Long-Term Treatments for Preventing Relapses

You can listen to the audio of this talk at: https://youtu.be/YXOfDFdGWMs

Dr. Michael Levy: [00:00:00] Thank you, Cristina, for the kind introduction there. I'm Michael Levy. I've been a neuroimmunologist for going on 10, 11 years now. I started at Johns Hopkins with Ben Greenberg and Doug Kerr in the good old days. And then I got the training that I needed and started my laboratory, and I work on mouse models of rare autoimmune diseases trying to develop tolerization therapies so we can turn the immune system off in the same way that it gets turned on during an autoimmune attack. But now I am at Massachusetts General Hospital and Harvard Medical School in Boston. I moved here last year. I'm expanding my work. I still work on transverse myelitis, MOG, and NMO, and as part of that work, I helped to develop these new drugs for NMO specifically, and these drugs are designed to prevent attacks. They're not intended to help you recover from previous attacks, but they sure are good at preventing the next one.

[00:01:07] Now the way we think about treatment for all of these autoimmune diseases, whether it's TM, or MOG, or NMO, or ADEM, is there's the acute period, and that's when the inflammation is raging. And that's when... We think of it as like a fire, and the fireman that's putting out the fire that we use steroids, or plasma exchange, or whatever it takes to kind of get the fire, put it out. And then on the other parallel treatment track is the preventive treatment, and these are the drugs that we use to prevent the next attack. And so, this talk is focused on preventive treatments, and this presumes that you have a relapsing disease. Neuromyelitis optica is a common example, so is MOG antibody disease.

[00:01:52] NMO was the classic rare autoimmune disease that the SRNA adopted and helped to develop these trials. And so these three trials were all performed in neuromyelitis optica specifically, but what I want to assure people who don't have neuromyelitis optica and are watching this presentation, is that NMO is just the first, okay. We've got- we've got MOG coming up, we've got seronegative NMO to deal with, and we have other relapsing diseases that we are going to tackle. But for this talk, we're going to focus on NMO.

[00:02:33] For those of you who have NMO, you've probably been on one of these drugs. This is a table of all the different medications that we've been using before the trials even launched. This is called off-label treatment. You pull the drug off the shelf that has worked in other diseases, and you think it's going to work for NMO, and so you try it. And if you have a center with lots of patients, and you put a lot of them on the same treatment, then you can publish an observational study. We could say, "I started 10 people on..." Azathioprine is the first one on this table, mycophenolate, rituximab, whatever your center uses, and then you publish your outcomes, and you could say, you know, "I had 30 patients, and only one relapsed."

[00:03:14] And while that's not a scientifically rigorous study because it's not placebo controlled, and there's some biases inherent in an open-label study like that, this table shows you how many different studies were published in NMO before we even launched trials. And they all point to the

same general direction that suppressing the immune system in these specific ways helped to prevent the next attack. Now they were all small studies, you can see the numbers there. And what we did, what we were still able to do with these open-label studies, is try to compare to them. So before we even had these trials, I'd offer this treatment menu to my patients, and I'd say, "Well, look, if you use azathioprine, your chance of failing is about 53 percent. 50, 50 chance of it working to prevent any future relapses."

[00:04:03] Whereas with mycophenolate, if you dose it correctly and optimally, you have about a 25 percent chance of failing, 75 percent chance of- of never relapsing, which is a pretty good number for patients who have NMO and are, you know, pretty freaked out about relapsing, these are pretty good numbers. And then for rituximab, if you show up every six months and you do your treatment, there's an 83 percent chance of remission, 17 percent chance of failure. And these are pretty good numbers and we were pretty pleased with ourselves for, you know, developing these kind of treatment options, but the science was moving forward, and pharmaceutical companies were paying attention to these studies and others. And what they did is they helped devise new treatments based on these scientific strategies.

[00:04:50] On the next slide, you'll see a schematic. This is a schematic of how we think NMO happens. From the top left, you'll see T and B cells that conspire. These are the cells of the immune system that are the thinkers, and they decide when and where to attack. They communicate with each other, if you can just click the button once. Yeah, you can see that they communicate with each other through the use of chemicals, and one of them is IL-6, interleukin-6. And you can block that with a drug called satralizumab, so you disrupt their communication.

[00:05:25] Now the B cell part, those B cells will eventually become plasma blasts, and the plasma blasts are what make the aquaporin-4 antibodies. If that's your disease, aquaporin-4 NMO, they're being made by those plasma blasts, and you can deplete those cells with the use of a different drug called inebilizumab. And then, while those two cells are conspiring, producing aquaporin-4 antibodies, then you have the disruption of the blood-brain barrier and an invasion to the central nervous system. At the level of astrocyte, you can see down there's a part of the immune system called a complement system that causes the destruction. And there's a drug called eculizumab that blocks that destructive process.

[00:06:09] And for all of these drugs, these are just how we think they work, there certainly could be other mechanisms at play, in fact I think there are. And a lot of the times we'll do the trials based on the studies, but then we'll look back and we'll realize, you know what? The mechanisms weren't what we thought they were, but we still learned a lot from the studies. So these trials were all launched around 2013, 2014. On the next slide, I show you a comparison of these trials.

[00:06:37] The first one that launched is called eculizumab, it blocks that complement system I showed you, and its dosing is not the most convenient. Even the company would admit it's an every two week infusion. That's a 35-minute infusion, and the company likes to brag that it's safe enough to use in the home, but it's still an infusion every two weeks in the vein. The second drug that launched is called satralizumab, that blocked the IL-6 receptor communication between T and B cells. And that route of administration is subcutaneous. It's an injection, you presumably will keep

prefilled syringes of this drug in your refrigerator at home, and once a month you take out the syringe, and you inject yourself. And that's only done once a month, and that's pretty convenient in that regard.

[00:07:28] Then there's inebilizumab, which is very much like rituximab in its dosing to deplete those B cells, and inebilizumab also depletes plasma blasts, but they are- both rituximab and inebilizumab are only infused once every six months. So twice a year the infusion for inebilizumab takes, I think, 90 minutes, maybe a little longer beginning to end, but still it's only every six months. And so, just keeping that in mind as I show you the trial results, you have to consider all of these different factors.

[00:08:02] So first one I'm going to show you is a comparison of the trial designs. If you could just advance through to the fourth trial, which - yep, keep going, one more - and you should be able to see all of them together.

[00:08:16] Okay, the eculizumab trial is the one on top. The notable thing about the eculizumab trial is they only included aquaporin-4 patients. You had to have the antibody to even enroll in the study. Whereas the other two, satralizumab and inebilizumab, you could be seronegative. Now it turns out inebilizumab didn't enroll enough seronegatives to really know if it worked, and satralizumab did, so these trials are a little bit different in that regard.

[00:08:42] Second is which trials allowed patients to use background therapy? So if you were on CellCept, and you didn't want to come off because you were afraid about being in a placebo arm, well, you could enroll in the eculizumab trial. They allowed a background arm. But you could not enroll in the inebilizumab trial, that was pure placebo. And satralizumab, it depended on where you were. In the US, you could not remain on your background therapy. If you were outside the US, you could. And so those were a couple of the differences among these different trials when you consider- when you look at the results.

[00:09:17] So, let's go to the first result. And this is a comparison of the patients that ended up enrolled in all of these trials. So, on the top line is the number that were aquaporin-4 positive. If you click once, you'll see a red box that comes up. And as I mentioned, in eculizumab, 100 percent were aquaporin-4 seropositive. In satralizumab, you can see that they targeted for about one-third to be seronegative, and they pretty much hit that maybe even a little more in some cases there. And then in inebilizumab, I think they were shooting for something like 30 cases or so, they only got about 17, so inebilizumab is still mostly aquaporin-4 seropositive.

[00:10:10] Then the other things, female, age, age at onset, and baseline disability levels, they're all about the same, so this is basically the same patient population that enrolled in these studies, except for the baseline annualized relapse rate. If you click one more time, a red box will come up around baseline ARR, annualized relapse rate. These are the number of attacks that you had to have in the past year or two to get into the study. And the eculizumab folks, they wanted the worst of the worst, so they had a higher baseline annualized relapse rate, most patients had at least two attacks in the past year. Whereas the others were somewhere between one and two. But for the most part,

whether you had one attack or two attacks in the past year, these were fairly similar patient populations when you consider the efficacy and safety of these drugs.

[00:11:02] Okay, the first efficacy data I'm going to show you is for eculizumab. This is the complement drug that's every two weeks. And these are called Kaplan–Meier curves, and I just want to take you through one Kaplan–Meier curve so you can understand how to read it. That top line there is the treatment arm, and then the one that's kind of sliding down, the light blue, is the placebo arm. And what happens every time the curve goes down is a patient is relapsing. So at the end of 48 weeks, you can see on the X-axis, that's time, at 48 weeks, 63 percent of the placebo arm was still in remission, meaning that 37 percent have relapsed. This is fairly expected for patients who are on background therapies, like CellCept or azathioprine.

[00:11:51] The population that was on the treatment arm with eculizumab, 98 percent remained in remission after one year. And in fact, when you compare the entire treatment arm over the course of the two, three years there to placebo, the reduction in risk of relapse with eculizumab was 94 percent. So that's one of the numbers you should remember when you compare these different treatments is reduction in risk of relapse. What are the chances... How much is this drug reducing your risk of relapse? With eculizumab, the magic number is 94 percent.

[00:12:26] On the next slide is the trial results for satralizumab, and I break this down into two groups. One on the right is the aquaporin-4 seropositive. You'll recall only about two-thirds were seropositive, about one-third was seronegative. The seronegatives, they didn't do so well, and so it's not completely fair to compare to eculizumab if you include all the seronegatives. So we took the seronegatives out after the fact. We're not trying to manipulate data, we just want to compare apples to apples, or closer than, you know, than we can. And if you look at that satralizumab data, you can see there that about the same number of patients on the placebo arm relapsed in a year. So that's fairly constant. And the number who relapsed in the satralizumab arm was three, but they had smaller numbers, so there only about 92 percent remained in remission. And if you look over the whole course of the study, the reduction in risk of relapse is 79 percent. Okay, so 79 percent is their reduction in risk of relapse.

[00:13:29] Now, if you recall, there were two different studies for satralizumab. In the US, they had pure placebo, and then around the world, they had an add-on study where you could be on background therapy, and so these were analyzed separately. And on the left side is the study around the world where you could be on background therapy, and so you could see there that the curves don't look so good when you include seronegatives, and that's because seronegatives just did not respond as well. In fact, those curves for the... I don't have it here, but the curves for the seronegatives completely overlapped the placebo. It's like they had no effect whatsoever. And we don't know if they're MOG antibody positive or double seronegative, that has not been released yet.

[00:14:10] On the next slide is the satralizumab data from the US study only. And again, this included seronegatives, you can see it really dragged the curve down. But for seropositive patients, again, the number is 74 to 79 percent, depending on which study you look at, fairly constant.

[00:14:30] And the third and final study - if you can advance - is inebilizumab. And inebilizumab, the reason the curves look a little different here is because this was a six-month study, not a two-year study. And over the course of six months here, you could see about 42 percent in the placebo arm relapsed, and none of these patients were on background therapy. That's why the relapse rate is a little higher than the other trials, but still fairly similar.

[00:14:57] And in the inebilizumab arm, in the light blue on top, you can see 87 percent remained in remission. And the reduction in risk of relapse here for seropositive patients was 77 percent. And so, you could... if you remember, eculizumab 94 percent, satralizumab was 74 to 79 percent, and inebilizumab 77 percent. So, when you think about efficacy, those are the numbers you're going to compare.

[00:15:26] Okay, if you could advance to the next slide, we're going to... Efficacy isn't everything, there's also safety and tolerability. So what are the safety numbers? Well, it turns out all three drugs were fairly safe. There are two boxes I want to point out, if you can click the button twice. One is just the total number of adverse events, and the next is deaths.

[00:15:50] For total adverse events, they're fairly similar, okay? So patients would have equal numbers of infusion reactions, or headaches, or things like that as placebo. And so, it wasn't a major deal. With eculizumab, there are headaches and there are upper-respiratory infections that were more common than placebo. With satralizumab, they had injection site reactions that were a little bit more common than placebo in one of the trials. And within inebilizumab, I believe headaches was the only issue, and then there were concerns of course with rituximab that we're aware of that are long term that we didn't see yet within inebilizumab, but again, it was a six-month study.

[00:16:32] And the numbers of deaths were very small in all the trials. Eculizumab had one death, not related to the drug in any of these studies. They were all just related to the underlying disease. So all safe and tolerable for the most part.

[00:16:48] If you could advance to the next slide. A lot of this is going to be decided by logistics. Okay, so people are going to have to consider do you want an IV treatment, do you want a subcutaneous treatment? Which one is your insurance going to pay for? These are all expensive drugs. Can you handle an every two week infusion or do, you know, is an every six month infusion more like your lifestyle, or what about an injection? So and then you have to balance this against the efficacy numbers.

[00:17:16] If efficacy is your primary priority, then you might want to go with eculizumab at all costs, no matter what. And if you have to balance everything, then you might consider, you know, with routes of administration, and the cost, and so on. So these are all the preventative therapies that have been developed and there are, again, as I said, in MOG and in other diseases, more to come. So don't worry if you don't have the aquaporin-4 antibody, I will be giving a talk like this for your disease certainly coming up in the future.

[00:17:51] Before I move on to the next speaker, I see a question from my colleague who I'm going to present in a moment, Dr. Pardo, he asked if I could briefly discuss whether age has an impact on the safety and tolerability of these three drugs, especially in the elderly population. And I would say

that there weren't a lot of patients enrolled who were elderly, so there were age cut-offs for the studies, and so we don't know. For the most part, these drugs appeared safe, there were no safety signals that we're aware of, especially with things like comorbidities, like diabetes and hypertension that older folks have. So, don't have a sense that that's going to be an issue, but we still have to see if that is true.

[00:18:43] I see another question here about IVIG. For aquaporin-4, it's something that has not really been effective, or published on very often. For the most part, when we don't see a lot of studies on something, it suggests to us that it wasn't worth pursuing because in the few cases where it's been done has not been effective. And so, IVIG for aquaporin-4, we don't see a lot of aquaporin-4. For MOG, we see a lot of, and that's something I use a lot as well for that ADEM/MOG spectrum, IVIG tends to be very, very helpful.

[00:19:19] And then I see a question about how long specifically until there are treatments for MOG? I have access to confidential information, and I can't say yet, but soon, I believe very, very soon.

[00:19:37] And... Okay, and so, now, I'd like to take this opportunity to introduce the next speaker, he is not just a friend and a colleague, but a person I consider to be my mentor. And his name is Carlos Pardo. And if you had been part of SRNA or the Transverse Myelitis Association at any time since its founding, you will have heard his talks. He is a full Professor at Johns Hopkins University, and original founder of the Transverse Myelitis Center. And not only one of the greatest minds in transverse myelitis, but in everything around transverse myelitis, including vascular myelopathy, and acute flaccid myelitis, and Zika... anything myelitis. This is the one and only Dr. Pardo.