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Investigating Immunotherapies for Peanut Allergy Management

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 is your host, Dr. Amy Mackey.

Dr. Amy Mackey: The prevalence of peanut allergy among children is on the rise, which creates a myriad of ongoing issues for patients and caregivers as this life-threatening condition extends into adulthood. But there is renewed hope within the health care community from a recently published study that may change the way we treat these patients going forward. This is Cracking the Code on Peanut Allergies, and I'm Dr. Amy Mackey. Joining me to review the findings and potential impacts of the PALISADE Trial published in the New England Journal of Medicine is lead author, Dr. Brian Vickery, Associate Professor of Pediatrics and Director of the Food Allergy Center at Children's Health Care of Atlanta at Emory University School of Medicine.

Dr. Vickery, welcome to the program.

Dr. Brian Vickery: Thanks for having me. It's good to be with you.

Dr. Amy Mackey: Dr. Vickery, before diving into this study, let's talk about the public health crisis of peanut allergies and how this led to your research investigation with the PALISADE group of clinical investigators.

Dr. Brian Vickery: Peanut allergy is currently estimated to affect about 1.5% of children in the United States with a similar prevalence in other industrialized countries around the world like the U.K., Western Europe, Australia, etc. One U.S. based study that found that this seems to represent a 300% increase in recent years, so peanut allergy is getting more common. The reasons for this are not clear, but likely involve a complex interaction of environmental factors, which includes actually the way that infants have been introduced to peanut in recent years. There are still a lot of knowledge gaps about why this is happening and, in addition to that, there has been a gap in terms of understanding how best to treat peanut allergy really with no FDA approved options up until this point.

Dr. Amy Mackey: What was the investigational background behind this new therapeutic approach as far as the earlier studies leading up to this one?

Dr. Brian Vickery: This approach that we studied here is called oral immunotherapy, often called OIT for short, and OIT is an old concept, in fact. It is actually over 100 years old with the first report being in the Lancet in 1908 with an egg allergic boy that was treated with egg desensitization. But this has really been poorly studied. Mostly small studies or case reports over this excessive 100 years and then, starting in the mid-2000s, there were several small academic trials that provided sort of proof of concepts for OIT with a little bit more regular and not so preliminary evidence that it could be a safe and effective form of treatment. A company was founded to move this forward with the idea that it could be potentially translated into the clinic if it looked good after wider testing. The company developed GMP methods to manufacture a standardized product and then had a positive phase 2 study in 55 peanut allergic patients a few years ago.

Dr. Amy Mackey: Let's focus on the methodology for this study. How did your team conduct this trial and monitor outcomes?

Dr. Brian Vickery: This trial occurred in 66 sites in 10 countries across the world, and enrolled peanut allergic patients aged 4 to 55. The prespecified primary analysis population in this study was children ages 4 to 17, but adults were included in this study and I think we'll talk about that a little bit later. The participants had to have a history of reacting to peanut, and had to be sensitized to peanut, and have positive test results. Then they qualified for this study by undergoing what's called a double-blind placebo- controlled food challenge during the screening period of the study, where they had to have a clear allergic reaction at or before 100 mg of peanut protein given in the food challenge, which, in real world terms, is about one-third of one peanut kernel.

Dr. Amy Mackey: Let's walk through what your team found throughout the study. Can you speak to the initial results?

Dr. Brian Vickery: The top line results show that in the 4 to 17-year-old age group, after one year of desensitization treatments, 67% in the active group compared to 4% in the placebo group could tolerate 600 mg of peanut protein at a double-blind placebo-controlled food challenge performed at the end of treatment. The difference was, from reacting in real world terms, from one-third of one peanut at the beginning to being able to tolerate two peanuts at the end, which doesn't sound like a lot but in fact, on average, there was a 100-fold improvement in the active group with clear separation from the placebo group and shows a term that we refer to as clinical desensitization.

Dr. Amy Mackey: There must have been some adverse events that happened as you were taking on this trial. Can you tell me how those were followed and what was reported?

Dr. Brian Vickery: Adverse events were collected by a variety of methods. Primarily, daily diaries that the participants filled out at home every day as well as direct observation. It is important to note that in this type of treatment, OIT, there are doses that are given throughout the study in the research unit approximately every two weeks as the doses increased. So, it starts from less than 1 mg and then builds up over about a six-month period of time to a maintenance dose of 300 mg. Each of those dose adjustments occurs in the clinic, but then all of the other doses are given at home. So, the investigational product is in a capsule that is distributed to the families. They open it up and sprinkle it into yogurt, applesauce, or something like that, and consume it orally everyday at home. The participants recorded their experience taking the dose in daily diaries and then, of course, were observed when they were in the research unit. The severity of adverse events was scored with conventionally used grading scales for allergy research that had been published, and the protocol had individual study stopping rules for adverse events of particular severity or frequency. There was also follow up and observation mandated for certain types of adverse events.

Dr. Amy Mackey: Can you elucidate for us some of the adverse events that occurred and what that looked like?

Dr. Brian Vickery: As you might expect, a type of therapy like this where participants are gradually exposed to the very thing that they are allergic to does produce adverse events, and this was a group of participants in the study that were actually quite allergic. About half of them had asthma, two-thirds of them had additional food allergies beyond peanut, and most of them had atopic dermatitis. So, adverse events were seen very commonly in both groups, upwards of 90% in both groups. Those that were more common in the active group affected the typical target organs that you might expect in allergy studies where you are giving somebody a peanut allergen to swallow, so that includes the GI tract, skin and the lungs. This was consistent with what has been seen in other studies of OIT. There was no unusual toxicity seen with this study. Overall, adverse events that were considered serious or severe were relatively rare affecting about 5.5% in the active group and about 1.5% in the placebo group, and then there were particular adverse events of interest in this study that were considered more significant like systemic allergic reactions and a particular type of GI intolerance, and the systemic allergic reactions affected 14.2% in the active group versus 3.2% in the placebo group. With respect to the GI side effects, we saw 4.3% in the active group that withdrew due to these GI events versus none in the placebo group. There is an allergic condition called eosinophilic esophagitis that has been described in participants undergoing this type of treatment. In this study, three participants underwent an endoscopy to have that evaluated and one of those three was positive for EOE in this study. (This rate of EOE was lower than has been reported in previous peanut OIT trials)

Dr. Amy Mackey: Why do you think there was such a high rate of adverse events in patients taking the placebo?

Dr. Brian Vickery: Well, it just reflects the fact that the participants in this study were primarily children and they were atopic children who are also going to have not only viral infections but viral infections that trigger maybe asthma flares or deterioration in their eczema control and that's why it's important to do studies like this that include placebo controls because there is a fair weight of background signal.

Dr. Amy Mackey: I can see that the efficacy for this therapy was not seen in participants who are 18 years of age or older. Why do you think this was the case?

Dr. Brian Vickery: That's an important question, and I think it's really key to understand that this study was not powered to detect in affected adults. So, as I mentioned, the prespecified analysis population was those ages 4 to 17. Adults were included, and the treatment effect in adults was a secondary endpoint of the study, but the study was not powered to find a difference. There was a relatively small number of adult patients in the study, only 56, and there was a relatively high withdrawal rate in this study for adults, which may reflect the rigor of this type of treatment where you're coming to the research unit every two weeks or so for about half a day and, you can imagine, for a working adult that's a lot of missed work and so on. When you analyze the data from a conservative intent to treat from a perspective where you treat all of the withdrawals as failures, you don't see a difference between the active and the placebo group, but we think that might actually be a type 2 error, meaning when you look at the completer data and you actually analyze

the efficacy of the treatment in those that are able to complete the study, the efficacy in adults looks basically the same as it did in children. The results were not statistically significant because of the high drop out rate. It is interesting preliminary data. Obviously, you need to rely on intent to treat analyses that suggest that perhaps a larger adequately powered study in adults where maybe there is some flexibility in the protocol could be indicated at this step.

Dr. Amy Mackey: Looking back over this study, what were the main takeaways for you and your colleagues, and what are the next steps on the research side?

Dr. Brian Vickery: I think, based on our experience, as I said, over 100 years, I think there was some general understanding that OIT works from an efficacy perspective. I think one of the main issues was, is it practical in the real world? Is it safe in the real world and would these smaller studies bear out in a larger study? So, I think one of the big takeaways from this study, is that this was by a long shot the largest study ever done in food immunotherapy. Again, 66 centers in 10 countries with a placebo control provided really the highest quality evidence that we've seen in this field, and actually quite closely replicated the face to efficacy results and some of the other studies that have been published without seeing any unusual toxicity and this is notable considering this was in, again, highly allergic people in diverse populations around the world that included not only the academic centers that have studied this most closely, but also community centers, some of whom who had no experience with this type of treatment, and this gives us pretty high confidence in the findings in that they have generalized ability to the real world. I think that is in part why you saw that it was published in the New England Journal, because these are the types of studies that have the potential to change practice.

Dr. Amy Mackey: Excellent. From a broader sampling, what roles do you see oral immunotherapy taking in food allergy management going forward?

Dr. Brian Vickery: I think you'll see continued study of peanut OIT in younger children. The lower limit of age here was age four, but peanut allergy usually presents in infancy or the early preschool years, and I think it's worth looking at this therapy in those young children where it might actually have the most benefit. I think you'll see study of peanut OIT with other adjuvants that might make it a little bit safer perhaps or more effective, and I think you're also going to see other food immunotherapy studies for milk, egg, tree nuts, and some of those other types of foods. Beyond that, there are still a whole bunch of research questions as we move this into the clinic in the so called sort of T3 and T4 translational research phase where we are looking at real world safety in tens of thousands of patients, long-term adherence, patient centered outcomes such as quality of life, cost effectiveness, all these types of things we haven't studied yet because we haven't had a therapy like this that is used in real patients.

Dr. Amy Mackey: That's a great way to round out our discussion. Dr. Vickery, thanks so much for joining me today to bring us up to speed on this recent advance to peanut allergy treatment. It was a pleasure having you on the program.

Dr. Brian Vickery: It was my pleasure. Thank you for having me.

Announcer: The preceding program was brought to you through an independent educational grant from Aimmune Therapeutics. To access other episodes in this series, visit ReachMD.com-slash-PeanutAllergies. This is ReachMD. Be Part of the Knowledge.

Aimmune is a clinical-stage biopharmaceutical company developing desensitization treatments to help protect people with food allergies from the potentially life-threatening consequences of accidental exposure. For more information, visit www.aimmune.com.