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Translating the Language of Food Allergy Research

Announcer: This is ReachMD. The following episode in the series, Cracking the Code on Peanut Allergies, is brought to you through an independent educational grant from Aimmune Therapeutics. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle: Clinical trials in the field of food allergy research have grown exponentially over the past decade, opening doors to new treatments and prevention approaches on the near horizon. But significant variations in the designs and definitions used from trial to trial are raising questions within the allergy community about how to interpret primary endpoints and reported outcomes.

On today's program, we will explore the language of food allergy research and its downstream impacts on clinical care paradigms. This is Cracking the Code on Peanut Allergies, and I'm your host, Dr. Jennifer Caudle. Joining me today are Drs. Drew Bird and Bruce Lanser. Dr. Bird is an Associate Professor of Pediatrics and the Director of the Food Allergy Center at UT Southwestern and Children's Health in Dallas, Texas. Welcome to you, Dr. Bird.

Dr. Bird: Thanks for the invitation. It's good to be here.

Dr. Caudle: Well, we're certainly happy to have you. And Dr. Lanser is an Assistant Professor of Pediatrics at the University of Colorado and Director of the Pediatric Food Allergy Program at National

Jewish Health. It's great to have you with us, Dr. Lanser.

Dr. Lanser: Thank you. Happy to be here.

Dr. Caudle: Absolutely. So, I'm really excited to talk to you both and to start, I'd like to open the floor to you both on this idea of a language within food allergy research. You know, first off, is there a common language in this field or are we dealing with something else? Dr. Bird, why don't we start with you.

Dr. Bird: You know, I think it has been confusing over the past few years as allergy research, in general, has been evolving and some of the initial confusion, I think, relied on our endpoint – how we are defining what the goal endpoint was, and so we would often start with saying, well, you know we all understand what desensitization is but how do we define whenever a patient is able to be off of any sort of therapy and then no longer be reactive. What do we call that? Initially, we called it tolerance and we decided tolerance wasn't quite accurate. So we used the term sustained unresponsiveness and now the term is moving to remission, and then we'll talk a bit more later about some of the endpoint definitions we've used within the trial itself to say how do we define where a patient's reacting, et cetera, and so just in general, when looking at all the trials and all the ways we're trying to define what we mean and use the common terminology, there has been a lot of differing language over the years, difference in how we define our outcomes and it has likely created some confusion within the allergy community of what we're talking about and what we're trying to explain, the trials we're doing.

Dr. Caudle: And Dr. Lanser, what's your take on this?

Dr. Lanser: Yeah, I think Dr. Bird is absolutely right and as you alluded to as well in the opening, that we've seen a huge growth and change in this field in terms of clinical trials and research and it required the development of new terms, and that has required modification as time has gone on. So that's, I think, to be expected because this is such an evolving and new area, and that leads to some confusion but ultimately I think we'll get to the right place and be able to make sense out of those, but certainly it can be difficult for providers and patients.

Dr. Caudle: Understood. You know, why don't we stay with you, Dr. Lanser, and talk a little bit more. What kinds of variations turn up in clinical trials for oral immunotherapies and can they influence clinical interpretations one way or another?

Dr. Lanser: Sure. You know, one of the things Dr. Bird mentioned was, he used the term sustained unresponsiveness and how that's been used and some studies have looked at that as an endpoint and others have not performed any form of sustained unresponsiveness, meaning that the therapy would be stopped for a period of time and then the challenge repeated to get a sense of some form of durability of that therapy. So that's one example, but others have been issues with what do we define

as a threshold? So, when does somebody react? is it more meaningful to look at the actual dose somebody reacted at or is it more important to look at the cumulative amount that had been ingested before a reaction and what kind of endpoints are you going to look at? So, it's made it somewhat confusing and difficult to compare trial to trial because of that variability.

Dr. Caudle: Right, you know that makes a lot of sense. Dr. Bird, have you seen any impacts from this issue?

Dr. Bird: Yeah, I agree with everything Dr. Lanser said. I think that the main thing that's confusing for the patient and also for other physicians trying to understand the trial design is understanding what does it really mean if the patient is able to eat X amount of protein of whatever food and then react at X amount of protein. When we talk about protein quantities of food and we translate that into how much is that? You know, how many milligrams of protein is one peanut or four peanuts or whatever, and then what does that mean when I'm talking about what's my risk of actually being exposed to a food product that might be contaminated? How does that translate? So, you have to look at not only for peanuts, but then look at that for every food, understanding what a milligram of protein really means, both in terms of quantity and exposure and then real-life risk in terms of how much might trigger reaction.

Dr. Caudle: So, now let's dive into the vocabulary of this language through the primary endpoints that are often used. Dr. Bird, can you review some of these endpoints to help us understand where the most common pitfalls are when they're applied or interpreted?

Dr. Bird: Sure, so I think the first thing to understand is a food challenge and what we're actually looking at when we're talking about entry food challenges and then after therapy, end of the study period food challenge, and translating that into protection or benefit from the therapy. So, when we do a food challenge, it is done in a standard way across trials, looking again at milligram protein amount, starting with a very, very small amount and then building up slowly to try to elicit a reaction. So, the doses start usually at 1 mg of protein, and then we go to 3, 10, 30 mg, et cetera, with about 20-30 minutes between doses being given. So, the example would be if I have a patient I'm trying to elicit a reaction, we start off at 1 mg of protein and the patient doesn't react until I get to the 100 mg dose, how do I define all of those points in between? And that's where a lot of the vocabulary has been just really a potpourri of terms being used. So, if I look at that patient and, okay, remember they reacted at 100 mg, what do I call that point where they react? And some trials would call that an eliciting dose or a reactive dose. Okay, your eliciting dose was 100 mg, or your reactive dose was 100 mg, but how do I define everything else in between? Well, we might want to revert to how much did you actually tolerate? So, we take the single highest-tolerated dose, that would have been 30mg well we might say it's the possibly consumed dose was 30 mg, well what about everything else? So you might say a

cumulative tolerated dose was the combination of all those milligram protein amounts that were ingested, so that would be a cumulative tolerated dose of 44 mg, but what about if you wanted to say, well you know, the patient really was exposed to more protein than just that single amount of the dose that caused the reaction, so how do we call that whole group of doses, and we would call that a cumulative reactive dose. And so, we say the cumulative reactive dose was 144 mg. So, you can see how we use all these different terms to describe basically the same concept, and a lot of times, that is really where the confusion lies is in describing that outcome of the food challenge. And understanding the amount of time it takes between stopping the therapy and then resuming exposure is also confusing, because there aren't any accepted standards. So those are the main pitfalls I see in trying to translate the trials to others who aren't as familiar with the research and trying to explain exactly what we mean.

Dr. Caudle: Excellent, Dr. Bird. Thank you for that explanation. And Dr. Lanser, are there any trouble zones you've come across that should get on our radar?

Dr. Lanser: Yeah, I think Dr. Bird really hit on the biggest ones, But the other I think is, as he mentioned is what is the true meaning of this outcome? And I think that's still where we probably have some more to do and none of those terms are probably perfect yet. Often times, what parents or patients themselves will think about is does this mean I have outgrown my allergy, or I've been cured? And those are things that so far this therapy really cannot do, and I think that's important for us as providers to remember that and teach our patients about that side of it and help them understand what this is actually doing. And so sometimes I think, for me, it's easier to talk about changes in the threshold or amount you're able to tolerate by doing this rather than getting caught up sometimes in some of those nuances – some of those terms.

Dr. Caudle: That makes a lot of sense. You know I'd also like to look at this from a global perspective where we're dealing with not only different interpretations of important terms, but different words and languages altogether. So, Dr. Lanser, you know, coming back to you, we know there's been a fair amount of momentum for food allergy research in Europe as well as the United States, but has there been anything lost in translation here or overseas?

Dr. Lanser: You know, good question, and I think overall big picture the studies have been done largely internationally and very similarly using, Dr. Bird eluded to earlier, similar challenge protocols and using similar doses. So even though we've been talking a lot about different terms, there are still a lot of similarity from what has been done in Europe and here in the US as well. One of the big differences we do see in terms of practice between Europe and the United States is that here in the United States we're kind of regarded as being a little more quick to treat with epinephrine, and that's one of the other

things that you can see being different – the food challenge outcome is not necessarily a dichotomous yes/no, pass/fail, kind of outcome. You can also look at what was the severity of reaction and how was it treated. That's where you could see some difference between sites in Europe and here in the United States where we're a little more quick, typically, to treat with epinephrine, whereas in Europe they are, not necessarily reluctant, but don't necessarily use it as quickly.

Dr. Caudle: Interesting. You know, Dr. Bird, what's your vantage point on the way food allergy research is conducted or interpreted outside of the US?

Dr. Bird: I think the good news about these trails that have been done is that they are huge trials. You know, hundreds of individuals in both North America and in Europe, primarily, and they have already been a great equalizer across the board of seeing how the therapy works in different cultures and different situations. But, again, it's the epinephrine use. I think that one of the big things that we may see from a practical standpoint, it seems that some European countries and maybe some Asian countries are more ready to move forward on implementation of some of the external therapies that many of us consider experimental at this point.

Dr. Caudle: Sure, sure. You know, looking ahead, what efforts are either under way or need to be implemented to bridge these gaps and really help us understand research terms, endpoints and outcomes. Dr. Lanser, do you have any recommendations on this along these lines?

Dr. Lanser: Yeah, of course. You know, I think the biggest thing is coming up with a way in developing tools to help educate parents and patients, you know, what is involved in these therapies? What is the normal course of treatment in day-to-day life going to look like with these therapies? And what do some of these terms mean and perhaps using easier to understand terms or more simplified terms, ultimately, so something that is meaningful to a patient, translating what do those numbers mean and what do some of those words mean, and I think we will get there and come up with the best way. But, understandably, the work that's been done so far has been focused on the research end, and so now we need to take that next logical step to really make it applicable and understandable to patients, but also, to some extent, to providers you know who have not grown up in their training with this experience and haven't been participating in trials or other you know similar efforts at undergoing immunotherapy. And so, you know there's certainly a lot of education down the road that will be necessary.

Dr. Caudle: Right. Certainly, all good points there. You know, Dr. Bird, what do you think? Do you think we're headed in the right direction with this?

Dr. Bird: I do think we're headed in the right direction. I think that the effort we're going to have to make

is really to normalize the conversation with physicians that they understand what they're talking about when they're talking about the trials, and then be able to communicate that to patients so that patients are a part of the decision making process of whether therapy is right for them or not. Because, ultimately, it's not a "one size fits all" sort of solution, and we really will need to empower the physicians that communicate that to the families so that they understand the realistic expectations of what therapeutic option might mean to them.

Dr. Caudle: Right. That sounds good. You know, before we wrap up, are there any new developments in food allergy research or take-aways on today's topic that you'd like to share with our audience? Dr. Bird let's start with you.

Dr. Bird: Yeah, I mean I think the main take-away is that it's really an exciting time not only in the science of food allergy research, but it's really a great time for our patients and for physicians who've been dying to have options for their patients so they can have this discussion and they can say more than, well avoid this, prepare yourself for a reaction in case it happens, and good luck, see you in a year. They actually have options in saying, you know, depending on your situation and your expectations, we may be able to offer therapeutic options that can improve your quality of life.

Dr. Caudle: Absolutely. That sounds great. Dr. Lanser, you get the final word. What are your thoughts on this topic?

Dr. Lanser: Yeah, absolutely I agree. I think we need to keep this patient focused and make sure that we are doing things that are helping the patient's quality of life and to do that I think we need to teach them about other things down the road and things we hope to see. Can we do this in a different or safer way? Are there you know other techniques we can use with the products being developed now to help make this more tolerable for patients or easier for them to do? Can we make this taste better? So, there's still a lot of little things I think that, you know as this continues to unfold down the road, hopefully we see improvements and we'll continue to do better for our patients in the future.

Dr. Caudle: Absolutely. Well, with those great take-away points, I really want to thank you both for helping us translate and refine the complex terms that are guiding food allergy research today. Dr. Bird and Dr. Lanser, it was wonderful having you both on the program.

Dr. Bird: Thank you very much.

Dr. Lanser: Thanks, my pleasure.

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