I-CAN, A Study of Inebilizumab in Children with AQP4+ NMOSD

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[00:00:02] **Rebecca Whitney:** "ABCs of NMOSD" is an education podcast series to share knowledge about neuromyelitis optica spectrum disorder or NMOSD, a rare relapsing autoimmune disorder that preferentially causes inflammation in the optic nerve and spinal cord. "ABCs of NMOSD" podcast series is hosted by SRNA, the Siegel Rare Neuroimmune Association, and in collaboration with the Sumaira Foundation for NMO and Guthy-Jackson Charitable Foundation. This education series is made possible through a patient education grant from Horizon Therapeutics.

[00:00:50] Welcome to the "ABCs of NMOSD" podcast series. My name is Rebecca Whitney, Associate Director with the Siegel Rare Neuroimmune Association. Today's podcast features Dr. Michael Levy for a brief overview of the I-CAN study of inebilizumab in children with aquaporin-4 positive NMOSD. Dr. Levy is one of the principal investigators for the study. Dr. Levy specializes in taking care of patients with neuroimmunologic diseases including multiple sclerosis, transverse myelitis, optic neuritis, and neuromyelitis optica.

[00:01:30] In 2009, Dr. Levy was appointed to the faculty as Assistant Professor at Johns Hopkins, where he started the Neuromyelitis Optica Clinic and Research Laboratory. In 2018, he moved to the Massachusetts General Hospital and Harvard Medical School where he is an Associate Professor and Research Director in the Division of Neuroimmunology and Neuroinfectious Disease.

[00:01:58] Thank you, Dr. Levy for joining me today to discuss the inebilizumab trial in pediatric NMOSD. Can you tell me a bit more about inebilizumab or I believe its brand name is Uplizna™?

[00:02:17] **Dr. Michael Levy:** That's probably a little easier to pronounce.

[00:02:19] **Rebecca Whitney:** Yes, indeed. Can you tell me what we know about it already, and perhaps what its mechanism of action is, how it works and in particular, what our goals are with this particular drug in pediatrics?

[00:02:36] **Dr. Michael Levy:** Yeah, this is a B cell depleting drug. The mechanism is very similar to rituximab and a lot of our NMO patients have been using rituximab for 15 years in some cases, it's been being used off label. The inebilizumab approach is a little bit broader in terms of what types of B cells are depleted. So, rituximab only removes B cells that express CD20 and inebilizumab removes B cells that express CD19, which includes CD20 cells, but also a few other cells, including the ones that make aquaporin-4 antibody in the bloodstream, for example.

[00:03:18] So, the approach is supposed to be a little bit broader. We were hoping we'd see a reduction in auto antibodies to aquaporin-4 and get that rituximab plus benefit. In adults, the trial was run 18 years old and older. It was run between 2014 and 2019 and it showed a reduction in risk of relapse by about 73% compared to placebo. If you look only at aquaporin-4 people, it's 77%. And these are numbers that were fairly similar to

rituximab. Of course, rituximab has never gone through the scrutiny of a Phase 3 trial worldwide. So, it might have been a little bit better if we had a rituximab comparator but was approved on that basis of the trial.

[00:04:03] And in the European Union, there's a requirement that any drug that's approved for adults has to be tested separately in children. And so, this is to fulfill that requirement and they can recruit from the entire world. I believe they're going for about 12 total children, maybe 15. So, a very, very small number and there's no placebo arm. So, everybody gets drug.

[00:04:34] The idea is really to just confirm that it's just as safe in children as it is in adults. And then the efficacy that we're expecting in kids is going to be what we're looking for. But in this case, we have to enroll only kids who have the aquaporin-4 antibody. Whereas in the other study, we could enroll seronegative NMO. In this study in kids, we cannot, only seropositive.

[00:05:02] **Rebecca Whitney:** And this is currently a Phase 2 study, is that correct?

[00:05:09] **Dr. Michael Levy:** Technically Phase 2. It's not a Phase 3 comparator. This is technically Phase 2, it is to fulfill that requirement. I don't think we're going to see a Phase 3 study after that. If this is positive and effective and safe, we'll file for approval and hopefully get approval in children without having to do a placebo-controlled study.

[00:05:31] **Rebecca Whitney:** And what are the ages for this particular pediatric study?

[00:05:37] **Dr. Michael Levy:** This is age 2 to 17.999 right up until age 18, they can actually be 17 years old when they enroll and then if they have a birthday and turn 18, that's okay. We can keep them in the study. They just have to be under 18 when they enroll. That age group is expected to respond just as well, but of course, there are issues about dosing. So, you do want to be careful not to give a two-year-old who is this big the same dose that you would give a full-size adult. And there are other considerations like pharmacokinetics and dynamics so you can see how well it's working. We know, for example, in rituximab, when you dose children and teenagers, their B cells come back earlier than older folks. So, that's something that we also have to keep an eye on in this trial.

[00:06:32] **Rebecca Whitney:** And what can one expect if they choose to participate in this trial? Are they going to have to come into the clinic more often? How often would it be administered? And how is it administered? Is it by infusion? Is it Sub-Q injection?

[00:06:48] **Dr. Michael Levy:** It's an infusion. It's every six months. Those have to be done in the clinic, you can't do them at home, for example. But in addition to those visits, there are MRI requirements and yes, additional blood draws that - I hate sticking kids for blood. I hate it, but it is part of the process. There's closer observation, more phone call surveys, that thing. But in exchange and we want to compensate families for the time taking off of work. For example, there are some payments that would hopefully offset those costs to the families. And the knowledge that they're contributing to science is something that some patients really do want to do. So, it's not for everybody. Certainly, we still have access to rituximab. But again, rituximab is not approved for NMO, whereas inebilizumab is. So, if there are any kids out there who are thinking about B cell therapy, my inclination would be to go into the trial rather than to use something off label.

[00:07:57] **Rebecca Whitney:** Thank you. It answers one of my next questions as far as if someone's on a current treatment and it is successful, what should they consider when looking at a specific trial such as this -

[00:08:18] **Dr. Michael Levy:** Well, in this study, you have to have had a relapse in the past year. So, if you've been stable on rituximab, you're not eligible, and if you're aquaporin-4 negative, you're not eligible. So, if you're doing well, there's no reason to jump into this trial. But if you have a new diagnosis and you're thinking about starting a therapy, this would be a very good opportunity. I should mention that kids who are 12 and older have access to satralizumab, which is also FDA-approved in the US. It's approved for aquaporin-4 seropositive NMO. And so, if you're looking for FDA-approved options and you're 12 and older, that is already available to you. If you're under 12, there are no approved therapies.

[00:09:09] **Rebecca Whitney:** Thank you. And you touched on this a bit. So, how would trial participation impact their current treatment? Would they have to indeed stop current therapies and move into this particular one?

[00:09:25] **Dr. Michael Levy:** Yes. If the kid is on CellCept, azathioprine, low dose prednisone, something like that, they would have to wean off to participate in this study. But I can honestly feel comfortable doing that because I know that they're going to have B cell depletion and whether it's B cell depletion with rituximab, which we also use as monotherapy. We don't combine rituximab with those other drugs. I know that they're getting the drug because there's no placebo arm and I know that they're going to deplete their B cells and I think that that's going to be helpful in kids. So, I really don't have any ethical concerns about stopping a medication like CellCept in order to participate in this trial.

[00:10:08] **Rebecca Whitney:** That's good to know. Thank you very much. And how long can one expect to be a part of this trial before we know what are the results? And how does that work after the study is over for someone who would be using them?

[00:10:28] **Dr. Michael Levy:** The human trial - I'm sorry, the adult study ran for six months. That was the double-blind period. That was the real comparison period of time with six months. And then after that, they got the drug without a risk of placebo. So, then everybody was on treatment. In the kids' study there's no double-blind period, but it's going to be that first six months, it's going to be really scrutinized and compared to the adult study. After that, kids can stay on the drug in an open label extension similar to the adult study. And the time that they're allowed to stay on it, I think right now, the promise is that if kids are doing well, they're not going to stop the trial. Unless there's some safety concern or other reason to stop the trial, kids who've gone through that period of time and who are doing well, can expect to stay on the drug and at least until it's FDA-approved for their age and then insurance should pick up the tab after that.

[00:11:34] **Rebecca Whitney:** Thank you. And just considering we talked a bit about the age and the requirement of a seropositive NMO, are there any other inclusion criteria or different things that they may have to comply with in order to be a part of the trial?

[00:11:59] **Dr. Michael Levy:** I think the two most - there's three difficult inclusion criteria. First, they have to be under 18, there are not a lot of seropositive NMO children under 18. A lot of kids who have NMO don't test positive for the antibody. So, that's rare, that's hard. The relapse in the past year is a challenge because a lot of children, started on treatment and some of them do well. And if they haven't relapsed in the past year, then they're not eligible. And the third difficulty is the history of rituximab use. So, if you had rituximab in the past, even if it's one dose, then you're not eligible. And so, this is going to be a difficult trial to recruit for, we know that going in, but we do want to make it available to all kids who are eligible.

[00:12:49] And I should also mention this because NMO is rare and because the inclusion criteria are so strict and there aren't that many sites that are enrolling, we are willing to compensate for all the travel that's

required. I'm in Boston, we're a site but if the kid lives in upstate New York and would require a one-hour plane trip to come in for that infusion, we would absolutely be willing to cover the travel for the kid and the parent and everything that's involved because we know how rare these kids are. And so, we don't want to make travel a burden.

[00:13:26] **Rebecca Whitney:** Thank you very much. That was actually my next question, and I know you had mentioned it earlier as well. So, definitely an obstacle that many have to overcome when considering participation in clinical trials. So, is there anything else that you believe is important for a child, a parent or guardian to know or even a clinician when considering this particular trial? Anything that you definitely inform patients of when this is an option that you may be looking at for them?

[00:14:08] **Dr. Michael Levy:** Yeah, I would say again that a trial is not for everyone and that if I was confronted with the case of, well, do we do rituximab or inebilizumab, I still in my heart believe that rituximab is effective even though it's not proven. But scientifically, inebilizumab has the data in adults that rituximab does not. And so, that's why I lean slightly towards inebilizumab. Do I have kids with NMO on rituximab? Yes, I do. And they're not eligible for the study anymore because they haven't relapsed. And that's why I think it's effective. But again, I think for the betterment of science, I think inebilizumab is the way to go and I honestly believe it'll work at least as well as rituximab if not better. And so, that is why I do support this study.

[00:15:03] **Rebecca Whitney:** Well, thank you very much. And for those who are interested or want additional information, I know we have information on our website, and they can also find information at clinicaltrials.gov as well as the Uplizna™ website that'll be included with this podcast when it is published.

[00:15:24] **Dr. Michael Levy:** Excellent.

[00:15:26] **Rebecca Whitney:** Thank you again very much. Always appreciate your time and your work.

[00:15:31] **Dr. Michael Levy:** Happy to be here. Thanks for the opportunity.

[00:15:33] **Rebecca Whitney:** Thank you.