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Practice Changing Advances: Expanding the Atopic Dermatitis Armamentarium

Narrator:
Welcome to CME on ReachMD. This segment: Practice-Changing Advances: Expanding the Atopic Dermatitis Armamentarium, is jointly sponsored by the University of Cincinnati and CoreMedical Education and supported by an educational grant from Sanofi-Genzyme and Regeneron. The target audience for this educational activity includes physicians and other healthcare professionals who manage patients with atopic dermatitis.

Your host is Dr. John Russell, and our guest today is Dr. Emma Guttman-Yassky. Dr. Guttman-Yassky is Vice-Chair of Research in the Dermatology Department and a Professor of Dermatology and Immunology. She is also Director of the Center for Excellence and Eczema and the Director of the Laboratory of Inflammatory Skin Diseases at the Icahn School of Medicine at Mount Sinai Medical Center in New York.

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Dr. Russell:
For clinicians, the treatment of atopic dermatitis can be challenging. Recent breakthroughs furthered our understanding of the pathologic mechanisms of the conditions. Clinicians now have new tools in their armamentarium to manage their patients with atopic dermatitis. Clinicians need to be knowledgeable about how these emerging therapeutic agents work, how they can modulate the immune response and understand the recent clinical trial data regarding their use in patients with moderate to severe disease. An online toolkit supplement is available to clinicians to download as a specialized resource on ReachMD.com/CME.

I am your host, Dr. John Russell, and I'd like to welcome Dr. Emma Guttman-Yassky to our program. Dr. Guttman?

Dr. Guttman-Yassky:
Hi, it's good to be here.

Dr. Russell:
So, atopic dermatitis probably means a lot of things to a lot of different clinicians. Could you give us an overview, prevalence, kind of a 30,000-foot view of this disease?

Dr. Guttman-Yassky:
Of course. So, for those of us that do not know, this is the most common inflammatory skin disease in adults, 4 to 7% of adults and 15 to 25% of the children worldwide, a little bit more in Asia, and a third of these are moderate to severe patients. Two-thirds are patients with milder disease. And currently, we don't have available good treatment for atopic dermatitis, not for topical treatment and definitely not for patients with severe disease that need systemic treatment, because the treatments that we have now, we have oral prednisone and we have immune suppressants like cyclosporin and methotrexate and Cellcept, and these treatments pose really many risks for long-term use and are not suitable for long-term, so we have a very large unmet need for safer and more effective treatments for both adults and definitely also for children.

Dr. Russell:

So, Dr. Guttman, as a primary care doctor, are there some patterns I should look at for these skin lesions? How should they look? How would I know atopic dermatitis is in front of me in the office?

Dr. Guttman-Yassky:
So, atopic dermatitis lesions bear some similarities to psoriasis. Both are inflamed lesions and erythematous lesions. What differentiates the two diseases is that atopic dermatitis lesions blend with the surrounding. They are not as well demarcated as you see in psoriasis lesions that are very demarcated, but both are scaly and erythematous. Only in atopic dermatitis the lesions are a little bit blending with the surrounding and, also, you usually will see scratch marks because it's a very itchy disease, and patients scratch their lesions. And, of course, you will see lichenification. When you look under the microscope, you see increased epidermal hyperplasia in chronic lesions because of the constant scratching. And the lesions are very thick, and when you stain with proliferation markers like keratin 16 and Ki-67, you actually obtain a very similar picture to psoriasis with thickened epidermis that has wide expression of these proliferation markers in the epidermis.

Dr. Russell:
So, you're talking about all these mechanistic things. Is there a hypothesis to explain what I'm seeing as a clinician?

Dr. Guttman-Yassky:
Atopic dermatitis has a true hypothesis. The initial one is the barrier hypothesis that basically claims that the barrier abnormalities in atopic dermatitis are the ones causing the phenotype of the disease. And when I say barrier, it's a complex phenotype. We're talking about the increased hyperplasia or the thickness that is increased. And, also, several studies show that there are decreases in many markers of differentiation in atopic dermatitis, epidermal differentiation such as filaggrin, loricrin. The tight junctions are also defective, and there is also increased transepidermal water loss and decreases in lipids, so very complex abnormalities in the barrier.

However, we must remember that all the lesions of atopic dermatitis increased more in chronic lesions. We have increases in the inflammatory cells. When I say inflammatory cells, these have multiple flavors. We are talking about T-cells, and dendritic cells. So, many inflammatory cells are increased in these lesions, and these T-cells produce cytokines or inflammatory markers, and the cytokines that we see in lesions are Th2 cytokines and chemokines and also some other cytokines like the Th22 cytokines and their respective inflammatory markers. So, there is very wide activation of cytokines in lesions of atopic dermatitis, and that led to the second hypothesis that now we believe is actually the primary one, and this is the immune hypothesis of atopic dermatitis. And this hypothesis is basically suggesting that it is the increases in cytokines that are produced by different T-cell subsets that is secondarily creating this abnormal phenotype of the epidermis and the barrier abnormalities that we have in atopic dermatitis. And one thing that we need to remember is that maybe these hypotheses are not mutually exclusive, that there might be a combination of the two hypotheses. We don't need to think that one potentially excludes the other, because the Th2 cytokines have several effects on the epidermis that are really important. They inhibit differentiation of keratinocytes, and that can cause a feedback hyperplasia. They induce really key features of the epidermis in atopic dermatitis, the spongiosis that we see in lesions of atopic dermatitis under the microscope, and also the inhibition of lipids that we see in atopic dermatitis. We have major decrease in lipids in atopic dermatitis; the skin looks very dry. And also in atopic dermatitis we have infections, and this is because we have low antimicrobial peptides, and the Th2 cytokines were actually shown to inhibit antimicrobial peptides. And also there is a very well-known relationship by now between the Th2 cytokines, IL-4 and IL-13, and staph binding and colonization. And again, patients with atopic dermatitis have increased infections and particularly staph aureus, and they also have increased MRSA. And lastly, the Th2 cytokines, IL-4 and IL-13, also increase T-cell secretion by keratinocyte. So, I would say that Th2 cytokines could potentially link the barrier and immune defects in atopic dermatitis, so we don't need to think that these hypotheses are mutually exclusive.

Another thing that I want to mention, the outside-in hypothesis or the barrier hypothesis, that's a major revival in 2006 when the filaggrin mutation was found. And then people thought, “Oh, we found now the solution to atopic dermatitis. This is filaggrin, it's a mutation, and that's the whole story.” But we need to remember that this mutation is definitely not the entire story. In the United States, the filaggrin mutation is only available in 12% of the American population with atopic dermatitis and, actually, in very few from the African-Americans with atopic dermatitis. They have very few percent of a positive mutation in filaggrin. And the other things that we need to remember about filaggrin is that the mutation is absent in the majority of patients, and most patients with a mutation actually outgrow the disease. And, also, filaggrin mutation is not specific to atopic dermatitis. It's found, for example, in patients with ichthyosis vulgaris. And, also, the differentiation of normality that we have in the barrier of atopic dermatitis patients extends far beyond filaggrin. Its many differentiation markers such as loricrin, involucrin and others raising the question: Is it due to some cytokine that causes this barrier differentiation abnormality? So, definitely, the filaggrin mutation is not the primary cause of atopic dermatitis as we understand it now, and that's very, very important to remember.

Dr. Russell:
So, certainly, you talked about lots of different cytokines and lots of different specific roles it was going on. You know, as a primary care

doctor, I probably would say IgE fits in there somewhere. I'm not exactly sure how it fits in. Is it pro-inflammatory? Could you elaborate on IgE for me?

Dr. Guttman-Yassky:
Absolutely. And, you know, IgE is another historic notion, because historically, we saw that maybe IgE is pathogenic in atopic dermatitis like in other diseases like food allergy and also urticaria, a disease that all of us treat, and I think as primary care physicians you treat as well. And in urticaria we know that there is a very important role that is pathogenic for IgE, and giving anti-IgE such as omalizumab reduces the allergic inflammation and prevents new lesions. So, the question was: Is that also the same with atopic dermatitis? And I want to point out that there are two studies done in atopic dermatitis patients that showed that IgE probably is not pathogenic despite the fact that in 80% of the patients IgE is highly increased, and these patients have extrinsic atopic dermatitis that's similar to asthma, is associated with high IgE, usually other atopic manifestations like food allergy, asthma and allergic rhinitis.

So, the two studies are one important study published by the group of Georg Stingl from Austria that gave omalizumab to atopic dermatitis patients, and omalizumab did mechanistically what it was supposed to do. It displaced the complexes of Fc receptor and IgE on blood cells. However, there was no clinical benefit. And this was reproduced again in an abstract presented at the European Academy of Dermatology and Venereology that happened recently in 2016, again, no effect clinically for omalizumab on atopic dermatitis patients.

The second study that I think was approved that there is no pathogenic role is the dupilumab study -- that I will talk a little bit more later on -- that showed that was an IL-4 receptor antagonist. Both extrinsic and intrinsic patients for both patients with high IgE and normal levels of IgE showed similar improvement in the disease, so there was no difference whatsoever with a Th2-targeting strategy between the effects of dupilumab on different subsets of patients based on their IgE level. So, I think that strengthens the emerging view of atopic dermatitis, that T-cells rather than IgE are mediating the pathogenic effects, and IgE probably is a bystander response rather than having a primary role in the inflammation that characterizes atopic dermatitis.

Dr. Russell:
If you're just tuning in, you're listening to CME on ReachMD. I am your host, Dr. John Russell, and today I'm speaking with Dr. Emma Guttman-Yassky.

So, doctor, I think most of us in primary care are very comfortable with emollients, topical steroids, but what are the newest treatment opportunities for our more severe patients with atopic dermatitis?

Dr. Guttman-Yassky:
So, you know, for many patients with mild disease, probably topicals and emollients and bleach baths may be all they need. However, we need to remember that a third of our patients with atopic dermatitis, or approximately a third, suffer from a disease that is systemic, and they cannot be treated just by topicals because they have severe disease and they have lesions all over the body, and you simply cannot treat these lesions just with topicals. And another important thing to remember, we show that in these patients, the moderate to severe patients, the non-lesional skin is already abnormal, so treating just topically will not fix the underlying abnormalities, so you have to treat these patients with a systemic medication.

Now, unfortunately, what we have now are not really good treatments, particularly not for long-term. So, Cyclosporin A we all know is effective for atopic dermatitis. It's a very wide immune suppressant. It will inhibit all immune axes, not just the axes that are relevant for atopic dermatitis, and we use it. However, there are papers showing documented kidney toxicity that is permanent after one year of use, and even more after two years of use, so none of us wants to use Cyclosporin A for more than a few months. And the other alternative, oral prednisone, I never give in my own clinic because you basically condemn the patient for a life of misery. Once you given one course of oral prednisone, everything comes back with a vengeance, and this truly perpetuates the disease. And I'm not even talking about the side effects of oral prednisone. It's just that after a course of oral prednisone, usually it will perpetuate the disease, so not a treatment that I would recommend whatsoever, even one course of oral prednisone.

And the other treatments that we have, methotrexate and Cellcept, don't work as well. And, ultimately, we do not have good treatments for long-term use for these patients that really need something safe and effective for long-term treatment. And this is the reason why now there is very important developments in atopic dermatitis that increase our knowledge of the disease and also, of course, are intended for treating patients with atopic dermatitis.

Dr. Russell:
So, there is a new biologic agent, correct, dupilumab? How does that work? What cytokines is it working on?

Dr. Guttman-Yassky:
There is a very exciting new biologic agent that we are hoping will be approved very soon, and that biologic agent is dupilumab, or I

think the company came with the name of Dupixent, and this is a fully human monoclonal antibody that targets IL-4 receptor alpha. And because it targets the receptor, it targets both cytokines of the Th2 axis, the primary cytokines, I would say, of the Th2 axis, IL-4 and IL-13, and of course the downstream molecules of the Th2 axis. And the first proof of concept study that was done with dupilumab was actually intended as a safety study, but was very successful, and that was a four-week Phase Ib study, and it involved weekly injections of several doses of dupilumab, 75 mg, 150 mg, 300 mg and placebo, and had a total of 67 patients across several continents, and 18 patients also participated in a substudy that involved skin biopsies. And immediately after two weeks, it was quite clear that there is a major effect, a significant effect in the higher two doses, and by week four there was a nice dose response with 71.4% of the patients in the higher dose achieving something we call EASI-50. What is EASI-50? EASI is used to measure responses in clinical trials, and EASI-50 means that you achieved 50% reduction in your disease. So, 71.4% of the patients were responders using EASI-50, and that's quite impressive for four weeks only of treatment. Of course, this will be different when you treat for more time. And these results were published in the New England Journal of Medicine in 2014, and very importantly, there were no differences between responses of patients based on IgE status or filaggrin mutation status, so all the patients reacted the same to the drug, and that was really important.

Now, when we looked into tissues of patients that were treated by the drug versus patients that were treated with placebo, we found that dupilumab 300 mg dose actually improved in tissue the measure of epidermal hyperplasia keratin 16 about 10-fold changes compared to baseline. So, we were quite impressed by the fact that dupilumab, the higher dose of dupilumab, dupilumab 300 mg, reduced keratin 16 that is a very good measure of epidermal hyperplasia, approximately 10-fold changes compared to baseline, whereas in our study, a very similar study that we did with Cyclosporin A that is truly heavy guns and basically reduces all the inflammatory markers, we only managed to get 6-fold change reduction in keratin 16, so very impressive because this is only four weeks whereas the cyclosporin was a 12-week study. And in placebo, we saw an increase of 2-fold changes compared to the baseline, so that was quite impressive.

Now, when we looked at many markers, many inflammatory markers of different T-cell pathways and how they were modulated with treatment and we did it using realtime PCR in skin lesions, we found that dupilumab did not just -- it's very interesting -- even though the drug is specific to the Th2 pathway, but we did find reductions in other pathways that are also relevant for atopic dermatitis including measures of Th17, measures of Th22 and others, so dupilumab inhibits, perhaps indirectly, also other axes in addition to the Th2 axis that we are expecting that it will be modulated with dupilumab. And we are still looking into why this happens. One possibility may be through the inhibition of the IL-4 induced differentiation of dendritic cells that may potentiate other axes, but that's something that needs to be still studied.

Dr. Russell:
So, it certainly sounds like it impacts the inflammatory aspect of atopic dermatitis. How about the barrier function you talked about earlier? How does this medicine impact that in the treatment for our patients with atopic dermatitis?

Dr. Guttman-Yassky:
Yes, that's a very good question, because modern systems in keratinocytes in vitro studies showed that the Th2 cytokines, IL-4 and IL-13, modulate, indeed, these barrier measures like filaggrin and loricrin, so this was a very good study to see if in vivo we can show the same by IL-4 receptor inhibition. So, what is nice, that when we accounted for the reduction in thickness by dividing with K16, we did find increases in filaggrin and loricrin. We need to remember it's a study of only four weeks, and definitely we need longer studies to understand it, and we are now doing these longer studies that are looking very promising, and we will publish them later on this year. But I think we can say that dupilumab also had major effects on barrier, inhibited the keratin 16, so it improved the hyperplasia and modulated the measures of epidermal differentiation. And we can say that overall dupilumab impacts both the inflammation but also the barrier dysfunction that characterizes atopic dermatitis, so it impacts all the characteristics of atopic dermatitis basically helping to reverse the disease phenotype,
So, this basically is the first, dupilumab, is the first targeted treatment that demonstrates dose-dependent clinical -- but also importantly molecular in tissues -- suppression of the disease phenotype, and I think this helps to establish IL-4 and IL-13 as pathogenic cytokines in atopic dermatitis. And this is the first proof that atopic dermatitis is reversible and immune driven, very similar to psoriasis, a disease that we are much more familiar with now, because for many years already we have targeting of biologics for psoriasis patients, that completely reverses the disease, and I think atopic dermatitis is emerging as similarly immune driven to psoriasis, and we can target it also with narrow-based treatments such as dupilumab, so very promising.

And this also extended to Phase III. You know, dupilumab now awaits registration, very nice responses in both Phase II and Phase III. EASI-75 responses in Phase III were very encouraging. Dupilumab met, in fact, all the endpoints of the Phase III, and very promising treatment and very safe according to the Phase III that was just published. And, again, we are waiting for the drug to be available for our patients with atopic dermatitis.

Dr. Russell:

So, you talked about this being a systemic disease. What features could be explained by some of the other cytokine effects?

Dr. Guttman-Yassky:
We did discuss up to now the relevance of the Th2 pathway to atopic dermatitis, and this pathway is certainly now we know pathogenic, but in atopic dermatitis, we have other cytokines and other axes that are also important, and I will explain. So, IL-22, a cytokine that is derived from Th22 cells, we now know that promotes epidermal hyperplasia, so epidermal thickening, and also impairs the terminal differentiation from studies done in vitro in keratinocytes models. And this is an NIH study that we have, and we hypothesized for this study that since IL-22 is involved in several processes in atopic dermatitis such as epidermal hyperplasia and barrier defect, that a treatment that targets IL-22 may prove to be effective in chronic atopic dermatitis patients. And we are happy to say that we are now finishing analysis for a study that we performed that is funded by the NIH in 60 patients with atopic dermatitis that is moderate to severe. Twenty were treated were placebo. Forty were treated with drug. And at least in a subset of patients, this will prove to be a positive study, and we are very excited about that study as well.

Now, we need to also ask: What is the relevance of some cytokines that are important for psoriasis with atopic dermatitis? And these are particularly IL-23 and IL-17. So, IL-23 is very important for induction of Th17 cells that are important for psoriasis, but we also need to remember that it's also important for induction of Th22 cells that is important for atopic dermatitis.
So, what about targeting IL-23 and Th17 in atopic dermatitis patients? So, again, this axis is expressed in patients with atopic dermatitis, not as high as psoriasis but might still have therapeutic potential. And recently we completed a placebo-controlled crossover-designed study with ustekinumab. Ustekinumab is a treatment that is available for psoriasis. It's anti-IL-12, IL-23 p40, so targets both cytokines, and we used for this one the psoriasis dosing. At that time we did not know that maybe psoriasis dosing may not be exactly the right way to go. And another mistake that we did that today we would not have done it, we also allowed patients to use topical steroids, which we understand now that may modify studies because you get very high placebo responses. And indeed that was the case. It was a very small study, only 32 patients, 16 in each group, and a crossover design. But if you look, I think you can appreciate that there is a clear drug effect; however, we could not achieve significance versus placebo due to potentially the dose that was used. Maybe the intervals should have been shortened. The psoriasis dosing of 12 weeks is probably not enough for these patients that have a lot of inflammation in blood, and also, the topical steroid use, that affected the placebo responses. But I think we need to think more about targeting IL-23 in atopic dermatitis patients. And we actually published a case report of a patient that was not controlled with cyclosporine and mycophenolate mofetil, and this patient we put on ustekinumab but higher doses of ustekinumab than used according to the psoriasis guidelines, and this patient cleared, so it's a treatment that we can think that may need to be tried again.

And we are now facing a very exciting time in atopic dermatitis because multiple axes and multiple inhibitors are now tested in atopic dermatitis patients with severe disease. We have JAK inhibitors that are a little bit more broad and apremilast that targets PD4 that also was tried in patients, and we are waiting to hear the results. There are several IL-13's that are now being trialed, tralokinumab and lebrikizumab. There is an anti-IL-31, the itch cytokine that is being tried, nemolizumab in patients. And we have some other markers like we have an OX40 antagonist that is being tried in patients and secukinumab targeting IL-17 in patients with atopic dermatitis, our study with IL-22, so really a myriad of agents targeting different molecules for patients in atopic dermatitis, and I think the next few years will be very exciting with many new emerging treatments for atopic dermatitis.

Dr. Russell:
So, doctor, it sounds like a lot of things are changing for a very common disease that we see very often. What would be the takeaway points you'd want our audience to think about on what's new and emerging in atopic dermatitis?

Dr. Guttman-Yassky:
So, I think several emerging things. First of all, the Th2 cytokine axis is very important. It's pathogenic for atopic dermatitis, and that is proven, and I think targeting this axis proved to be beneficial for patients, and we'll see more and more agents that target this axis similar to dupilumab, only maybe different molecules in the axis. But we need to remember that unlike psoriasis that is really focused on IL-17 and IL-23, the phenotype, the skin phenotype, of atopic dermatitis cannot be explained completely by one single cytokine pathway. There are contributions of several pathways including Th22 and potentially IL-23, Th17, and currently, we are not sure if we can completely reverse the disease targeting one axis or maybe we need to target several axes. And I think we need to see how these clinical trials will evolve and if one cytokine targeting is enough or we may need to target more than one cytokine. So, that will need to be determined in future years, as well as how each one of these axes are contributing to the disease phenotype, but a very exciting time in which we have new treatments for atopic dermatitis that are being developed now.

Dr. Russell:
That's terrific. Thank you very much.

Dr. Guttman-Yassky:
Thank you.

Dr. Russell:
I'd like to thank our guest, Dr. Guttman, for discussing atopic dermatitis and emerging therapeutic agents on the horizon for this disease.

Narrator:
Additional resources are available to complement this program. An online toolkit supplement for clinicians is available at ReachMD.com/CME. These resources are fully downloadable and include: From the NIH, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Atopic Dermatitis Fast Facts and Handout on Health, the American Academy of Dermatology Current Treatment Guidelines, a key publication for participants wishing to go into greater depth of the some of the clinical trials discussed in our program, and lastly, a listing of key websites and resources.

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