Biologic injectables could change the eczema trajectory

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Lynita: Hello and welcome to the podcast. Preventing eczema and changing the disease trajectory is our aim at GPER. So we were excited about a poster presented at the European Academy of Pediatric Sciences conference in Austria last year that found that children on Dupixent, or dupilumab, the terms are used interchangeably, were more likely to go into remission than adults.

Dupixent is a breakthrough treatment for eczema that was approved by the FDA for adults in 2017 and for [00:01:00] children six months and older in 2022. It's taken by injection every two to four weeks either at home or in the doctor's office and was the first biologic treatment approved for eczema, and there are now several others available or coming soon.

Lynita: Full disclosure, this poster is reporting an industry funded study. The full peer reviewed paper is coming out later this year. But we invited the researchers to explain what they found. Here with me today are: Dr. Amy Paller, she is a Professor and Chair of Dermatology and a Professor of Pediatrics at Northwestern University in Chicago. She has directed a Pediatric Dermatology Trials Unit for 30 years. Also joining me today is Dr. Elaine Siegfried, she is a Professor of Pediatrics and Dermatology in the Dermatology Division of the Department of Pediatrics at St. Louis University of Medicine, Missouri. She has served as a principal investigator in multiple industry sponsored clinical trials for over 30 [00:02:00] years.

Dr. Paller and Dr. Siegfried, welcome to the podcast.

Dr. Paller: Thank you so much, Lynita.

Lynita: So tell us about this study. You follow kids aged six months to five years old with moderate to severe eczema that was not well managed with tropical steroids. You then put them on Dupixent for a year and measured their response to it while they were on the drug. And then you measured what happened with their eczema when they stopped using it. Tell me more.

Dr. Siegfried: Sure, this study is just one in a whole string of studies looking at remission. And there's more data that's being accumulated and more that's going to be reported. It's that first question that every parent asks when I recommend systemic treatment, well, how long are they going to be on it?

This study was 150 kids who are on medication who got to clinical remission.

Lynita: I'm pausing the interview here to drop in an explainer and I'll do so as necessary throughout the podcast. Clinical remission in this study is defined as clear or almost clear skin, so no signs of eczema or barely perceptible signs of [00:03:00] eczema, for at least 12 weeks. And now we'll go back to our discussion.

Dr. Siegfried: So about a third of them got to clinical remission after a year on treatment. And then after that year, if they got to clear or almost clear, they were stopped and then followed along to see if their disease came back. And at the end of that second subset analysis, about a third of them could stay off drug for a minimum of six months follow up. So that's making us hopeful that there is a light at the end of the tunnel, and that early treatment may, in fact, have an impact on the natural history of the disease.

Lynita: So of the approximately 150 kids on Dupixent per year, 50 had clear or almost clear skin at the end of the study and when those kids stopped using Dupixent about a third, [00:04:00] say 15 to 20 kids did not need to go back on Dupixent 6 months later, their disease was minimal or gone. And of those kids, whose eczema did come back, 80 percent only had mild eczema, which could be managed with topical steroids.

Dr. Siegfried: Right

Dr. Paller: Part of the question about that is, would this have happened anyways? Or was this really the effect of being on a highly successful medication systemically changing the immune system? I will say that there's a lot of conflicting data out there on the natural history of atopic dermatitis.

Lynita: Jumping in with another explainer here, natural history of disease means how it naturally progresses over time without medication.

Dr. Paller: Wan's study suggested that children who were 10 years or above had a much lower chance of being able to outgrow their disease, but also that 80% of atopic dermatitis, which starts very often in the first year of life, would not persist past eight years of age.

On the other hand, there's the PEER study. That suggested quite the opposite. That 80% were persistent of some of these often milder to moderate disease severities. So very controversial, and that's one of the problems is that we really don't know the natural history for Children, pre adolescence.

Lynita: I'll also share a study that I found because this concept of spontaneous remission, eczema just going away on its own without drugs, is one that gives hope to many parents. It did for me certainly. So this was a Swedish study and they found that at least 30% of 1 to 3 year old kids with severe or early onset eczema will outgrow it and that percentage only increases as you get into milder cases or later onset eczema. I'll share the study in the [00:06:00] links.

But out of your study, what percentage do you think might have gone into a spontaneous remission without ever having been on Dupixent?

Dr. Siegfried: it's about the study population. So in the patients who were six months to five years of age that we got enrolled in the first place, they only had severe disease.

Dr. Paller: I think we're talking about a relatively small percentage, at least in the Children within the study. What we know is that these are children who did not have an adequate response to even medium strength or stronger topical corticosteroids, or they wouldn't have been allowed in this trial, and they have severe disease. And these are 2 factors that speak to greater disease persistence. So it's probably not a large percentage, certainly nowhere near what we saw with dupilumab during this period of time. More likely, they would have flared very quickly because that's what was seen before when we stopped these potent topicals that they were on.

Dr. Siegfried: So it really is hard to compare. [00:07:00] It's apples and oranges, you know. And as tell parents, I mean, I wish we could say whether your child is specifically going to have a chance to outgrow this, but… We still can't predict.

Lynita: Could it also be that if children are not suffering for so long, maybe that's going to impact how things turn out for them with comorbidities

Dr. Paller: Yeah it seems like you have a better chance of having an off drug remission as you get younger. It is pretty clear. For example, in another study that Elaine presented, we have 60% who maintained clear, or almost clear off of the drug, who were in the six to 11 year old age group versus only 43% in the adolescent patient group over an average of about four to five months. And when we look at so many immune disorders, we know that the longer it goes, the less propensity there is to [00:08:00] clear, even clear spontaneously, but probably also with treatment.

Lynita: So from other diseases we know that they are more likely to go away if we have suffered for a short time rather than a long time, and that seems to be what your study is finding also, that if we control the eczema with Dupixent early on, we are more likely to be able to successfully stop it and maintain remission.

Dr. Siegfried: Right. Holy grail is always to cure the drug. So the question becomes, if you use systemic treatment, is that going to be more effective at helping you outgrow your disease?

And we don't know the answer to that. But when we looked at some biomarkers specifically total IgE because we know a lot of kids with severe disease have very high IgE levels, many years ago in the pre biologic era, and if their skin stayed clear, or maybe they either use their topical treatment well or it was just the natural history of the disease, that their IgE goes down anyway.

Lynita: Jumping in again, IgE or immunoglobin E are are antibodies that are produced by our immune system when we come into contact with an allergen. These IgE [00:09:00] levels are biomarkers of allergic reactivity in our bodies, and they can be measured with a blood test.

Dr. Siegfried: So there is maybe some data that's going to come out with biologics about impact on these biomarkers, and I don't know that the impact on the biomarkers is specific to any treatment. I think, if you clear your skin, it's going to inform your immune maturation anyway, you know. So that's the bottom line is that we think you get your disease clear as early as you can, and that'll increase your chances for getting off the injections and systemic treatment and be able to use safe, more cost effective topical treatment long term. But, it's all evolving.

Dr. Paller: Well, I just want to chime in for a minute about the reduction in IgE because there are studies coming out from the allergy world suggesting that at least during treatment with dupilumab we're certainly seeing a decrease in their food allergies or other allergic manifestations, which do relate to the IgE level. So it's intriguing [00:10:00] and I think we still need to have more information about the relationship between having this reduction in and control of other atopic disorders and potentially even reduction in risk of developing these.

And one of the questions that I keep wondering is in our eagerness to get kids off of systemic drugs is there an added benefit to being on the drug that is lost if you stop it, especially if we're talking about a younger child. Will the other

biologics similarly bring down the IgE levels to the same extent? I think there's evidence that they at least do lower it somewhat.

Lynita: So you're saying that being on a biologic seems to help lower IgE levels, which may help inform a developing immune system and possibly change the allergic trajectory for kids.

Dr. Siegfried: Right

Lynita: Let's talk about tapering because for two thirds of the kids that [00:11:00] didn't reach remission, tapering was an option.

Dr. Paller: We don't really know the answer for the best way to do this. I will often talk with families and say, we want to keep you on for at least a year because maybe we can actually change your immune reactivity if we have a longer period of time of being on the medication. So I think there's a good rationale for keeping people on for a while, but we don't have the evidence of how long that needs to be to change the immune system, so to speak.

The other question, though, is then what do you do? There's no particular prescription for exactly how to do this. So, I think we're just each deciding how long to stay at each level, how to do this, kind of on our own, but then at what point do you stop? We know that for example, that dupilumab can stay in the system for, let's say, 6 weeks, So, if you're continuing to see a good effect as the drug level [00:12:00] goes down then they're really retaining a response off of drug. So, remission has to be after a certain period of time if we're talking about off drug. So I'll pass it to Elaine in terms of what's been your experience, what you usually do.

Dr. Siegfried: Yeah, my experience is, once they get to clear and I really like them to be clear for about six on the drug. I'm just making this up. Is their barrier function restored? Are they going to have more resilience? And then I start to increase the interval between their injections. So go from every two to every three weeks for three months and then every three to every four, and then once they get to every six is when I'll stop it. Mostly based on the data that we have about anti drug antibody development.

Lynita: Sorry to interrupt you, but can we have a little explainer of what exactly anti drug antibodies are and what the consequences of them are?

Dr. Siegfried: So biologic medications are antibodies. And some people have a tendency to make antibodies against [00:13:00] biologic stuff, and if you make a

certain kind of antibody, you are just likely to react to things and some of that reactivity may make the drug less effective.

Lynita: So basically you're adding antibodies with a biologic to your body and your body might create something in reaction to those antibodies and that's going to cause some other illness or consequence.

Dr. Siegfried: No, it doesn't really cause illness. It just makes the drug less effective.

Lynita: Got it. Thank you.

Dr. Paller: These concerns really came from the biologics that were for psoriasis and other diseases, where we did have issues with anti drug antibodies of a neutralizing type that were decreasing responses. We haven't really seen that with dupilumab to that same kind of a level. And even when there have been, in a very small percentage, neutralizing antibodies, they've not been correlated with decreased response to [00:14:00] the drug. So our concerns about stopping and starting with biologics, particularly, prolonging intervals to more than every eight weeks, for example, maybe unfounded. And so to me if they've gone six weeks, maybe you go to eight weeks and they're not having a flare, I think it's great to try to stop the drug and just restart it if there's a problem. And for most of my patients in whom I've done that, I've been able to at least get months of good control off of the drug and then restart the drug with a good response.

Dr. Siegfried: We know that some people have anti drug antibodies that are detectable before they've even ever been treated with this drug. I'm a little concerned about people who stockpile the drug and then use it here and use it there. That's what I think is the biggest risk. But it's not a huge risk in the grand scheme of things because we do have other drugs in the pipeline that are going to be alternatives if this happens. But I just think [00:15:00] it's a risk that people need to be made aware of.

And so I talk about that to patients and then I don't have them dose any less frequently than every 6 weeks and then if they've been off it for a while, I think they're candidates for going back on it. But there's a lot we don't know about poor response. So I like to prevent that as much as I can, even though there's no glory in prevention,

Dr. Paller: I just want to raise the point too,that the hardest thing about using a biologic for atopic dermatitis, is an injection. So the idea of stopping the

medication if things are going very well for a period of time is something that we as pediatric dermatologists are very focused on. We don't want to continue to inflict pain and familial stress with a drug that we use, even though it is so transformative, so we have to weigh all of these various factors,

Lynita: It is also stressful for families who have to watch their children [00:16:00] feeling the anxiety of a needle and holding the guilt that they have chosen to subject their child to this experience. And all that just adds to the parental guilt of, what did I do to cause my child to have eczema?

Dr. Paller: Yeah, I want to thank you for raising that because I think it's really important. There's rarely a parent who comes in, usually a mother, who is trying to figure out what she could possibly eliminate and make this go away. And unfortunately, it's not so simple. There isn't one thing. And for very few families is it possible just to identify something, eliminate it and get away from the treatment that we otherwise would be using.

Dr. Siegfried: Parents are always racking their brain to just understand and sometimes blame themselves about something that they did that made all of this happen. And, I would like to pick parents up from that because it's not your fault, you know, and trying to figure out what you did that somehow put your [00:17:00] child at risk is not going to really be of any benefit. So you just take what you see and you try to manage that as it comes up.

Lynita: I guess the take home message here is what's happened has happened and we should really focus on what we can control.

Dr. Siegfried: Right

Lynita: So let's bring this together now. What does this mean for parents? Should they say yes to Dupixent because it might improve the outcome for their child in the long term?

Dr. Siegfried: If you have a clinician that you trust and your child is impacted and one of the easiest ways to judge impact is if they're not sleeping at night, you know, that's an easy thing to measure so if you have a child who has disease like that I think they're good candidates for systemic treatment. So as a bottom line, yes, it's a great drug. You have to have a provider who understands the complexities of this disease, and then you're on it for as long as you need to be. And then, the good news is you probably can get off of it. And probably the earlier you go on it, especially in children who have very severe disease and a [00:18:00] lot of other morbidities, those are the ones that really need it.

Dr. Paller: From the standpoint of safety, they seem to be very safe. The biologics have really only had one side effect and that is in the minority of children and even less as you get into younger ages having some redness of the eyes that is largely manageable. And then in a small percentage, also having injection site reactions, which also are transient and easy to handle. And that is basically lowered the threshold for us to use this as appropriate for a broader number of children. To your question of what does this study mean for parents? I want to stress that any patient who went to stopping their drug in this study was already on the medication for 52 weeks. And that's telling us that perhaps the best opportunity for having this kind of a [00:19:00] result is staying on the drug for at least a year and then thinking about a taper or stop and seeing what happens. But it does tell parents that there is hope to get away from even being on a systemic injection for a period of time, and that's something we need to think about, giving families a break.

Lynita: Absolutely. I have one last question that I'd like to ask. Where to next for this research? I know it's ongoing, but please let me know what's coming up.

Dr. Paller: We really need to understand not just control of the atopic dermatitis and its continued control off of drug, but the implications of stopping this successful drug on comorbidities. How this all relates to the allergic comorbidities, but also the neuropsychiatric ones. Will we change the mental health status, the risk of anxiety and depression? In [00:20:00] children just by keeping them in good control. Are there other factors?

Dr. Siegfried: Yeah, there are so many, so many unanswered questions, and I do want to give a shout out to our industry partners who are investing an inordinate amount of resources into asking these questions, especially finishing these large prospective long term trials. Now we have mounting data that says that growth is improved in children on Dupixant. We have mounting evidence about the safety and efficacy of immunizations and even live virus vaccines so there are many questions that come up day to day, but fortunately, we have industry partners who are willing to invest in those questions.

Lynita: Thank you very much for those wonderful answers, and thank you so much for your time. Have a good day. [00:21:00]