty resistant to treatment, usually. The non-segmental seems to be much more indolent in nature, starts later on in life, late teens to early twenties and can be progressive, but again, usually follows an indolent course. Can be bilateral, multiple areas of the body can be affected and is much more amenable and responsive to treatment, whether systemic or topical.

The one thing I would say as a word of caution is, if there is leukotrichia. In other words, if the hairs, the majority of hairs, within a patch of vitiligo are white, then there is likely going to be a very poor response to any treatment because we just don't have those melanocyte stem cells in the bulge from which to derive the adult melanocytes and then, of course, the pigment production. So always look out for the predominance of white hairs or leukotrichia because that can portend a poor response to any kind of treatment.

In terms of the future of JAK inhibitor therapy for vitiligo, as I mentioned, I think the systemics are going to be the future. I think trials would show the combination of systemics plus narrowband are going to be really interesting to more quickly elicit a pigment response. And then, as we progress and we see some more phase 4 trials or even, investigator initiated trials, looking at combination therapy will

be, I think, the future of vitiligo therapy.