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Journal Club: A Comprehensive Update

Dr. Christopher Bunick:
On behalf of Practical Dermatology, welcome to Atopic Dermatitis Journal Club. I'm Dr. Christopher Bunick, associate professor of Dermatology and Translational Biomedicine at the Yale University School of Medicine. With me today is a special guest, Dr. Emma Guttman.

Emma, thank you for being here.

Dr. Emma Guttman:
Thank you so much for this opportunity. I'm Emma Guttman. I'm from New York City where I'm the Waldman Professor of Dermatology, and I'm also the system chair of the Department of Dermatology at Mount Sinai in New York City. Great to be here.

Dr. Christopher Bunick:
Thank you for being here. If you're not aware, Dr. Guttman recently published a seminar in-depth paper in the Lancet on atopic dermatitis, and we are going to be talking to her about key insights from this article about atopic dermatitis.

So Emma, one of the first things people are going to be interested in is understanding what are the most important elements of the pathogenesis of atopic dermatitis that you identified in this paper?

Dr. Emma Guttman:
So we know that atopic dermatitis is a complex disease, it's highly heterogeneous, unlike psoriasis that really is centered on IL-17, IL-23, atopic dermatitis, I like to think of it, it has multiple flavors and it depends on different phenotypes, based on age, ethnicity, other factors. So many, many factors will influence what immune pathways may be related to it, but it is centered on IL-13. So it's important to know that there is a central cytokine, IL-13, that is really central in atopic dermatitis. IL-4 probably also plays a role, but nobody really understands because we know we learned from treatments for atopic dermatitis that treating atopic dermatitis with dupilumab, the target IL-4 and IL-13 or treating with IL-13, it's about the same. It's hard to tell which one is better, but it's about the same.

So we learned that IL-13 likely is the most important one. But we also know that targeting with IL-13 only covers most of the patients, but not all of the patients. And we don't have the EASI-100 or EASI-90s, meaning really clearing the disease numbers that we have in psoriasis. So in atopic dermatitis we have EASI-90 numbers only about a third. So we still can do much better and likely it's because many immune molecules are involved depending on the phenotype. So we may need dual cytokine targeting or other means and the field is evolving.

Dr. Christopher Bunick:
So along those lines, I think what you're speaking to is that there are bi-specific, tri-specific types of biologic therapies being developed to hit not just IL-4, 13, but also IL-31 TSLP, L-22.

Dr. Emma Guttman:
Exactly.

Dr. Christopher Bunick:
And one of the interesting things about interferon gamma that I've learned in speaking about atopic dermatitis is interferon gamma is actually connected to ceramide synthase. And so when you have too much interferon gamma it down regulates ceramide synthase and hurts your skin barrier.

Dr. Emma Guttman:
Absolutely. And in atopic dermatitis people don't appreciate, but similar to alopecia, reata and psoriasis, in chronic stages of atopic dermatitis we have a lot of interferon gamma. You are absolutely right.

Dr. Christopher Bunick:
So Emma, with this explanation of the heterogeneity of atopic dermatitis from an immune profile standpoint, how useful do you think it is subdividing atopic dermatitis patients into molecular endotypes?

Dr. Emma Guttman:
So I am a great believer that that's important, but it needs to be also feasible in clinical practice. So I'm thinking that maybe several years from now, maybe it'll be possible using tape strips, something minimally invasive that is feasible in the clinic or finding some biomarkers that relate to some blood biomarkers. So that's my wishful thinking. I think we will be able to do that at some point because I think in atopic dermatitis, maybe more important than psoriasis, will be the idea of which drug for which patient, now that more drugs are coming. Like, a very itchy patient, maybe an IL-31 antagonist, a patient that has a more atopy, maybe either dupilumab or one of the IL-13 antagonists. We need to consider all of these and at some point maybe we'll have a cookbook that will tell us which drug for which patient.

Dr. Christopher Bunick:
Yeah, unfortunately that cookbook doesn't exist right now and it can be very challenging to treat the heterogeneity of atopic dermatitis patients. And I think it speaks back to why we're clinicians. You really do have to be a doctor and have that patient-doctor relationship and treat each patient uniquely.

Dr. Emma Guttman:
I agree.

Dr. Christopher Bunick:
One of the things that we see in atopic dermatitis a lot is super infection or impetiginization with Staph aureus. How important do you think it is in recognizing the Staph aureus component and how much is it driving atopic dermatitis and how do you generally handle that in clinic?

Dr. Emma Guttman:
That's a wonderful question and usually when I see an infection, whether it's Staph or actually viral infections, we have many of our patients also will have eczema or herpetic wound, so I always tell the patient or the parents that that's a sign to step up the game. I actually think that it's not... We learned it also through studies that the infection is secondary rather than the primary cause of atopic dermatitis. And we learned that, we know from the studies with the microbiome, they are not holding as much promise as we hoped for.

So I think it's primarily the immune abnormality that causes that barrier defect and the infection is secondary. We also see it in reality in a clinical practice when we treat a patient with an infection with a better treatment and we step up the game, then the infection also goes away.

Dr. Christopher Bunick:
That's been my experience clinically. Sometimes when you focus on inflammation, treating the inflammation of atopic dermitis, the barrier improves and the infection or super infection with Staph aureus improves even without an antibiotic therapy.

Dr. Emma Guttman:
100%. With that being said, we all need to err on the caution side and yes, I give some antibiotic but not for many months. I have patients that were maintained on doxycycline for months, so that's not the case. Step up the treatment and then give them for a week doxycycline just to make sure.

Dr. Christopher Bunick:
Absolutely. I think that that's a good conservative approach, but one that's based in science. I think what's really fascinating, so I did a lot of research in filaggrin and keratins early on in my career coming at atopic dermatitis from a barrier first approach. But I do feel that my own opinion has changed and that it's really the inflammation underlying inflammation that drives the barrier disruption first. But then it becomes a cycle, the more barrier disruption, the more inflammation.

Dr. Emma Guttman:
Completely agree and that's why for some patients who disrupt the cycle, we can give them like an IL-31 antagonist because their problem is each and that may disrupt the cycle. That's why it's amazing now that we have many drugs coming into the field and we can see this drug may be more for this patient, whereas this drug is primarily for this patient. And also we can choose a drug for patients that

failed other drugs.

Dr. Christopher Bunick:
The pharmacogenomics of atopic dermatitis is still for the future. We hear now more and more in the news media because I think it's very catchy about environmental triggers of atopic dermatitis. What do you believe in terms of the evidence? Is there strong evidence for or against environmental triggers of AD?

Dr. Emma Guttman:
First, I don't think there is a very strong evidence. It's more kind of cultural, Instagram, TikTok and so on. And I have many patients or many parents actually, it's usually parents come to me, "Oh, doctor, can you design a diet for us so that our child will outgrow atopic dermatitis?" And I'm telling them there is no such a thing. We need to treat the inflammation. And actually many people do not know that usually atopic dermatitis is the first occurrence and the food allergies come later. So treating atopic dermatitis early is so important because it may prevent the other atopic associations. So I don't believe, I tell patients, "Listen, you need to live a normal life. You don't need to diet." I am not designing diets that are low in dairy or other things, but we do need to target that inflammation and most of the time it works.

We need to also consider, when we have a patient, the comorbidities. Of course, an atopic patient, we'll put them on different treatments than a patient without atopy. With that being said, there are environmental things that we do need to think about. For example, if a patient runs all the time or they run marathons, they will sweat, sweating of course exacerbates eczema, contact with water exacerbates eczema, being in very dry areas will make them worse. I have patients that go to Colorado because it's very high, high altitude also is not good for eczema. These are things we need to consider, but they're secondary. We still need to treat inflammation.

Dr. Christopher Bunick:
So what I think I heard you say is that this concept that we've been taught very early in our residency in dermatology training is about the atopic march and this Th2 proclivity of inflammation is really initiated in the atopic dermatitis and then allergic rhinitis, food allergy, asthma may be more secondary, or subsequent.

Dr. Emma Guttman:
Yeah, 100%. I view atopic dermatitis as the window for the atopic march. And that's why I'm really happy that now we have the approval of the dupilumab for six months and up. And many times I see that children that we treat early, they don't get, their parents already have asthma and their brothers, and that may be preventive and there are studies that the NIH is doing now to test for that. I wonder if in the future maybe giving it to women that are pregnant may also solve this problem in babies. They're countless ways to think about it.

Dr. Christopher Bunick:
No, I'm glad you brought up giving biologic therapy for AD down to six months of age because there's actually a children's book that's been made that help parents educate their children and desensitize them to the need for injections of a biologic therapy, and I use that book pretty commonly with my patients.

You've touched on this briefly, but to come back to it, the idea of predictive biomarkers for atopic dermatitis. In order to get to that ability to select the perfect therapy for each individual atopic dermatitis endotype a patient may have, what are those biomarkers that you think are going to be most relevant or have we not discovered them yet?

Dr. Emma Guttman:
So we discovered them, but we discovered them in small cohorts. So what we are doing now, we are trying to do it in much larger cohorts to really understand if it stands in larger cohorts. And also it's important because of the heterogeneity. We want to make sure that it'll be across all patients or maybe a subset of patients. So at some point I think we'll be able to have these.

Dr. Christopher Bunick:
I mean it certainly is going to be much needed in order for us to advance that personalization of the treatment of atopic dermatitis patients.

Dr. Emma Guttman:
Could not agree more. I think personalized treatment will be the name of the game in atopic dermatitis, much more important than psoriasis because psoriasis is much more homogeneous and most patients right respond to IL-53 antagonists. And we have amazing PASI up to 80%. In atopic dermatitis now we can only dream about these numbers, but one day hopefully we'll get there.

Dr. Christopher Bunick:
Hopefully. I think over the last year to two years, one of the biggest advances in understanding the atopic dermatitis patient has been recognizing how much itch plays a role in quality of life impairment. And we're seeing a lot of movement to pair a clinician-reported

outcome like EASI-90 or IgA-01 with a patient-reported outcome like itch zero or one and using these composite endpoints. Do you have a strong feeling about how these more stringent criteria may impact how we treat AD patients?

Dr. Emma Guttman:
I love it because like you said, even though we are scientists, we are also clinicians and you need to always think how to bring it back to the patient. And for me it's actually important because itch is the hallmark of AD.

Dr. Christopher Bunick:
Itch is the hallmark of AD. Absolutely. And that's why we see in these data coming out about patient-reported outcomes, that itch really does play a huge role in quality of life.

So Emma, I think it's really amazing that you have an article in Lancet detailing atopic dermatitis. Are there any other important takeaways from that article you published or about AD in general that you'd like our listeners and our audience to understand?

Dr. Emma Guttman:
No, just the idea that now there are amazing advancements that are also moving into children, and I want people to think that they need to treat also the children very early on, relatively aggressively. Because many times people are like, "Oh yeah, we can wait to treat you like this later when you'll be an adolescent or adult." But, it's not a good idea because now there is the concept of systemic inflammation. We need to treat early systemically to prevent comorbidities in the future. So I want to leave the audience with that idea.

Dr. Christopher Bunick:
Thank you Dr. Guttman for joining me.

Dr. Emma Guttman:
Thank you so much.

Dr. Christopher Bunick:
And thank you to all of our listeners joining me for this Atopic Dermatitis Journal Club for Practical Dermatology. Thank you.

Dr. Emma Guttman:
Thank you so much.