More Than Hair Loss: Understanding the Role the Immune System Plays in Developing Alopecia Areata and Its Treatment Implications

CMEO Journal Club Transcript

Emma Guttman-Yassky:

Hello everyone and welcome to the first episode of the three-part journal club series titled "More Than Hair Loss: Understanding the Role the Immune System Plays in Developing Alopecia Areata and Its Treatment Implications." Today we will discuss fresh research into alopecia areata pathogenesis and immune-modulating therapies. I'm Dr. Emma Guttman-Yassky. I am the System Chair of the Department of Dermatology and the Waldman Professor of Dermatology and Immunology at the Icahn School of Medicine at Mount Sinai in New York City. I'm also the primary author of today's journal club article entitled *Ritlecitinib and Brepocitinib Demonstrate Significant Improvement in Scalp Alopecia Areata Biomarkers*. This activity is supported by an educational grant from Pfizer and brought to you by CME Outfitters, an award-winning accredited provider of continuing education for clinicians worldwide.

Alopecia areata is a disease that can affect any race or ethnicity. It starts at any age. We see it even in babies, infants and young children, and really throughout life. And many times, it starts as one or two patches but can extend to total scalp or total body hair loss, and then it's alopecia totalis and universalis. About 10% to 15% and some would even say 20% will develop into alopecia totalis and universalis. And alopecia areata has a huge impact on the quality of life of patients and not only the patient; it's the patient and the family.

You see families of a patient and families of children are really devastated because our hair is in a way our identity, our business card, and losing that really impacts the way we see ourselves and the way we look ourselves in the mirror. And not only that, it's the way society is looking at us. We hear about children and adolescents being bullied by their peers and also adults who lose confidence when they deal with other people, and they really become withdrawn. So, it has a huge impact on quality of life, and we really need better treatments for alopecia.

So, let's dive deep into this Allegro biomarker substudy. So first, what were the methods of the study? It was a phase IIa, randomized, double-blind, placebo-controlled, multicenter clinical trial, and the patients included in this study agreed to give skull tissues and blood. We took skin biopsies, we and others who participated in this substudy, but my lab participated in the analysis of the study.

In fact, the analysis was done in my lab, and it was an unusual study because it took two JAK inhibitors as compared to placebo in a study. So, what did we see? We saw that hair growth was associated with decreases in lymphocytes, CD3 cells, and CD8 cells, and also NKG2D were associated with alopecia areata, and they also showed decreases. We also showed decreases in some dendritic cells that also are involved in alopecia areata and in mass cells and Langerhans cells. So, basically, the cells that were implicated in alopecia areata were decreased in this study. Not only that, we are seeking in each study to see how it relates to improvement in hair growth, so we associated these decreases to hair growth of patients.

Alopecia areata is believed to be mediated by T cells, both CD4-positive T cells and also CD8 cytotoxic T cells, resulting in damage to hair follicles. Basically, think about an attack of T lymphocytes on the hair follicle and the

patient ultimately will lose the hair. There are multiple immune cells besides T lymphocytes involved. T regulatory cells are involved, dendritic cells, mast cells, Langerhans, and other cells.

And there are different immune pathways that were suggested to be involved in alopecia areata, Th1 immune pathway and, more recently, also the Th2 immune pathway. That is also an important pathway because, remember, patients with alopecia areata many times also have other atopic manifestations such as asthma and atopic dermatitis, explaining in a way why the Th2 immune pathway is also involved in some of the treatments going into alopecia areata that also target specifically the Th2 immune pathway, and JAK inhibitors target both Th1 and Th2 immune pathways. And we know that JAK inhibitors are effective in alopecia areata. Now we have that knowledge from multiple case studies, case series, and recently also major clinical trials that show efficacy in early-stage and later-stage studies, including phase III studies.

These results really shed light into the pathogenesis of alopecia areata, positioning alopecia areata not only as a Th1-driven disease but also as a Th2-driven disease, also supported now by other studies. So, alopecia areata is a Th1 and Th2 immune-driven disease with abnormalities in hair keratin, potentially induced by the cytokines that are upregulated, the Th1 and Th2 cytokines such as IL-13 for Th2 axis and interferon gamma for the Th1 axis, and potentially IL-4 also for the Th2 axis. These have effects on reducing hair keratin that are very low in patients with alopecia areata. So, we gained a lot of insights into the alopecia areata pathogenesis and into understanding the local impact of immune modulation in the scalp and also on the systemic inflammation in treatment responses because by this modulation you modified also some systemic responses.

So, by giving a JAK inhibitor, you modify the activity in the scalp but also reduce the systemic inflammation. And we know that patients with alopecia areata have systemic inflammation, particularly when they have moderate to severe disease, and when I say moderate to severe disease it is significant involvement in the scalp, such as in this study of 50% scalp involvement and more. So, you also have systemic inflammation that you need to modify, and that has also been modified by these drugs. So, I think it's a revolutionary study that besides the fact that it introduces a new treatment for patients, it showed that we can modulate this disease, both in the skull tissues and also, we can modify the systemic inflammation. This is a treatment that can provide patients hair growth and also reduce their inflammation in the skull and the systemic inflammation. When we think about alopecia areata, we usually don't think about inflammation, right? Because when you see a patient, the patient doesn't have hair, but the areas don't appear red, and this is a mistake. We need to understand they have inflammation.

They have inflammation in the scalp. They have inflammation in the body, and they need a systemic anti-inflammatory modulator that will decrease that inflammation and systemic is important here because studies with topicals in alopecia areata did not pan out. The follicle is very deep and, not only that, they have systemic inflammation. A topical will not do it. You have to give a treatment systemically. I think that's important and, with that, I will leave you with the idea that now I think we are really changing the way we think about the pathogenesis of alopecia areata. And we really are opening, through these studies, the door for new treatments, providing help to our patients with moderate to severe alopecia areata.

Now, as I told you, multiple biomarkers were associated with the clinical improvement as determined by the SALT score. I told you that the SALT score ranges from zero to 100, and our intent in such a study is to bring SALT score towards zero. Many of the biomarkers that we saw, both Th1 and Th2 and hair keratin biomarkers, were

associated with this clinical improvement. Why this is important is that this is basically the first study done that showed in a placebo-controlled fashion that placebo doesn't change biomarkers, but the drug changed biomarkers and changed it early.

Even for the best dermatologists, it's hard for us at 12 weeks to see clinical improvement because it takes a very long time for hair to grow. However, in the tissue, you see these changes early. I think it's the first study that also associated clinical response with decreasing inflammation and increased hair keratins. In very successful hair growth, you have to have these three pillars. You have to grow hair, you have to decrease inflammation, and you have to increase the hair keratins. We saw with these JAK inhibitors the three pillars identifying biomarkers of response and now we can take them on to other studies with alopecia. And, again, we can do it early, even before you see clinical improvement.

We saw that molecular responses were much better in patients who had less time since the initiation of alopecia areata. For example, we found that if you had activity of heavy growth in the last 3.5 years, you had a better chance to get better hair growth than if you had the last incident of activity of your alopecia areata in more than 3.5 years. So that is a very good example of why, if you have alopecia areata, you need to go to your doctor today because you cannot postpone your treatment. It's super important to do it early because you do not want to get to the dead-end disease phenotype when we cannot grow your hair. You have to have active disease and you have to have inflammation because then we can switch that inflammatory phenotype. But if you don't have that inflammation anymore, then there is nothing to do. So it’s very important to go really early and seek help from your physician.

We also saw that the lesional phenotype of patients with alopecia areata started to become more similar to the non-lesional scalp or more normal-looking scalp of patients with alopecia areata. We saw a shift between lesional phenotype and non-lesional phenotype.

What does it mean? It means normalization. This is what we want to achieve. When you grow hair, you are normalizing your skull towards the non-lesional or the skull that has hair of patients with alopecia areata. And that was quite impressive. That started already at week 12, so sometimes even before we see clinical responses, we see that shift towards non-lesional phenotype. And this is the beauty of biomarker studies because we saw the results earlier than we saw the clinical responses. We saw a shift towards normal scalp at 12 weeks and even more at 24 weeks with both of the JAK inhibitors in this study. We also found multiple biomarkers that were associated with the responses. Among these biomarkers were Th-1 and Th-2 biomarkers, so Th-1 biomarkers such as interferon gamma and Th-2 biomarkers such as IL-13 were the two leading cytokines of the Th-1 and Th-2 pathway were associated with the response against strengthening the idea that both Th-1 and Th-2 axes are involved in alopecia areata. And, importantly, it also associated the clinical response with increases in hair keratins. Multiple hair keratins were significantly induced by both JAK inhibitors in this study.

In terms of how we score alopecia, there is a score called SALT that scores the severity of alopecia. And in SALT, we are dividing the scalp into quartiles, and we are scoring these quartiles with the total SALT score being 100, meaning if you have 100, that's not good. It means you lost the entire scalp hair. If you have a SALT of zero, it means you don't have alopecia. When we think about total scalp hair loss, we think about 95% and up. That's really alopecia totalis because if you have just a few hairs left, it's irrelevant. You have total scalp loss. And here

we see some examples ranging from patchy alopecia to significant alopecia areata. Now let's dive deep into the pathophysiology of alopecia areata.

This has been episode one of this three-part journal club series covering innovative alopecia areata research. To view additional episodes on clinical evaluation and disease management, please visit www.cmeoutfitters.com. Thank you for joining and providing the best care for your patients. Thank you.

