Transcript Details

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Evolving Pathogenic Concepts on Atopic Dermatitis, its Systemic Nature and its Therapeutic Implications

Announcer:
Welcome to Grand Rounds Nation CME on ReachMD. This is the National Jewish Health and Prova Education segment, Evolving Pathogenic Concepts on Atopic Dermatitis, its Systemic Nature and its Therapeutic Implications.

The faculty for this activity is Emma Guttman-Yassky, MD, PhD, Associate Professor of the Icahn School of Medicine at Mount Sinai Hospital in New York, NY.

Dr. Guttman-Yassky receives consulting fees from AbbVie, Almirall, Anaco, Asana Biosciences, Celgene, Dermira, Eli Lilly, Galderma, Glenmark, Kiowa Kirin, LEO Pharmaceuticals, Medimmune, Mitsubishi Tanabe, Novartis, Pfizer, Regeneron, Sanofi, Stiefel/GlaxoSmithKline, Vitae, and has contracted research for Celegene, Eli Lilly, LEO Pharma, Medimmune, Novartis, and Regeneron.

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After listening to this activity, participants should be able to:

- Discuss the pathophysiologic mechanisms of atopic dermatitis (AD)
- Provide an update on the development of new management approaches for AD

Dr. Guttman-Lasky:
Hi, my name is Emma Guttman-Lasky. I'm from Mount Sinai in New York, and I will be talking to you today about Evolving Pathogenic Concepts on Atopic Dermatitis and the Systemic Nature of Atopic Dermatitis with Therapeutic Implications.

Atopic dermatitis is a very complex disease that has abnormalities in immune responses but also has skin barrier abnormalities, as Donald Leung and I showed a few years ago. And due to the abnormalities in immune responses and the barrier abnormalities, this led to two proposed mechanistic hypotheses for atopic dermatitis. The first one was the outside-in hypothesis that suggested that atopic dermatitis is a disease of fixed or genetic epidermal barrier defect that may trigger abnormal keratinocyte hyperplasia in secondary immune activation, and this hypothesis got the revival in 2006 with a finding of the filaggrin gene mutation. Now, we must remember that the filaggrin gene mutation is only present in 10 to 40% of the atopic dermatitis patients, so it's not present in the majority of patients. And in African-Americans, which we have 12% of African-Americans with atopic dermatitis, less than 3% have the mutations, so definitely the mutation is not the entire story of atopic dermatitis.

Now, the second proposed hypothesis was the inside-out hypothesis, or the immune hypothesis, and this hypothesis suggested that the abnormal epidermal phenotype that we have in the lesional skin of atopic dermatitis patients is driven by the increased expression of cytokines that are produced by distinct T-cell subsets.

Now, the barrier defect in atopic dermatitis also has clinical correlations. What we see when we examine our patients, we see epidermal hyperplasia, or epidermal thickening lichenification, and when we look under a microscope on atopic dermatitis lesions and even

sometimes in the nonlesional skin, we see epidermal hyperplasia. We see a thick epidermis when we stain for H & E, and when we stain for proliferation markers for keratin 16 and Ki67, two recognized proliferation markers, we find wide expression in the epidermis of these proliferation markers, also characterizing the epidermal hyperplasia in atopic dermatitis very similar to what is seen in another inflammatory skin disease, namely psoriasis, as compared to normal skin when you see a very thin epidermis.

Now, invariably, atopic dermatitis skin lesions in even nonlesional skin are invariably characterized by immune activation. Both acute and even more in chronic atopic dermatitis skin lesions we see large T-cell infiltrates and also large dendritic cell infiltrates, so many immune infiltrates. T-cells and multiple dendritic cells are characterizing both the acute lesions of atopic dermatitis patients and even more the chronic lesions.

Now, these T-cells are basically secreting cytokines and chemokines. And what are these cytokines and chemokines? They are mostly Th2 and Th22 cytokines and chemokines, although there are some Th1 and Th17 associated markers also upregulated in skin of atopic dermatitis patients. We will go over several of them.

So, Th2 markers that are widely increased in both acute and even more in chronic lesions, what are these? They are the main Th2 cytokines. We have here IL-4, IL-13 and the itch cytokine IL-31 and associated chemokines such as CCL17, CCL18, CCL13, CCL26 and others, and we have the Th22 cytokines and chemokines, the cytokine IL-22 that increases from nonlesional to acute disease and even more in chronic disease and the associated S100 that are induced by IL-22, also by IL-17. As you see by staining of S100A7 and S100A8 from the lesional skin where they are entirely not expressed, there is suddenly appearance of an expression in acute disease and even more in chronic disease of the S100. As we saw also by realtime PCR, there is a big jump from nonlesional to acute disease and even more in chronic disease.

Now, very important work done by the group of Donald Leung showed that the Th2 cytokines, the primary Th2 cytokines, IL-4 and IL-13, are able to downregulate in keratinocytes. In an in vitro experiment, they are able to downregulate epidermal differentiation proteins. What are these proteins? These are very important proteins that are downregulated in atopic dermatitis lesions and even in the nonlesional skin. So, what are these? These are filaggrin, loricrin and involucrin. We can see that each one separately and together they are downregulating the expression of the filaggrin, loricrin and involucrin as compared to keratinocytes that did not have the cytokines, and that is important because these cytokines are contributing to the barrier dysregulation that we have in atopic dermatitis.

Now, importantly, in atopic dermatitis we now have a paradigm shift in the pathogenesis of the disease that we started to have a few years ago, and that is fairly relevant to treatments that are now going into atopic dermatitis. So, let's review it together. Already in nonlesional skin we start to have activation of cytokines and chemokines, and that continues further to acute disease and even more to chronic disease.

So, what are these cytokines and chemokines? We have the Th2 cytokines that are really important, IL-4 and IL-13. They have several things that they are doing here. They inhibit antimicrobial peptides such as HBD2, LL-37, that are very important to fight infections. And we all know that atopic dermatitis patients are colonized more by bacteria, and we have more infections in patients with atopic dermatitis. They also disrupt the barrier. As we saw, they reduce filaggrin, loricrin, involucrin, and also lipids, as was shown by others. And we have the IL-31 cytokine that starts the “itch scratch” lichenification cycle. We have IL-22 cytokine that is derived from Th22 that starts the onset of the hyperplasia and together with IL-17 synergizes to produce the S100. And all this process continues forward to chronic disease perpetuating the disease, so it is the immune responses that are responsible for perpetuating the disease, and that's very important. And again, now we have targeted treatments that target multiple axes in the disease.

So, now we need to ask, after we learned what's happening in adults with atopic dermatitis, is the pediatric atopic dermatitis phenotype similar to that that we see now in adults? And why are we asking this? Because the paradigm shifting discoveries in atopic dermatitis are all based up to now on the adult biomarkers, and these reflect decades of disease activity, because usually, 85% of the cases begin before the age of 5. And when we sample adults they have activity of disease for many years. So that's collaboratively, together with the group of Amy Paller from Chicago, we aim to determine differences and similarities between early-onset atopic dermatitis in children and chronic atopic dermatitis in adults with similar activity of disease. How did we do that? We assessed blood and skin samples from 20 atopic dermatitis children that are less than 5 years old, and they are within 6 months of disease onset, as well as 14 age-matched controls, and, of course, we compared to the adults.

So, what did we see? We first studied the blood, and in blood we saw that there is only one game in town in children. In blood in children, we had strong Th2 skewing in blood, and this Th2 skewing was only confined to CD4-positive cells, so only CD4-positive cells were shown to be producing IL-13, and that was seen mostly in skin-homing cells, cutaneous lymphocyte antigen-positive cells that are homing to skin, not in CLA-negative cells that are what we call systemic cells, and that was not seen in CD8-positive cells, unlike adults. What happened in adults? In adults, the Th2 activation was also seen in CD8-positive cells and also seen not just in the CLA-positive cells, it also extended to CLA-negative cells, but in children, the activation in blood was only seen in the Th2 cells that are homing to

skin. We did not see Th1, Th22, Th17 or Th9 subset expansion in the blood of atopic dermatitis children, only Th2 skewing in blood in early atopic dermatitis in children.

Now, we need to ask: What is happening in the skin of these children at the initiation of disease? Remember, these children are within 6 months of disease initiation. We found very large activation of Th2 cytokines and chemokines such as IL-13, the main cytokine of atopic dermatitis, or the main cytokine of Th2, IL-13, IL-5 also another important Th2 cytokine, and also CCL26, CCL18 that are important chemokines of the Th2 axis, and also the itch cytokine, IL-31, very large increases in children. So, the Th2 axis is also activated in skin of atopic dermatitis children, and, in fact, it is activated as in adults or even more than in adults, and that surprised us to find this activation already within 6 months of initiation of disease, whereas the adults have chronic disease.

Another surprising factor that we found, we found that filaggrin, that is one of the main proteins of differentiation, was not reduced in children, unlike adults where we are used to seeing it very reduced, not only in lesions but also in the nonlesional skin. As you can see, in children it's not reduced, not in the lesional skin and not in the nonlesional skin of atopic dermatitis children. In fact, it's slightly upregulated compared to healthy children, and that was very surprising to us. So, you do not find that reduction in filaggrin. So, we saw that there is early and potent Th2 activation in blood and skin of atopic dermatitis children, and this really establishes the systemic nature of new-onset atopic dermatitis, already at that stage.

Pediatric nonlesional skin, as you saw, is already hyperplastic. It's already thickened, and it's accompanied by significant inflammation, as we saw, Th2 inflammation, highly-activated cytokines to levels often higher than in adults, and possibly this reflects true disease initiation. So, the nonlesional skin of children really provides a window to true atopic dermatitis initiation, because in adults, again, they have many years of disease activity, and we cannot really assess true atopic dermatitis initiation. Now, importantly, what I showed you, the filaggrin deficiency of adult atopic dermatitis is missing in early atopic dermatitis, and this challenges the notion of filaggrin as central for disease solicitation and instigator of the “atopic march.”

Now, we need to remember the allergic march starts or the atopic march starts with eczema. It starts around 3 months of age, and after that come food allergies that come around 1 year, maybe a little bit before 1 year, after that allergic rhinitis, and only after that comes asthma. So, we need to ask the question: Can the atopic march be prevented by appropriate immune manipulations using broad or specific T-cell targeting once the skin phenotype has developed? So, once children already have this moderate to severe disease that I show you that actually lead to systemic disease, can we prevent the other atopic associations such as asthma, food allergy, allergic rhinitis by treating early potentially with a systemic drug that will be either targeting T cells in general or target one specific immune axis such as Th2? And I think that's a very important question to be answered in the next few years.

Now, how do we test the immune hypothesis of atopic dermatitis that I put forward? A prediction of the immune model is that immune suppression is able to reverse the epidermal pathology. The hypothesis can be rejected if immune suppression is achieved but the epidermal phenotype is persisting. And I want to show you a test of this hypothesis, our study with dupilumab. Dupilumab is a specific immune antagonist that targets the Th2 immune axis. So, dupilumab is a fully human monoclonal antibody that targets IL-4 receptor alpha, and because it targets the receptor, it potently inhibits both IL-4 and IL-13 signaling, basically suppressing the entire Th2 pathway. And the study that I will show to you was the Phase 1b study, a 4-week study with weekly injections of dupilumab, 75 mg, 150 mg, 300 mg and placebo. It had a total of 67 patients, but 18 of these patients participated in the biopsy substudy that I will show you its results.

So, for the biopsy substudy we had 18 patients. Ten completed pre- and post-assessments, and patients had biopsies. The biopsies had genomic studies done on them. We did not have immunohistochemistry for this study. But keratin 16, as I showed you, is a very good marker of epidermal proliferation, so that gave us a window to see how the epidermal hyperplasia is reduced, and we found a dose response in K16. As you see here, major reduction with dupilumab 300 mg in K16, actually around 10-fold changes, around 2-fold changes with dupilumab 150, and the placebo exacerbated about 2-fold changes. I want to tell you that this reduction with keratin 16 with dupilumab 300 is actually higher than that seen with cyclosporine in 12 weeks. So in only 4 weeks of dupilumab, we had higher reduction in the keratin 16 compared to cyclosporine A that is very heavy guns of 12 weeks.

Now, we also performed many inflammatory markers, a genomic expression of many inflammatory markers pre- and posttreatment using realtime PCR, and what I show you here is a heat map of all these markers so that you can appreciate the reductions or elevations in these markers. Blue is downregulation and red is upregulation. So, what you can see in the dupilumab 300 group, there is marked downregulation of multiple markers; in 150 dupilumab a little more mixed result, and with placebo there is upregulation of many markers. We were surprised to find that the reductions are beyond the Th2 pathway that we expected, of course, to see downregulated with dupilumab. So, yes, we do have reductions in the Th2 chemokines CCL17, 18, 13, 22 and 26 that are part of the Th2 axis, but we see major reductions also in Th17 and Th22 markers such as the S100s, IL-23 and IL-17 genes such as elafin, PI3, IL-23, p19, which is IL-23A, and IL-23 p40 and IL-17A cells, and also hyperplasia-related genes such as keratin 16 that we discussed that are not direct

targets of IL-4 receptor alpha, but yet they are extremely downregulated here.
So, one possibility may be through the inhibition of IL-4 induced differentiation of dendritic cells, but more studies are needed to see how basically targeting the Th2 axis also affected the Th17 and Th22 axis. But, importantly, what I think it showed, the study showed that dupilumab impacts both the inflammation but also the barrier dysfunction of atopic dermatitis. It reduces the epidermal hyperplasia, as shown by K16, and other measures of the barriers such as the S100s. So, it doesn't reduce just the inflammatory molecules. By targeting the Th2 axis, you basically are also able to reverse the epidermal pathology. So, I think this establishes IL-4 and IL-13 as pathogenic cytokines in atopic dermatitis and truly cements atopic dermatitis as a reversible immune-driven disease like psoriasis. And longer studies were done and are underway of publication that will show longer effects of dupilumab.

Now, I want to also show you the pivotal Phase 3 studies, EASI-75 responses from SOLO 1 and SOLO 2. The studies were recently published in the New England Journal of Medicine in the end of September with very nice and very comparable results. Both of them showed very significant differences between dupilumab and placebo. In fact, all the regimens of dupilumab showed significance compared to placebo, as you can see here, and a very nice EASI-75 responses with very significant P values at week 16.

Now, there are other pathways or targets that are also investigated now for atopic dermatitis. In fact, many, many products are now being tested for atopic dermatitis. It's a very hopeful time for the disease. I think once we figured out the pathways that are elevated, now there are multiple therapeutic approaches that are trying to inhibit these. So, what do we have? We have more general targeting like JAK inhibitors that target several pathways. They target Th1, Th2, Th17 and Th22. We have apremilast that also targets Th2 but also Th17 and Th22. And we have crisaborole, a topical PD4 antagonist that also targets a little more broadly, targets Th2, Th17, also Th22 and also the Th1 axis.

Crisaborole, a novel nonsteroidal phosphodiesterase 4 inhibitor has been recently approved after two large Phase 3 studies for the topical treatment of atopic dermatitis in children and adults. It was investigated in two large Phase 3 studies in which patients were randomized 2:1 crisaborole to vehicle and the patients included were two years or older with an Investigator's Static Global Assessment, or ISGA, score of mild or moderate and they were randomized for twice daily applications for four weeks or 28 days. The primary endpoint was the ISGA score at day 29 of clear, zero, or almost clear, one and two grade or greater improvement from baseline.

Now, both Phase 3 studies that were identically designed achieved significance in their endpoints. Crisaborole ointment showed improved global disease severity and reduction of severity of the signs and the symptoms of atopic dermatitis and it provided early and sustained improvement in the prurital severity. The crisaborole ointment was also quite safe, it was low incidence emergent AEs and there was a lacking of serious treatment related AEs. So this provides a novel treatment for patients with mild-to-moderate atopic dermatitis in both children and adults.

So, dupilumab is a Th2 antagonist that targets the IL-4 receptor, but you can also target just the IL-13 cytokine. And there are several drugs that target that, tralokinumab and lebrikizumab. At least one of them showed preliminary nice results. We also have targeting of IL-31, the itch cytokine, also showed hopeful results for each and also for disease severity, nemolizumab. We have targeting IL-22, and later on we will show, my group will show, also hopeful results for targeting IL-22.

There are also studies being done with treatments that are designed for psoriasis like anti-IL-17, secukinumab, and we hope to see results of these later on this year. With secukinumab that targets the IL-23, was also tested in atopic dermatitis. The results were not conclusive, but I think other studies should be done since the study may have not been optimal but did show a trend of efficacy. And there are studies targeting some barrier products like TSLP, barrier/immune products, and many, many others that are now being targeted for atopic dermatitis such as OX40 ligand is being targeted. This is part of the inflammatory Th2 pathway, the OX40 ligand TSLP axis.

So, be tuned, stay tuned. I think it's a very exciting time for atopic dermatitis, and I think 5 years from now we'll have many other targets in atopic dermatitis, and many drugs going into atopic dermatitis are already approved for our patients with atopic dermatitis.

Now, we need to remember that IL-22 also has an important role in atopic dermatitis. It promotes epidermal hyperplasia and also, similar to the Th2 cytokines, impairs terminal differentiation. So, very important to also see what the study that targets IL-22 in atopic dermatitis patients is going to do and, again, we hope that we will publish it later on. The study is still in process.

Now, so summarize, unlike psoriasis that is really centered on the Th17 axis, atopic dermatitis is not that simple. The atopic dermatitis phenotype cannot be completely explained by a single cytokine pathway like the psoriasis one, but the consistent cytokine axis that is activated across all the phenotypes appears to be the Th2 axis, and thus far dupilumab indeed shows similar efficacy in intrinsic, extrinsic and filaggrin-positive and filaggrin-negative phenotypes, but this does not exclude that other cytokine targeting may also be effective in atopic dermatitis.

Now, also importantly to remember, atopic dermatitis emerges as a systemic disease, very similar to patients with severe psoriasis. And

we need to remember that we now start to see many publications showing high-grade systemic immune activation in atopic dermatitis, and this systemic immune activation extends to T-cells, B-cells, but also circulating cytokines. And probably this is the basis to the atopic march, to the allergic associations, to the asthma and the entire atopic march and now to the newer publications that talk about cardiovascular comorbidities and other comorbidities that we see in atopic dermatitis. So, probably, the systemic immune activation leads to all these comorbidities.

Now, we need to remember while asthma and other comorbidities involve only approximately 30% of atopic dermatitis patients, all the moderate to severe atopic dermatitis patients were associated with systemic immune abnormalities, and that probably is the common denominator driving the entire comorbidity panel, both the allergic comorbidities and the cardiovascular comorbidities.

We recently showed that severe atopic dermatitis patients are characterized by excess systemic T-cell activation compared to psoriasis and controls. Activated T-cells that are defined by ICOS positivity or HLA-DR positivity are much higher in atopic dermatitis, not only compared to control but also compared to psoriasis, a disease that is established to be a systemic disease, and that is really important. And we also showed using serum cytokines that these cytokines are really upregulated in atopic dermatitis patients, in patients with severe disease, and it was associated with disease severity.
So, what are these cytokines and chemokines? We see here the Th22 cytokine, IL-22, the Th2 cytokine, IL-13, and many chemokines from the Th2 pathway such as CCL17, CCL22, CCL13. And these were also shown by us to be reduced with treatment, so very important because we probably can reduce this risk. Maybe we can reduce the cardiovascular risk or the risk to have other comorbidities.

So, what are the therapeutic implications? The high-level systemic immune activation we have in atopic dermatitis is reflected in the wide immune abnormalities seen in the nonlesional skin of atopic dermatitis patients. So already at the nonlesional skin level we have increases in immune markers, unlike psoriasis, a disease where the nonlesional skin is much closer to normal, and that probably is because of the systemic immune activation that affects the nonlesional skin. And I think this shows you that we need systemic treatment for patients with moderate to severe disease, because what's nonlesional today may be lesional tomorrow. You cannot chase the entire body just with topical treatments for patients with severe disease.

I want to thank you very much, and with this I'm concluding my lecture.

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