NMOSD and MOGAD Clinical Trials

You can view this presentation at: youtu.be/75Bwop2jNXo

[00:00:05] **Dr. Michael Levy:** When we think about trials in MOG and in transverse myelitis and in NMO, we're thinking about it in four different ways. Here are two ways: one is acute therapy. The way you can think about this is, there's a fire going on in your optic nerve or in your spinal cord, it's burning, we need to put it out. That's acute therapy.

[00:00:25] Preventive therapy is: we don't want another fire coming, so can we use a medication to prevent the next attack? We also have regenerative therapy. You heard Dr. Greenberg's talk: this is like the Servpro, "like it never even happened." You want to regenerate. There are trials in that area. And then there's symptomatic trials, where you just want to improve people's quality of life. And these are four different arenas.

[00:00:49] And the way I'm going to organize this talk is by disease, and I'm not going to go through all of these, but I want you to know what's out there. In NMOSD, there's basically only one trial going on in the US, and that's using satralizumab or Enspryng. Maybe some of you are on it and wondering why there's a trial. It's for people who weigh over 100 kilograms, to see if maybe a higher dose is needed.

[00:01:15] This is something we realized in the Actemra population, who were using the older version of satralizumab, that there might be a dose response. Nabiximols is to improve quality of life using a marijuana derivative drug, and I will mention that trial. CAR-T cells, I think Dr. Yeaman is going to discuss in the next presentation. You heard Ken Schultz talk about TRE-515 for ADEM. This area under ADEM was blank for the last 10 years that I've been giving this talk, and now we finally have something to list here that's great.

[00:01:54] Restorative was also blank for a long time; thank you, Ben, for occupying that space. And then, I'm going to spend the most of the time talking about these trials in MOG antibody disease: the rozanolixizumab trial (cosMOG), satralizumab in a trial called METEOROID, and a dairy-free diet that is really a little bit premature to discuss here, but I just want to give you a flavor of that. And then, two acute treatment trials that are just launching that I think are really exciting.

[00:02:23] So, we'll start with the MOG trials. These are both preventive studies. These are not acute treatment. This is to prevent the next attack of MOG, and this is using a drug called rozanolixizumab that blocks a receptor

called the FcRn. And what FcRn does is, it lives inside your blood vessels. Your blood vessels are constantly crunching up your blood, and recycling it, and purifying it, and taking out all the impurities.

[00:02:49] When it takes up some of that blood shown here in the schematic, all of these antibodies in green are saved. Okay? They bind to this little Tylenol-looking thing called the FcRn, and this FcRn protein holds on to the antibody. It recycles the rest of the blood components, throws everything else in the trash, and then releases the antibodies back in circulation.

[00:03:16] So, this is a way of holding on to your antibodies and preventing them from being degraded as your plasma and your blood are being constantly purified. The way this drug works is it blocks the FcRn. So, what happens if you block FcRn? The antibodies are no longer saved. Even a single dose in you right now, even if you're healthy, if I give you one dose of this, 50% of your antibodies will be gone by the end of the week. That's how fast you recycle your plasma.

[00:03:46] And then, in this trial, we give it weekly. So, as antibodies are made back again, you recycle them over, and over, and over again. Now, this drug is being used in anything where IVIG is helpful. The way IVIG works is also by binding to FcRn, preventing your natural antibodies from being saved, and those get degraded.

[00:04:10] So, anything that IVIG works for, these FcRn drugs are being developed. That includes myasthenia gravis, CIDP, and MOG. This trial launched, I think, about two years ago now. The way it's designed to prove that it works -- this is a Phase 3 placebo-controlled international blinded trial -- is when you come in, you get randomized 50/50 into the drug arm (in green) or the placebo arm (in gray).

[00:04:40] And you might be thinking placebo is horrible. It is. So, if you end up in the placebo arm, your risk of relapse is a lot higher. The good thing about this trial is that: if you relapse, you'll end up in this orange phase, the open-label phase where you get free drug guaranteed. And so, if you end up with even just a single relapse, you get out of that blinded phase, and you get guaranteed drug.

[00:05:07] This placebo design is the only way we can really know if the drug works. This is in order to get FDA approval. The trial is more than half enrolled now. If you're interested, please, please let us know. We would love to enroll you in Boston or many other sites. I think there are eight or 10 sites in the United States, and worldwide about 65 sites. So, if you come back to hear this talk in 2026, I should read out the results; that's the idea.

[00:05:38] The second trial in MOG, this is also preventive, is using Enspryng. The Enspryng is already approved for aquaporin-4-seropositive NMO. We started using the precursor, the older drug tocilizumab, in MOG, and it worked really well. The company paid attention, and now we have this Phase 3 trial going on for MOG. It's also preventive. It's also double-blinded, placebo-controlled, 50/50 chance that you'll end up in the placebo arm.

[00:06:09] The drug blocks the interleukin 6 receptor. We know interleukin 6 is pro-inflammatory. If I give you a shot of interleukin 6 right now, you'll get a fever and you'll feel crappy, like you have an infection. If you block that, you block communication among immune cells, and the whole immune system just dies down. If you get an infection, the immune system can get activated again, but if you don't have an infection -- the idea is, during your autoimmune period, you want everything calm.

[00:06:40] We found really high levels of IL-6 in the spinal fluid of people with MOG, especially during a relapse. So, the thought is that IL-6 really is involved. We already knew that because we've been using tocilizumab, the

old drug, and this is a once-a-month subcutaneous injection. The trial design is the same as rozanolixizumab. 50/50 chance that you'll end up in the placebo or the drug arm.

[00:07:06] The nice thing about this trial is: if you're already on CellCept or a little dose of prednisone, you can stay on it, and you'll still get randomized. You'll either add the drug or you'll be in the placebo arm. But if you're in the placebo arm with CellCept, maybe your risk of relapse is a little lower compared to the rozanolixizumab trial. This trial is also about half enrolled. And in 2026, it's expected to read out. If you ask me my personal opinion, I think they're both wonderful drugs, and I think they'll both probably be approved. That's my guess.

[00:07:39] All right. This is the premature study that I wanted to just mention. You see a cow here with milk. I have lactose intolerance. I tell people I get a stomach ache just looking at this glass of milk. What was discovered back in the 1990s -- before they knew what MOG was -- a subgroup of people with MS had antibodies to MOG, and that it also bound a cow protein called butyrophilin.

[00:08:07] And the thinking at the time was that maybe multiple sclerosis was triggered by milk. Again, they didn't know what MOG antibody disease was at the time. But if you look at the MOG protein -- here it is, this is a schematic -- what it looks like outside the cell to the immune system is, this blue blob here, that's called an immunoglobulin variable domain. Many other proteins look the same way.

[00:08:33] They first they discovered MOG in the ‘80s, but in the ‘90s, as they looked around, they said, “You know, the immune system, when it sees MOG, it really does look like a lot of other proteins. Maybe these other proteins are confusing the immune system, and that includes a protein called butyrophilin found in cow's milk.” There's also butyrophilin found in chicken that does not have that same cross-reactivity.

[00:08:58] But what this group in Scotland found in the ‘90s is that a subgroup of people with MS have antibodies to MOG, and it also binds this cow butyrophilin. So, we took that a step further and did what's called a cell-based assay. We put cow butyrophilin on a cell, we put MOG on a cell, and we said, “If you have antibodies that bind MOG, does it also bind cow butyrophilin?” And we only looked at MOG people. We didn't look at MS because we know MS is a whole different disease.

[00:09:28] So, we took all these people with MOG -- they all had MOG antibody -- and then we compared them to different butyrophilins. This one is cow, almost the exact same titer. Anyone who had antibodies to MOG also bound to cow butyrophilin. That really does look the same. There were also a lot of people that had the same binding to a different human butyrophilin.

[00:09:53] You saw that there were several different butyrophilins. We started looking at all of them. Many people had binding to this one, butyrophilin 1A1. There were others as well. We think that there's cross-reactivity going on that may be triggered by cow's milk and then binds other butyrophilins, including MOG, in the body.

[00:10:13] So, what we did as a result of this, as I said, is premature. Before we could verify everything, people got excited about this because you could do something about cow's milk -- you could try to avoid it. It's actually a lot harder than you think, but you could do it. You could avoid all cheese, dairy, butter. Basically, if you go out, you have to make sure your steak is grilled. It's really hard to do. We learned that McDonald's French fries are frozen in milk when they're shipped.

[00:10:41] So, I didn't even know McDonald's French fries are dairy product, but they are. But if you can manage to avoid all dairy, you could be part of our study. We only enrolled a few people right now, and we're looking

at MOG antibody levels over time. So, if you'd like to be involved in that, I'm afraid you might hate me after those three months of no ice cream, no butter, no nothing. But you probably will lose weight because a lot of people have, as a result of not being able to eat anything except rice.

[00:11:09] And, really, what we're looking for is, again, MOG antibody levels, to see if this does have an impact. All right. And the last three studies I want to mention are these: two are acute treatment trials and then one for NMOSD quality of life. We are just launching a trial using efgartigimod. This is just like rozanolixizumab but made by a different company. Of course, we approached the company that makes rozanolixizumab.

[00:11:38] We said, "Hey, we want to try this in acute optic neuritis. We know it works for MOG. We want to see if people who come in with a brand-new optic neuritis, instead of doing plasma exchange (which we do a lot of), can we use an FcRn blocker instead?" Rozanolixizumab said, "Wow, we already have a big trial in MOG. We're spending a lot of money." So, we went to this other company. They have the exact same product. They have it approved for myasthenia gravis, and they said, "Optic neuritis? Sure. That sounds cool."

[00:12:06] So, if you have optic neuritis and you come into the Massachusetts General Hospital, and we don't know if you're MOG positive, we don't know if you're aquaporin-4 positive, even MS. We're going to take all comers at first, but you have to have a severe case of optic neuritis that would normally prompt a treatment course with plasma exchange.

[00:12:24] And we want to see if we can give you this drug and get better a lot faster so that you don't need plasma exchange. So then, maybe we could distribute this nationwide, worldwide, and then people won't need to find a big center with plasma exchange when they come in with their bad optic neuritis. So, like I said, we're just about ready to launch that trial.

[00:12:44] The second acute treatment trial that's launching now was just approved by a PCORI branch of the Department of Health and Human Services. This is a federal program that was started at the time of Obamacare, and they're funding big studies. And one of these just got approved by our colleagues at Johns Hopkins and Mayo.

[00:13:07] And what they're doing is: they want to prove, once and for all, that plasma exchange in optic neuritis and transverse myelitis is helpful. And so, you could have either one of these attacks, optic neuritis or transverse myelitis, and you'd be eligible. I don't know how many sites they'll ultimately enroll. They just heard that they got the funding. We'll certainly be a site. I have a feeling we're going to enroll a bunch of people because, normally, plasma exchange is a go-to option for us.

[00:13:33] So, you could see both of these people look miserable, whether you have pain from your transverse myelitis or your optic neuritis, and then you're smiling when you're hooked up to the plasma exchange machine. Honestly, we've had a lot of experience with it, and we really believe it works, but this is the scientific proof that we need to get approval. So, look out for that as well.

[00:13:55] Last trial I want to mention is with a drug called nabiximols. This is a pharmaceuticalized preparation from marijuana that uses one-to-one ratio of the THC and the CBD active compounds. It contains a bunch of other derivatives as well. And what this does -- it's already approved in Europe and Canada for people with multiple sclerosis who have spasms. I think most of you already know that these marijuana products do really help with pain and spasms, so we're going to prove that in NMOSD or disprove it. We want to see if it helps.

[00:14:33] And we're not just looking for spasms. We're going to check neuropathic pain. We're going to check sleep, anxiety, fatigue. We want to know what it really works for and what it doesn't. It's a crossover

placebo design, meaning half the time you're going to be spraying placebo in your mouth and half the time you're going to be spraying real drug product. And then, we'll be surveying you and asking about your pain levels all throughout.

[00:14:55] It's a single site at Mass General, but you don't have to live within driving distance of Boston. You could be anywhere, and we will mail you the drug anywhere in the United States that you could participate. So, if you're interested, please do let us know. This trial was about a year and a half in the making. All of Dr. Greenberg's problems with the FDA, we had twice as many, because we had to deal with the DEA, which does not like Schedule I drug trials, but we finally got this approved. So, look out for that. And with that, I thank you for your attention. Do I have time for a question? Maybe one or two questions, and then we'll move on to Dr. Yeaman.

[00:15:34] **Audience Member 1:** The rozanolixizumab, do you know yet? Do they have the same side effects as IVIG?

[00:15:44] **Dr. Michael Levy:** It does. Surprisingly, all of the high-risk problems with IVIG, like aseptic meningitis, are exactly reproduced with high doses of rozanolixizumab. But what we've figured out with rozanolixizumab is, you can tweak down the dose so that you don't get those side effects anymore. And since that happens -- since the dose has been reduced -- there have been no cases of aseptic meningitis. You can't do that with IVIG because you lose potency, but you could do that with rozanolixizumab. Good question.

[00:16:22] **Audience Member 2:** That last study that you said if you're interested, is it open for TM patients or just -- which patients?

[00:16:30] **Dr. Michael Levy:** With the nabiximols spray? It's for NMOSD, but you could be seronegative or seropositive NMOSD.

[00:16:40] **Audience Member 3:** Any visual symptoms?

[00:16:42] **Dr. Michael Levy:** Actually, you know what? You could qualify if you have seronegative NMOSD, if you've had a brainstem lesion. So, your vision could be normal and you could still qualify as seronegative NMOSD. Last question here, Larry.

[00:17:05] **Audience Member 4:** Thank you. Dr. Levy, if you find that the nabiximols is effective for treating the spasms and the other bad symptoms of NMOSD, what does this portend for cannabis-based product in general for these other neuroimmune diseases? Thank you.

[00:17:23] **Dr. Michael Levy:** Yeah. A lot of the marijuana products, and even in states where it's all legal, it's not really well regulated. You don't necessarily get the same product twice. The benefit of using nabiximols is that it's really well processed. They know exactly how much THC, how much CBD, and all the other components are in there, and it makes studies reproducible.

[00:17:47] If that proves positive and people start using marijuana on their own, they may find variable levels of benefit depending on what product they're getting. It's not to say that they shouldn't do it that way because I'm sure they'll get it less expensive than a pharmaceuticalized product. But people are already doing it now, and we've heard from a lot of people in the survey that it's helpful.