In-Person Breakout Session II

MOGAD and ADEM

You can view this presentation at: youtu.be/xOmLucFA5vg

[00:00:05] **Dr. Teri Schreiner:** Welcome, everyone. Please come in. Take a seat. Welcome. We're gonna get started. I will begin with my own introduction and those of my co-panelists. And then, since we have time together, I'd like to hear more from each of you about how you are connected, if you are connected, to MOGAD and ADEM. And then, we'll go through a presentation where we touch on some of the high-level aspects of both diseases.

[00:00:43] And fortunately, we have time, so we can entertain questions. We have an opportunity to talk more after the presentation as well. So, with that rough outline, I am Teri Schreiner. I am a pediatric neuroimmunologist in Colorado, and ADEM and MOGAD are diagnoses that I am familiar with, and I have many patients with both diagnoses, as well as some of the others that we've already heard about today and are in the other breakout sessions as well. So, first, let me turn to my co-panelists and ask them to introduce themselves.

[00:01:26] **Dr. Michael Levy:** I'm Michael Levy. I am an adult neurologist, but I see kids in my clinic too. I've been taking care of patients with NMO since probably about 2006. We added ADEM, I don't know, 2011, and MOG in 2017, whatever; but always had this big-tent approach, especially with seronegative NMO as well. And thanks.

[00:01:49] **Dr. Grace Gombolay:** Hi, I'm Grace Gombolay. I'm a pediatric neuroimmunologist. I'm based out of Emory, down in Atlanta, Georgia. And I also see patients with these rare neuroinflammatory disorders including MOG, ADEM, like we're gonna talk about today, NMO. -- Can you not hear me? Okay. That's not good. -- And just happy to be here to talk more with you guys.

[00:02:15] **Dr. Teri Schreiner:** I will proceed next with the slightly more formal part of the presentation, which is talking about acute disseminated encephalomyelitis. I did put up our disclosures. This is commonly done just to put everybody on the same page, and know that we do participate in different areas and receive funding from different sponsors. Hopefully, this will not color any of the information you receive today, and I did not have Dr. Levy. So, you can specify any or say you are unconflicted, and that would be great too.

[00:02:52] **Dr. Michael Levy:** I have lots of conflicts, but they're equally distributed.

[00:02:57] **Dr. Teri Schreiner:** Okay. All right. Wonderful. Okay. So, first, let's talk about, again, acute disseminated encephalomyelitis. We'll go through this briefly, but this will sort of set the stage then for a subsequent discussion about MOGAD, which is our newer, though not brand new, understanding of some of the cases of ADEM.

[00:03:27] So, ADEM is a diagnosis that, in my training 10 to 15 years ago, was very common. We saw patients in the hospital who were usually school age, not always but usually in elementary school, were presenting with sometimes confusion, sometimes coma, but certainly a state of being off of their baseline, and then with multifocal other neurologic deficits.

[00:03:59] And this phenotype, this description of the patient, became very familiar. And we would say, "Okay, we understand. This is ADEM." There are diagnostic criteria, and you see some of them here. Encephalopathy is the word that we use to describe being off of your baseline -- you're not thinking like yourself, you're not acting like yourself. And in order to meet this diagnosis of ADEM, there can be no fever, because fever itself can contribute to that.

[00:04:33] What we would see in these patients in the hospital, I will show you an example of in a moment. But a brain MRI that showed areas of inflammation that were oftentimes bilateral, so on both sides, but not symmetric; distributed in different areas and without a clear edge, a clear border. Here's an example that you see in the top right-hand of the screen. Even if you're unfamiliar looking at MRIs, I think you can look and say, "Oh, there's some white splotchy areas on both sides." Those are the typical lesions, the markers of inflammation, that we're seeing with this disorder of ADEM.

[00:05:22] Now about three-quarters of patients, before they present with this, will have a viral illness, and it oftentimes is unremarkable, and it is among the many, many, many viral infections that kids will have. But this is an atypical sequelae or uncommon sequelae of that. In addition to the confusion, kids may have headache, they may subsequently develop fever, they may have a stiff neck. Some, I think about a third, may have seizures as well.

[00:06:01] Now, typically, ADEM is monophasic, meaning it happens just once. But it isn't quite that clear, as anything that happens within three months of presentation is still technically considered one event, even though it very well does not feel like just one event when there are fluctuations over a three-month time frame. And then, this entity called multiphasic disseminated encephalomyelitis, it was coined to describe episodes of ADEM, this typical presentation of confusion with brain inflammation, that were separated by three months.

[00:06:50] Okay. Here's some more images just to show these diffuse, white matter lesions, again, on both sides of the brain but not symmetric. Each area here that you see in the white, that sort of bright areas, is inflammation of the parenchyma. Now -- yes, ma'am?

[00:07:15] **Audience Member 1:** Is there any way to remyelinate the white matter brain loss?

[00:07:20] **Dr. Teri Schreiner:** Mm-hmm. So, the question is, is there any way to remyelinate? And I think this ties nicely to your question earlier, which is: What about recovery? And the answer is: yes. Your body has intrinsic reparative capabilities. But a more precise answer to your question about recovery depends a lot on what initiated the attack.

[00:0] So, MOGAD, which we'll get to in one minute, is an antibody-mediated disorder where we think we know what the antibody does to create the damage. ADEM is a little bit different in that there may be more than one thing contributing to this picture -- this clinical description of a child, usually a child, who has this type

of inflammatory brain response. And understanding things on this cellular level helps us to say, “This is the damage that has happened, and this is what we can forecast for recovery.”

[00:08:35] **Audience Member 1:** I had insomnia for four months before I had my brain loss.

[00:08:39] **Dr. Teri Schreiner:** Oh, gosh! Insomnia for four months! Oh, that sounds awful.

[00:08:43] **Audience Member 1:** It was awful.

[00:08:44] **Dr. Teri Schreiner:** Yeah. Okay. Let me pause on further delving into that question. But I know that is a hot topic, recovery in general. So, I promise we won't be done with that answer. So, the differential diagnosis, the things that can be confused for ADEM, is long. And the top three diagnoses you see there -- ADEM (we're talking about now), MS (multiple sclerosis), and NMOSD are all labels that can be given to a disorder that can be caused by the MOG antibody.

[00:09:32] The other diagnoses that you see there have different pathophysiologies. They come about in a different way, but they can present very similar to ADEM. They can't present as ADEM. And so, again, sussing out what actually is causing the clinical picture of ADEM helps us to know how to treat it, whether to expect relapses, and what the recovery can be in broad brushstrokes down the line.

[00:10:07] Now there are medicines that are used acutely, and we heard about some of them this morning. The first one is steroids. Methylprednisolone, also called Solu-Medrol, is sort of a hallmark of treating any brain inflammation, and it is not a gentle or a very specific treatment. I liken it to the mallet approach. You know, you're taking a big mallet. You're pounding down the inflammation.

[00:10:40] It's not specific to one part of the inflammatory cascade. It's a very blunt instrument. But it's also very effective at just really calming inflammation quickly. That's typically used. IVIG, intravenous immunoglobulin, can be used. And then, we heard also about plasmapheresis or plasma exchange as a means of taking the plasma out, cleansing it of those proinflammatory signals, and then allowing the body to recover. So, with that, I think I'll transfer it over to Dr. Gombolay, who can take us now into MOGAD, unless there are any other questions right now.

[00:11:31] **Audience Member 2:** Is there an increased risk for MS that you've had ADEM later on in life?

[00:11:36] **Dr. Teri Schreiner:** So, the question is: Is there an increased risk of MS? And I think we could say ‘no,’ unless that first presentation of ADEM was actually MS. But then, we get into kind of a tricky business of looking at the different biomarkers and how did the diagnosis come about. And then, we also have the benefit of time that helps us to know whether or not something is relapsing. But, in and of itself, it is a different entity than MS.

[00:12:15] **Dr. Grace Gombolay:** All right. So, I'm gonna take over and talk about myelin oligodendrocyte glycoprotein associated disease, or MOGAD is what it's called for short. First, let's step back and ask: What is MOG? What is this protein that we're talking about? And so, this is actually a picture of a nerve cell. This blue circle here is the cell body, and then this yellow area is called the myelin sheath.

[00:12:41] And so, what happens is: I think about it where your nerves in your body are just a whole bunch of highways, in terms of electrical signaling, that connects to each other. And the myelin is that covering to sort of help the transmission of those signalings better. It's like the covering of these wires that's insulating and trying to do that.

[00:13:02] The MOG protein is a very, very small portion of the myelin. Because it's on the surface, what we think is that it's more exposed and more amenable for the immune system to come in and sort of try to attack it, and so that's where this comes from. So, despite it being a very, very small portion of the proteins, because it's exposed, that's where we think it comes from.

[00:13:21] And one of the things that came up recently, that was really important to know, is that there is this group of people at the International MOGAD Consensus Criteria. And it's pretty small on this on purpose. But what I would recommend is that, if you're not sure if you fit this diagnosis of MOGAD, I'm not gonna talk too much about this, but happy to if there's questions about it, because everything that we put together in terms of a diagnosis is not based on a single test. I mean, maybe Aquaporin-4 is gonna be one exception to that.

[00:13:46] But generally, when a patient comes in, they have symptoms, you have different MRI or imaging features, and then you look at the MOG testing, and you sort of say, "Okay. How does everything fit together? Do you fit more like an ADEM picture? Do you fit more of an MS-type picture? Do you fit more of a MOGAD picture?" And so, there's a lot of different nuances to it. But one of the things that the MOGAD Consensus Criteria talks about is the clear core clinical events features. That's how MOGAD can present.

[00:14:14] And the other thing to know is that the antibody testing for MOGAD -- most people do end up sending it to the Mayo Clinic, which is a cell-based assay, and the titer levels help us in terms of the diagnosis. It doesn't help us in terms of predicting treatment response or whether or not you're gonna relapse, which I know makes zero sense, right? You think if you have a super-high antibody, that means you're gonna be have more severe disease or more likely relapse, but that's not the case.

[00:14:38] But what people have found is that you can have neurological symptoms, you can have brain symptoms that are involved, but you have a very, very low positive titer, so that may or may not be MOGAD. And this definition actually keeps evolving as we learn more about what MOGAD is and what MOGAD isn't. So, what are the different types that people can have when they have MOGAD? It is a type of demyelinating disease. So, going without that myelin, that covering around the nerve sheath, is that it's affecting the myelin.

[00:15:08] So, you can have things like optic neuritis, where you have inflammation in your optic nerves. We heard some stories about it this morning where you have vision changes and pain with eye movements. Usually, what happens is color vision will go first before you actually get changes in blurry vision, but people don't realize it until it's worse, as the disease progresses.

[00:15:29] It can look like NMOSD or neuromyelitis optica spectrum disorder. And so, it's sort of interesting how the field has evolved from the Aquaporin-4 story to now to MOGAD. And now, we have the double seronegative that we still have to figure out what that biomarker is. Acute encephalomyelitis, meaning you have brain involvement and spinal cord involvement.

[00:15:49] And multiple sclerosis-like phenotype. Again, when you have a lot of people who look at just a few MRIs here and there, they look at it and they're like, "Oh, this is clearly MS." But for people who have seen a lot of images for patients with MOGAD and other related disorders, we start to learn this pattern, and it's like, "Oh, I understand how this could meet the criteria for MS in terms of their diagnostic criteria." But when you look at it, you're like, "This does not look like MS whatsoever."

[00:16:15] And then, transverse myelitis, which is gonna be an interesting term as we start redefining these diseases where you have the spinal cord that's involved. And one of the things to mention is that, oftentimes in MOGAD -- this is also in Aquaporin-4 NMOSD -- in the terms of the spinal cord, you have the center part that's

more involved, which is what we call the gray matter or the cell bodies that are involved. And it sometimes can mimic acute flaccid myelitis or AFM.

[00:16:42] I know we have a different session that's on AFM going on concurrently. But sometimes and the treatment for this is really critical, or knowing what it is, because I've definitely seen cases where someone says, "Oh, this was AFM," so they just stopped there. They didn't test for MOG. They didn't test for Aquaporin-4. And then they're like, "Oh, they had recurrent AFM," which is not a thing. And so, just to be aware of that, there's lots of overlap in a lot of these diseases as we're trying to learn all of this.

[00:17:07] And then, you can also have what's called a meningoencephalitis, meaning that it looks like a brain infection of sorts, where people are always confused. They can have really high fevers, they can have neck stiffness, sort of looks like an infection inside their brain, but it turns out it's related to MOG.

[00:17:25] One of the features that can be helpful -- this is not perfect, you know, each person is different, they don't read the textbook -- but if you look at the different areas of the brain and the optic nerves that are involved, you can start to get a sense of, "Oh, is this more likely MOGAD? Is it more likely MS? Or is it more likely Aquaporin-4?" So, we're gonna look at this, and this is looking at starting in the top left corner here. So, this column here is the NMO Aquaporin-4 picture, the middle column is gonna be the MOG or the MOGAD picture, and on the right is gonna be their MS column.

[00:17:55] So, when you first look at the optic nerve, here we're looking at the eyeballs, or here up in the top, and the red areas are the areas that are affected. In Aquaporin-4, usually that's closer to the back part of the optic nerve plus what we call the chiasm -- what happens with your optic nerves as they come together, and they cross, and they make this X. And so, that area is usually more affected in Aquaporin-4, and it's usually bilateral, meaning both sides are affected.

[00:18:24] This is in contrast to MOGAD, where usually it's just the front part of the optic nerves that are more likely involved. It can be unilateral, or one side, or it can be both sides affected. And then, MS usually affects it one at a time; it doesn't usually come at the same time. And now, when you look at the spinal cord, you can have different areas.

[00:18:40] So, in NMO, you could usually affect the upper part of the spinal cord. You can have that central involvement, like I mentioned earlier, that looks like something like AFM or acute flaccid myelitis. You can have other areas involved, more of the outer areas of the spine. And the same thing with MOG.

[00:19:00] So, you can sort of see here on the spinal cord image that, even though they can have central gray involvement, you can also have the outer parts involved. But they, in MOG, generally, it's the more lower parts of the spine, whereas MS, it's smaller lesions or shorter areas of the involved, and they're more spotty, meaning it's not all together; it's usually different areas.

[00:19:22] And then, in the brain, basically, there's different areas that can be also involved. So, for example, here in the MS picture in the bottom right, you're going to have these small areas, these smaller lesions that can happen, whereas the Aquaporin-4 and the MOG can be different. So, here, we talk a little bit more about the different imaging features. For example, what we call long segment transverse myelitis, meaning you have inflammation of the spine, more than three levels are involved.

[00:19:53] Sort of what patients will experience when they have this is gonna be things like weakness, numbness. They can have urinary retention, where they can't pee -- I think one of the panelists talked about

that earlier this morning -- or constipation, where they have trouble with pooping. Again, the MRI shows more than three segments, and that's altogether contiguous, meaning all connected together. And then, in MOGAD, you have more of that lower part of the spine involved.

[00:20:20] You can have brainstem involvement with this. And so, it can mimic things like some people will think about -- a cancer or a tumor can look like this. And so, what we're looking at here is: here we're looking at the front, this is the back of the head, here are the eyeballs right here. -- Oh, good. My cursor's come showing up.

[00:20:37] And then, what we're seeing here is this increased area of white spots right here in the pons, and this is the area of inflammation. And when you have that brainstem involvement, you can have different things where your cranial nerves, which are these special nerves that come out of the brain, that do different things. You can have ataxia where -- it's not like you can't walk -- you just have really difficulty with your balance with walking.

[00:20:59] You can also have what's called cortical encephalitis, something that looks like inflammation or an infection, but it turns out it's actually related to MOGAD. And people come in with fever, headaches, encephalopathy, seizures. Sometimes, they can get really, really severe brain swelling to the point where parts of their brain, unfortunately, can get squished. So, they can be very severe at times.

[00:21:22] One thing to know, which I think is interesting, is: What happens when you have repeat MRIs? Because usually when we have a patient who comes with an MRI, you have something abnormal, you'll repeat it again six months later just to see what's going on. And in the MS world, if you have anything new in terms of new brain lesions and things, you start worrying about ongoing disease activity. There's ongoing inflammation, your treatment's not working, all of those things.

[00:21:47] MOGAD seems to be slightly different. This has been shown in a couple of different large cohorts now, where in that first few months, right after the initial attack, it's very dynamic. The MRI, the inflammation is actually quite dynamic. And so, to have new lesions was not uncommon, actually in about 14% of MOGAD patients, but didn't necessarily mean that you were going to have a clinical relapse. So, just because you have new lesions on your MRI in MOGAD doesn't necessarily mean you're having a second attack, which is very different from, example, like the MS world.

[00:22:22] And the other thing I think is interesting, which a lot of you, I think, have already experienced in your own personal lives, is that the first episode versus the second episode can look very differently. Like I mentioned earlier, MOGAD can present in a whole bunch of different ways, but the second event doesn't necessarily mean it's gonna look like the first attack.

[00:22:40] So, this was a study from actually, the US network of pediatric MS centers, where they looked at what was the first attack in MOGAD and what did the second attack look like. For example, in this top column, a lot of patients looked like ADEM, but they actually had MOGAD, versus optic neuritis transverse myelitis, versus like an NMOSD-looking-like picture, versus other vague demyelination or encephalitis where it didn't quite fit in any of those categories, but they had that.

[00:23:08] And so, a good proportion of patients who had ADEM, optic neuritis, transverse myelitis, NMOSD, and/or the other things, good proportion of them were monophasic. Because I think there was a question in the room already, “What's the relapse risk?” And right now, we think it's still about 50-50.

[00:23:24] Unfortunately, we don't have any good biomarkers of predicting who is gonna relapse versus not, but there's a lot of interesting research and work looking at how to predict relapse and all of those things.

That's a very important thing. The second attack may be something else. Like Dr. Schreiner had talked about earlier multiphasic ADEM, or MDEM as it is called, optic neuritis, optic neuritis or NMOSD or transverse myelitis.

[00:23:52] So, it's interesting to think about: Why did the first attack happen? Why does the second attack look different? And also, who has a second attack and who doesn't? So, one of the things to know is that -- and this is important for people to know and this is one of the things that we just sort of make sure that doctors and physicians and clinicians are aware of -- is that when you're sending testing for the MOG and Aquaporin-4 antibodies, make sure that you're sending it from the blood or the serum because it's more sensitive in the serum than CSF.

[00:24:21] There's a few places that will do CSF-specific MOG testing. The Mayo currently is not offering it on a commercial basis, but CSF Aquaporin-4 can be sent on the commercial basis. And I've definitely seen patients who send the CSF Aquaporin-4. They say, "It's negative," and they say, "We are done," but you really need to send serum testing.

[00:24:43] And the other thing to note is that it can be positive up to many years after the initial attacks. For people who are having multiple attacks, I make sure I resend it at different things. And this is in contrast to other antibody things that can affect the brain and the central nervous system, where few exceptions are in this too. But for the most part, the CSF test is a better test than the, cerebral spinal fluid test or the spinal tap. It's a better test than from the blood, but MOG and Aquaporin-4 are gonna be those exceptions to that.

[00:25:14] And then, going back to the CSF MOG question. So, this is some newer information, and there's ongoing work looking at: What's the role of CSF MOG? Does it help? Is it helpful? How does it help in terms of what patients look like, how they present, their relapse risk, all of those things? But, generally, the patients who had CSF MOG antibodies, they all had brain involvement and didn't necessarily have other areas involved.

[00:25:41] There's one MS patient who actually had positive CSF MOG antibodies. So, it goes back to that single test comment that I made earlier. It's not a single test that's gonna help you with your diagnosis. You have to take the whole picture in hand. This was a very, very small number, so it's really hard to say. And so, this group was suggesting, "Does the CSF MOG antibody testing predict disability, project recovery or poor recovery, or increased relapse risk? But again, this was a very small number, so there's a lot more work that needs to be done before we can do that.

[00:26:11] Recovery from attacks in MOGAD can be various different ways. And so, there's a lot of different things in terms of not only the type of attack that you've had, but the age also plays a role into that, because there's some discussion about what can help in terms of predicting recovery. So, in this left graph here is: we're looking at recovery from the distinct onset attack types. The full recovery is here in the whites, good is in this gray, moderate is this dark-pinkish here, and poor is in this super-dark red, which is at the top.

[00:26:45] And generally, patients who have a single eye, you know, single optic neuritis, or if they had an ADEM, they generally recovered a bit better than those who had, for example, both eyes involved, or especially, if they had spinal cord involvement, they were less likely to recover from it. And then, the other thing is that when you're younger, you're more likely to recover than you are from older. And there's a lot of questions of why that is. Is it the repair mechanism? Is that better? As we're getting older, some of those cells don't work as well. Is that what it is?

[00:27:18] The other thing is that, especially in ADEM, even though we're calling all of this as demyelination, meaning you have myelin that form, you have inflammation that attacks it, and then you're affecting the myelin. Why is recovery better in, for example, ADEM or MOGAD compared to MS and Aquaporin-4?

[00:27:37] And there's a lot of questions about that. What's actually happening in your brain and the body? Are you actually losing myelin? Because in the MS world, especially, you can see it where you have loss of myelin and that is what, you know, the cells are actually eating it up. Whereas in ADEM, for example, are we just seeing inflammation with extra fluid involved, but as the fluid goes away, that's why you're not actually having true, true injury. And so, there's a lot of discussion around that, too.

[00:28:03] **Audience Member 3:** What causes the severity of the relapse? My relapses are progressively severe. My left eye, completely blind. My right eye, completely blind. My brain is being affected.

[00:28:13] **Dr. Grace Gombolay:** Yes. Yes. So, that's a very, very good question. I invite my panelists if they have any other comments for that, but we don't have a way to predict right now who's gonna have a very severe relapse -- kind of what we were talking about -- or how they're recovering from it. There's a lot of people who are looking into that, though. Other questions? Okay. Yes.

[00:28:42] **Audience Member 4:** We're in the middle of flu season right now. People taking the COVID shots and that sort of thing. Can the vaccines, particularly in our age, can the vaccines affect MOGAD?

[00:28:55] **Dr. Grace Gombolay:** Yeah. So, right now, we do recommend, depending on what treatments and stuff you're on, definitely getting all your recommended vaccines is important. There's not really that I know of -- I mean, let me step back. So, we know that there can be potentially vaccines that can trigger inflammation in the body and that can cause symptoms. But generally, all of those things are what we call associations, meaning the timing of something happens, and then you happen to have something else right around that time. And so, they're associated together, but we can't really prove whether or not it caused it, if that makes sense.

[00:29:32] **Audience Member 5:** And what about recommend taking the COVID vaccine and the flu vaccine at the same time? So, I'll start (inaudible)

[00:29:40] **Dr. Grace Gombolay:** So, there are definitely some patients who feel like they have more symptoms coming on when they have multiple vaccines. So, if it's one of those things that you will feel more comfortable phasing out, I think that's reasonable. The other thing, which I didn't talk about yet, but there's something called pseudo relapses too or false relapses, where if you've had an attack in the past of anything, even if you're repaired pretty well and you don't have any symptoms, if you get sick, if you have a fever, if you're more tired that day, those old symptoms can come back. They should go away. And they look and they feel like a new attack. They look like a new attack. But they'll go away after the fever and infection goes away. I saw another question. Yes. Hi.

[00:30:20] **Audience Member 6:** So, from my experience of (inaudible) and seeing patients, it seems to me there are a lot of adults who get ADEM who don't have recover as well versus kids who generally have neuroplasticity is that your experience with respect to last chart that you showed the data, people in adulthood recovers better or is that (inaudible)?

[00:30:49] **Dr. Grace Gombolay:** So, as a pediatric neurologist who doesn't see too many adults, I can't make that comparative thing. But I'm curious, Dr. Levy, if that's generally what you see. Do the adults with ADEM recover not as well as the kids with ADEM?

[00:31:01] **Dr. Michael Levy:** Yeah. That's been my experience too. Adults with ADEM have it much worse than kids with ADEM. But in either case, it takes years to get back to where they were. But kids, yeah, generally recover better. And I think a lot of kids at a younger age, when they get symptoms, they could have, if their

ADEM is at 7, then even when they're in high school, they're gonna have attention deficit, lots of these other symptoms as well that's attributable to the ADEM damage they had as a child.

[00:31:32] **Dr. Grace Gombolay:** I saw another hand. Oh, yeah. Go ahead.

[00:31:34] **Audience Member 7:** This might be a question that maybe you're not ready to answer, but with only a certain amount of data over time for MOGAD, is there a notion that patients who are on pretty good treatment, maybe not a 100% successful treatment, could have what they think might be pseudo-relapses that may actually be really low-level relapses. And over time, that there may be a progressive nature to the damage that occurs -- maybe over 10 years -- or maybe their eyesight gets much worse over that time from those low pseudo-level relapses. Has anyone been looking into that kind of thing?

[00:32:18] **Dr. Grace Gombolay:** Yeah, that's a really good question. There are people looking into that, including there's something called, 'steroids in the pocket,' meaning that -- we're, yeah, we're being able to efficiently look at -- Yes. Yes. Exactly. Dr. Chen, that's his point -- where physicians will give patients a steroids prescription. So, as soon as they feel anything, it may or may not be a pseudo-relapse, they'll go ahead and give the steroids right away to hopefully prevent that.

[00:32:46] And it's one of those things where there is ongoing studies looking at ongoing involvement. I think the optic nerve is a beautiful example of that because we have special ultrasounds at the back of the eye called optical coherence topographies, where you can actually start tracking different levels of different areas of the back of the eye of what's being involved. And monitoring: Are those layers getting thinner? Or is there ongoing injury or damage that we're seeing that we may not get to detect clinically or on an MRI, we can see in other ways. So --

[00:33:19] **Audience Member 7:** But just one comment on that is that if your RNFL has bottomed out, like mine is bit low than it should be, and it's not going to change with the relapse very much or at all, how does that OCT lend to that, or do they have to completely rely on field vision tests and things like that?

[00:33:40] **Dr. Grace Gombolay:** Yeah. I think that's where we have to put everything together what the patient's reporting, because our tests are just as good as they can be, right, including the OCTs, like you mentioned. They do bottom out, meaning that there's a certain level at which it's really hard to detect any change. That's why you have to take everything together: the physician's exam, and then all the testing that we have. Unfortunately, our MRIs are not perfect either, and if you can't get contrast, it makes it even harder to know what's happening. So, yeah. I'm so sorry. I think your question, and then I'll take you. Yeah.

[00:34:15] **Audience Member 8:** It's really a comment. In our case, the understanding that it was MOG was delayed a little bit, the comment that we got at the time was it was a young person's disease, it was supposed to get after somebody who was 70. So, it didn't kind of slow down. They kept trying to put us in the MS bucket and finally realized, no, it's actually MOG. And they (inaudible) slowed down.

[00:34:46] **Dr. Grace Gombolay:** Oh, that's kind of unfortunate. I took this slide out. I should have put it back in. But there's a really nice age distribution graph in terms of MOGAD, and there's clearly patients who are older. They fit more the NMOSD-ish phenotype whereas the younger patients fit the ADEM, but it shows that older patients are…

[00:35:04] **Audience Member 8:** (inaudible) listening and talking to each other. (inaudible) just MOGAD.

[00:35:10] **Dr. Grace Gombolay:** Yeah. What's the oldest patient you diagnosed with MOGAD, Dr. Levy?

[00:35:15] **Dr. Michael Levy:** Oldest is 75 so far. 75, wow. But Aquaporin-4 NMO, 91 years old, in the hospital.

[00:35:27] **Dr. Grace Gombolay:** Wow.

[00:35:28] **Dr. Michael Levy:** Not the same.

[00:35:30] **Dr. Grace Gombolay:** No. And then, sorry. Your question. Yeah.

[00:35:33] **Audience Member 9:** I am just gonna make a comment really quick that, when you were talking about, in terms of the pseudo-relapse possible progression, one of the things that I've heard recently from another doctor was of the importance of looking at both, again, the imaging in the beginning and the imaging itself and that's why it's so important that we do have a biomarker now.

[00:35:55] And so, we can look at titers that can help determine whether or not this is a potentially progressive thing versus a pseudo-relapse. And again, the 'steroids in my pocket' is very much a real thing, and I think just about any of us can attest to the efficacy of that and how important that is. But no, I was just gonna say that I think that's why there's a big reason that we need to have both the imaging and the other biomarkers, and they have to work together.

[00:36:28] **Dr. Grace Gombolay**: Mm-hmm. Yes. Exactly. That's exactly correct. Yes.

[00:36:31] **Audience Member 10:** Okay. So, I'm just kind of piggy-backing on that, with the pseudo-relapse. So, at the beginning, when everything is new, and you first have ON, but then you get TM, it's not really the same. And you don't really know what to expect. After the initial TM, I was on a lot of steroids, like 100 a day. But I kept having. So, that's where I would get confused. Is this a pseudo issue, or is this new?

[00:37:02] Because I would get a new symptom, or was it being masked because I was taking preventative treatment? I was taking plasma exchange, but I was still getting new symptoms. So, I think that part, for me, the disease was new, but then I felt I didn't know what was legitimate, a new something. Was I having an attack or was it a pseudo? So, that would be my question. What about the people that are -- all the treatment is new and you're on a steroid daily. How do you determine and what would be your plan of action for people like that?

[00:37:41] **Dr. Grace Gombolay:** Yeah. You're looking at Dr. Levy. So, I'm gonna let Dr. Levy answer that question.

[00:37:49] **Dr. Michael Levy:** Well, I'll tell you. I absolutely hate prednisone.

[00:37:51] **Audience Member 10:** I do, too.

[00:37:53] **Dr. Michael Levy:** I have, like, 160 MOG patients, and a few of them are on prednisone and all the phone calls come from them.

[00:37:59] **Audience Member 10:** Okay.

[00:38:00] **Dr. Michael Levy:** They're having symptoms that fluctuate. I try to get them off of prednisone as quickly as possible. I hate the steroids-in-a-pocket idea because you take a bunch of steroids, you feel great for two days, and then you come off, and you call me again. And it's always up and down and up and down. I'd much rather people go on a preventive medication, if that's what they're using, on a stable dose, and then just keep it. Stay off of prednisone as much as possible. That's been my --

[00:38:27] **Audience Member 10:** I am, since February, so that's been a . It took a long time. I have a question about that. Okay. So, for those of us where the only treatment that we were given with (inaudible) steroid dependent, how do you address that? And again, because now I've got secondary immunoinsufficiency. And also, how much do you think -- I don't look like somebody that's on steroids, but I still am -- so again, how much do you think that the drug delivery system impacts the long-term use of the steroids?

[00:39:07] **Dr. Michael Levy:** I would rely on some of my endocrinology colleagues to help you come off. What happens when you use steroids for a long time is that your adrenal glands don't need to make steroids anymore, the natural steroids, so they just shut down. So, when you bring people off of steroids, who've been on them for a long time, you got to wait for the adrenal glands to wake back up and make their own natural steroids. And some people, it just never turns back on.

[00:39:30] Which means, in order to maintain your own blood pressure, your own body chemistry, salts and everything, you have to give them a little bit of steroids on a regular basis from now on. I don't know what long-term strategies there are these days to get people off of steroids, but that mark usually comes after about three years of being on steroids. And so, we really, really try to get people off as soon as possible, as best as we can. And I do feel if you overlap steroids with something like IVIG or tocilizumab or something like that, you have a better chance of being able to come off of prednisone without relapsing.

[00:40:05] **Audience Member 10:** I was just wondering particularly, specifically, about the drug delivery system and how much that's been investigated. At least in terms of this space. The neuroimmunology space. It must just, like, (inaudible).

[00:40:21] **Dr. Michael Levy:** What do you mean the drug delivery system?

[00:40:22] **Audience Member 10:** In terms of IV steroids versus oral steroids.

[00:40:25] **Dr. Michael Levy:** Oh, yeah. Yeah. IV steroids don't have as many side effects.

[00:40:29] **Audience Member 10:** Yes.

[00:40:30] **Dr. Michael Levy:** But the idea is this. So, you're gonna take, like, maybe a 1,000-milligram dose at the beginning of the month, and then you don't take anything for the rest of the month. So, if you average it out, over 30 days, it's about 33 milligrams a day. You could do that or you could take 33 milligrams every day. It has the same effect, but there are many, many fewer side effects if you do intravenous. I don't know why. There are also fewer side effects if you do, instead of 20 milligrams a day, if you do 30 and then 10 the next day. And 30 the next day and then 10 the next day. There are also fewer side effects with that. So, there's still mysteries about steroid dosing that we need to explore, but I just try to avoid them as much as possible.

[00:41:13] **Dr. Grace Gombolay:** I saw a hand up in the back. So, yeah.

[00:41:15] **Audience Member 11:** Yeah. I was just gonna bring up the steroid-in-the-pocket thing and here Dr. Levy's thoughts beat me to it.

[00:41:24] **Audience Member 12:** Is it true that your body produces 5 milligrams of prednisone on its own each day?

[00:41:31] **Dr. Grace Gombolay:** That's yeah. That's approximately in an adult. Yeah. Somewhere between five and 10. Yeah. Yeah. Okay. Yes.

[00:41:43] **Audience Member 13:** Some MRIs, like with MOG and ADEM and stuff, after it's over, a year or so later, the MRIs are clear but it's not marked. So, is that normal to have?

[00:41:58] **Dr. Grace Gombolay:** Yeah. So, I've seen a wide spectrum where -- and that's in different conditions. In MOGAD and ADEM, more likely to have those lesions go away. I said more likely. It's not true across the board. Whereas MS, those lesions are more likely to persist, meaning that you'll still see them even if they're a year or two out from them. I've definitely seen the lesions or those white spots slowly go away over time, meaning that we see it and then over the next few years. And so, it goes back into that: Is there a repair of that myelin? What's going on with that? Why is the MRI not picking it up as much? Lots of, lots of questions with that.

[00:42:35] **Audience Member 13:** So, five years later?

[00:42:37] **Dr. Grace Gombolay:** I've seen it many years later, where there was a spot there and then many years later, we're not seeing it again. But in general, MOGAD and ADEM, generally, those, most if not all, the lesions go away. You can see a little bit left, like a scar. Whereas MS, you're more likely to see those lesions stay around. I think I saw more questions. Yes.

[00:42:56] **Audience Member 14:** I have a question. I was misdiagnosed with MS prior to my MOGAD diagnosis. I was just wondering there were so many people that have been diagnosed with NMOSD and then been classified as MOGAD. Is that gonna happen to us?

[00:43:11] **Dr. Grace Gombolay:** That's a good question. Well, I think there's a few things. It goes back to the philosophy of what is a diagnosis. Right? Diagnosis gives you an idea. A) you're naming something of the symptoms and everything this patient's experiencing, so you name it. Right? B), it helps you define what's the treatment specifically for it. And for many, many years, there are patients who have, now we know MOGAD, who look like the Aquaporin-4 NMOSD. They fit that NMOSD criteria.

[00:43:41] Now we're realizing those diseases actually behave a little differently from each other, right? The Aquaporin-4 versus the -- I know people hate that term -- the double-seronegative NMOSD versus the MOGAD. So, I think now we're realizing MOGAD is sort of its own entity of itself because now we know the treatments are slightly different compared to NMOSD. Obviously, there's some overlap with the treatments, including with MS, right? I think rituximab is probably a good example of that. But, generally. Go ahead. Yeah.

[00:44:12] **Audience Member 15:** We thought that some of my friends who had lost their vision because they were on MS meds and then they were diagnosed with MOG. That happened as well. I mean, we're all of a sudden thinking ?

[00:44:30] **Dr. Grace Gombolay:** Yes, what's confusing is that if you look at a lot of the older literature looking at MS versus MOG and MOGAD and all of that, there's so much overlap that people were still trying to define it, which I think is why it was very important for this International MOGAD Consensus Criteria to try to come out to really help define, "Okay, this is what MOGAD looks like." Because if you look at some of the older papers after MOG became more commercially available for testing, you'll see some patients with MS, like, 5% of MS patients can have MOG titers, but that doesn't make sense because MOGAD is a different disease from MS.

[00:45:05] And then, you'll see these other papers saying, "Oh, certain MS medications can trigger an MS flare or relapse, so you shouldn't use those. We know that's very true for the Aquaporin-4 literature, all the papers on Aquaporin-4 studies, but in MOGAD. So, that's what makes this very confusing because there are

patients who can sort of, like I said earlier, fit the criteria for MS. But when I look at it, I'm like, that's not an MS patient. That looks more like MOGAD. I saw a couple more hands. Okay. Go ahead.

[00:45:38] **Audience Member 16:** Yeah. I was wondering about if there are studies looking at the effects of steroids and the side effects that they cause in patients with MOG, because in MOG, specifically, because there are friends of mine, who might not be in this room, who is having symptoms that could be TM, whereas like skin sensitivity or pain or something can also come with steroids, either the acute, high-dose, prolonged component. So, is that really looked at? Why people would recently in the middle of steroids and came off and ?

[00:46:13] **Dr. Grace Gombolay:** Yeah. So, that actually leads me to -- let's see. So, this is one paper that looks at relapses related to steroid wean. It doesn't quite answer your question about side effects. It's interesting. So, one of these MOGAD conferences, like the one in Boston, it was really interesting to hear different people's perspectives on MOGAD because it was an international conference. There are people, clinicians, researchers from around the world, who came to this. So, it's very interesting hearing how different people in different countries around the world, how they treat MOGAD.

[00:46:47] We have certain groups who are very strong proponents for, 'put patients on steroids for many months,' whereas you have other people who are strong proponents for, 'steroids are terrible, don't put patients on steroids for very long.' But I also think it's about access. Unfortunately, in certain countries, it's really hard to get, for example, IVIG or tocilizumab, and sometimes, all you have is steroids. So, there's a lot of things around that. I don't know of anybody in particular who's looking at steroid side effects in MOGAD, but I don't see why someone isn't looking at that. I don't know anyone specifically, but it'd be a straightforward study to do.

[00:47:26] **Dr. Michael Levy:** I think that's a great project for the SRNA survey. And, Jim, no matter what your title, what your disease name will be, you're always welcome to the SRNA. They'll take you in. Don't worry.

[00:47:41] **Audience Member 17:** I actually -- the way I have been talking to you was I had relapsed 12 times, became steroid-dependent with optic neuritis. It was getting so bad, I decided to pass by and see Dr. Chen in Mayo Clinic. He kept telling me about this trial that's coming up. This trial, trial. I kept relapsing and I was on 65,000 milligrams in an 18-month period. He rushed me into the trial, and I did relapse -- I hate to say this, sorry (inaudible) -- from the beginning of the trial, when everything was (inaudible), because they weaned me very quickly. And I know that's a big thing.

[00:48:21] In two weeks, I was weaned and I relapsed. Then, it was determined as relapse. They put me on the drugs (inaudible) this. Again, because it's a trial, they wean you again in two weeks, which I was absolutely panicked. So, I had two weeks of this drug in me -- I think or maybe a little more -- and I did not relapse, which I think is really interesting that all these relapses you have when you're getting off prednisone. Here it was just one-two weeks of this new drug and a two-week wean, after all this prednisone, and I have not relapsed now in two years on that. So, I think (inaudible) everybody and sometimes partially at the end of the (inaudible).

[00:49:12] **Dr. Michael Levy:** Group effort. Group effort, Jim.

[00:49:17] **Dr. Grace Gombolay:** All right. I do have a few more slides, but I wanna give time for questions, and there's some important points that were brought up earlier. I think fatigue is one of those things that doesn't get talked about as much in MOGAD or in ADEM, but it's something that a lot of -- like I said, I see pediatric patients. I see children. Fatigue is a really common thing that they even bring up to me. It's something that's talked a lot about in the MS world. But I was just curious for the panelists, how do you counsel your families and patients on fatigue, and what are some strategies that you recommend for them?

[00:49:55] **Dr. Teri Schreiner:** Well, I wish I had the cure to fatigue. It is incapacitating in so many ways, and I think it exists across the spectrum of demyelinating disorders, and it's frustrating because you can't see it, right? You can't see a weak arm or anything that physically gives a clue that you are exhausted, there is no juice left. So, I wish I had the cure for that.

[00:50:30] Some of the techniques that we talk about are energy conservation. So, pacing yourself, sleep, making sure that sleep at night is restorative. If you're not sleeping well and you've got fatigue from your disorder, whatever it may be, things are gonna be worse. If we can improve the sleep, maybe it's 10% better during the day, but that's 10% that is functionally important.

[00:50:59] We talk about exercise. Although exercise just can wipe you out in the short term, it is one of the things that can build your endurance and your ability to overcome fatigue over time. There are medicines that I will occasionally use for fatigue. And I think somebody pointed out having tried stimulants, but seeing the negative sequelae of that, it's not my favorite way to treat fatigue either, because of adverse reactions to the medicine itself or because it's something that you can become reliant on, and it doesn't actually solve the problem; it just kind of pushes you through it.

[00:51:45] We talk about things like diet. Is eating five servings of vegetables a day going to make your fatigue go away? No. Can it make it 5% better? Maybe. Hydration is important. All of these things play a role in trying to overcome this, but I don't want to oversell any of them because it is a hard thing to treat and to live with.

[00:52:18] **Dr. Michael Levy:** The only thing I would add is that a lot of medications can cause fatigue, like muscle spasm medications and things like that. So, trying to minimize those if you can. Even gabapentin is tiring for a lot of people. So, minimizing the amount of medications you're taking.

[00:52:36] **Dr. Grace Gombolay:** Do you have other questions? Yeah. Go ahead.

[00:52:37] **Audience Member 18:** I have a comment because I'm actually doing a panel on fatigue tomorrow with Dr. Nourbakhsh. I have a lot of experience with fatigue. It was my onset disease really. I had a two-year battle with debilitating fatigue. And one thing that got me through the day was to time my being awake time. So, I'd get up and be awake for a few hours. I was allowed in my job to have a couch in my office, somewhere I can go, and I would do a power nap.

[00:53:09] I would not fall asleep, but I would lay there and rest very heavily for 20-30 minutes, maybe even an hour if I needed to. That got me at least good enough to go through another three hours. And so, I jumped in my day from three hours' nap to three hours' nap. I had to get rid of any substances like caffeine and alcohol. I had to eat perfectly. And I had to sleep. And so, that's how I managed to --

[00:53:40] **Audience Member:** No staying up till midnight Julie?

[00:53:37] **Audience Member 18:** Now it's a different story, but I mean if I had to pass on any advice to anyone who is dealing with fatigue, since I had two years to figure it out, and nobody would give me any medicine. I didn't have a diagnosis. That's how I did it. And, it did work and it did help.

[00:54:08] **Dr. Grace Gombolay:** Other questions? Yes. Go ahead.

[00:54:10] **Audience Member 19:** I think I'm curious to know, how do we know -- I am going to use my teacher voice -- what do we know about the reason why fatigue is so prevalent? What has been explored? I know that it's a little bit harder to quantify. Like, we can't hook someone up. I always joke that I wish I could take my

son to AutoZone and plug him into the thing, and they're like, “Oh, it looks like part 17 has got to be replaced.” Like, that would be so much easier.

[00:54:38] But I feel for a patient for whom really 100% of his symptoms are invisible, and I sometimes wonder if the difficulty measuring those things that are not as visible, where you're relying on self-report -- authentically, he can't accurately self-report. It's been his norm since he was seven, and he has cognitive issues that are impairing his ability to self-monitor and report.

[00:55:15] Yeah, so, I understand that there are things that hinder the ability of science to address these things, but they're very real. And so, I'm curious what work is being done or what ideas there might be to ensure that we're continuing to push on these, I mean, like, truly life-altering things that the group of us who have emerging adulthood kind of kiddos. It's like, my son would tell you he's gonna live in a tiny home in my backyard, and I think that's likely maybe our reality, you know?

[00:55:49] And so, but we don't know. So, what can we do? What science is being done to explore how we can overcome these fatigue issues or the cognitive functioning pieces that are more invisible? Things I just was curious about it. It’s sort of like: we tried all those things, it predates all the meds, we've done all the sleep hygiene. At some point, as a parent, I think you just kind of wanna roll your eyes whenever people tell you the same thing. Like, “I get it.” And also, what else might science be able to bring us?

[00:56:24] **Dr. Michael Levy:** Is Bardia still sitting in front of you? There he is. Hand the mic over to Bardia because he's gonna tell us everything he knows about fatigue.

[00:56:32] **Dr. Bardia Nourbakhsh:** All right. As Julie said, you're gonna have a session about this tomorrow. You brought up great, great questions, and we don't have good answers. I think, again, getting back to MS fatigue. So, MS is a field that's probably decades in front of rare neuroimmune disorders. And only maybe in the past 10 years, the field is paying more attention to these invisible symptoms.

[00:56:59] So, hopefully, with the help of groups like Siegel and other funding mechanisms, we could pay attention. We could really study these invisible symptoms, would be great. Most of the attention is paid towards prevention of attacks and relapses, and for good reasons. But, as you said, many, many patients, if not majority, but a very, very good proportion of patients, deal with these invisible symptoms that affect their quality of life, and that's actually the case with MS.

[00:57:36] As you may know, fatigue is considered the most common symptom of MS, and people have done research about it. People who have MS prefer less fatigue, and they are okay with exchanging it with more relapses, which sounds crazy. But just again, I think we need more research about measurement of fatigue in these rare neuroimmune disorders, about the markers that are associated with this condition -- again, not necessarily causal, but this association -- and definitely more treatment trials.

[00:58:18] There have been a lot of treatment trials in MS, mostly in the past 15 years. We are learning more slowly, but can we translate what we learned from MS to these other rare neuroimmune disorders? I'm not sure about that. That's the best we have for now, but to improve the field, I think we need more research. We need good measurements. We need more attention first. That's number one: to pay attention to invisible symptoms. Second: paying attention to ways to measure these symptoms. Third: doing clinical trials of different interventions.

[00:58:59] As we talked about, exercise has been tested in MS with good results. Cognitive behavior therapy. Julie mentioned some of the techniques that are part of cognitive behavioral therapy has been tested in MS

with good results. Medication have been tested in MS with not very good results. So, at least if we could try the same thing for people with MOGAD, myelitis, NMO, that would be great. Again, more advocacy from patients and family members like you.

[00:59:33] **Audience Member 20:** I have a quick question about fatigue. Last question.

[00:59:36] **Dr. Bardia Nourbakhsh:** Please.

[00:59:39] **Audience Member 20:** Just briefly. I know we've discussed fatigue in this particular group, but if you were to rank fatigue as self-reported, which disease seems to self-report fatigue the most and cognitive disability?

[01:00:01] **Dr. Bardia Nourbakhsh:** If you are comparing MS and rare neuroimmune disorder, there have been a couple of studies comparing MS and patients with NMO. It seems that people with MS have a bit higher self-reported fatigue compared to NMO patients. Again, the study is very small, and getting to the nitty-gritty, there was no statistically difference between the levels, but numerically, in at least two studies that I recently reviewed, fatigue in MS was more severe on average.

[01:00:35] **Audience Member 21:** What about MOG disability?

[01:00:37] **Dr. Bardia Nourbakhsh:** Again, I have not looked at studies that tested cognitive abilities comparing MS and rare neuroimmune disorders. Again, that's one of the invisible symptoms that can cause a lot of disability and lowered quality of life. So, again, more studies.

[01:00:57] **Audience Member 22:** What about rashes? Like little bumps all over on your body. If you scratch them, they can get big to the size of (inaudible).

[01:01:08] **Dr. Bardia Nourbakhsh:** So, neuroimmune disorders, as the name implies, affect the central nervous system. So, they should not directly cause rashes; however, you can think factors associated with the diseases, such as chronic steroid use causing skin atrophy, and blood vessel fragility may be causing rashes, or decrease in activity and ambulation that can cause edema in the legs, edema in dependent areas of the body, skin breakdown, and those kind of things. But the diseases themselves, they only affect the central nervous system, brain, spinal cord, and the optic nerve, and they should not directly affect skin or other tissues in the body.

[01:01:54] **Audience Member 22:** So, maybe a good nutrition (inaudible)?

[01:01:56] **Dr. Bardia Nourbakhsh:** Absolutely, nutrition, medication side effect.

[01:02:03] **Audience Member 23:** Just to touch upon that. I've had two patients now recently who had new psoriasis, actually. They had family history of psoriasis, but they're on rituximab or a (inaudible). One happened to be MS, one is a NMOSD patient, but they had new psoriasis that was probably unmasked by this (inaudible).

[01:02:23] **Julia Lefelar:** Don't get us started on that. I don't know if there is anyone in this room that doesn't have that happen.

[01:02:39] **Audience Member 24:** Thank you. I know there was a slide on treatment options. I wanted to talk about the financial side of that. I've been on IVIG for a couple of years, and I know that Dr. Levy's published research that it's probably one of the more effective treatments or preventatives. Yeah. It's not covered by

insurances. So, it's kind of a tough pill to swallow, to look at my out-of-pocket maximum as a guarantee of what I'm gonna have to pay for essentially something that I couldn't control. I know that there's treatments and trials, but I'm just curious. I know IVIG has been around for a long time, and obviously, MOG just got its new insurance code. I guess, what's being done there?

[01:03:26] **Dr. Teri Schreiner:** If I had a dollar for every time I fight with an insurance company about IVIG for MOGAD, I'd be wealthy. It's so frustrating. So, first of all, I just wanna reflect your pain, and understand that it's very, very expensive. Part of what drives us to do research is to conquer these real-world difficulties that patients have, like getting a medicine that is important to stabilize the disease and providing more and more evidence for it to subsequently, hopefully, make the process easier.

[01:04:11] That being said, we do research to find out, is in fact IVIG the best? Are there other things that would help as well? I think we're in a space right now with MOGAD where we have learned so much since 2017. I mean, oh, my goodness. So much. But there is still so much left to know and to try and do better. One of those realms is treatment. I don't know if you wanna talk about your work in clinical trials or anything else, but --

[01:04:47] **Dr. Michael Levy:** I'll say about IVIG, so far, we only have observational studies. Meaning, we would go sit around, have a drink and say, "Well, what's been your experience?" Put all the data together and say, "Okay, this is what we find." But that's not really scientific. It's not really saying we compare this versus this. We were all blinded. Nobody knew who was taking what. To do really good science takes a lot of effort and a lot of money and the folks behind you are doing that. And that's really what you want to depend on ultimately. Otherwise, you're just using our collective experience, which is helpful, but it's not like you could take that to the bank and say you should be paying -- how much does it cost you? Probably, like, $300,000 a year, right, for IVIG? Something like that?

[01:05:35] **Audience Member 25:** Costs about $35,000 every treatment. So --

[01:05:38] **Dr. Michael Levy:** $35,000 in treatment? So, it's hard to go to insurance companies and say, "Well, Dr. Levy said this."

[01:05:44] **Audience Member 24:** No, that's not what I'm saying, obviously.

[01:05:46] **Dr. Michael Levy:** Yeah. But that's what we do. We call them and we say, "This has been our experience. Here's some studies to support it." Sometimes they approve, sometimes they don't. I'd say I'm about 60%. I don't know.

[01:05:58] **Dr. Teri Schreiner:** Yeah, similar. Yeah.

[01:06:01] **Audience Member 26:** So, if I just want to give an opinion on how I deal with that, with insurance, because I'm the nurse and I do this, I fight this all the time, especially IVIG with MOGAD. I do two things. Number one is: I make sure that if there's a different brand you can use that has a bigger assistance program, because there are vast differences in IVIG.

[01:06:26] The other thing I'll tell you that I've done -- and it's worked three out of the four times -- is when I've fought and fought and fought with insurance and they keep saying, "No. A lot of times it's experimental." I find the president of the insurance company in my state. And I'm not kidding you, within about 45 minutes, I have some response from them that leads me to the next person that can help me get it done. Because, most of the time they are saying it's experimental, but when you put a real story behind it, right, it makes the president go, "Huh, I probably should do something about that."

[01:07:05] And I'm not saying it works every time, but it's worked three of the four times I've had to do it. So, I just go to the top. Because the people that are doing that insurance, they don't understand. A lot of times, I feel, they're not even reading our clinical information. They don't know what they're doing. So, that's just my -- that's how I handle it.

[01:07:24] **Dr. Michael Levy:** I've also had state senators intervene, and that seems to work. I don't know who they're calling. I don't know who the state senators are calling, but things happen.

[01:07:38] **Julia Lefelar:** I just have one more comment. On the MOG Project website and actually on the SRNA, there is a space for help in getting insurance coverage for or at least letters, templates and things like that and information about what to do. We have a letter template for appeal that Michael Levy was kind enough to -- and he may not remember, he's looking at me like, "I don't remember doing this." -- helped us create. And the other thing is, I think there's help coming down the road and, there's the option of subcutaneous IG for some, which can be, you know, for me it's $14,000 a month. But you know it's less. And there are also, I think I can say this, is that there is a clinical trial possibly, right? So, that will come down the line. And I think that will change things drastically.

[01:08:34] **Dr. Michael Levy:** Once it's approved, FDA-approved, then you're done, then it's pretty easy to get insurance coverage.

[01:08:40] **Audience Member 27:** Dr. Chen wrote a paper and he was trying to get IVIG for trial for me and we could not get -- I have great insurance -- we could not get them to approve it. He got a final denial and on his own, he took the paper he wrote on that IVIG and MOG and just sent it to my insurance and they approved it. I could actually finally start

[01:09:01] **Julia Lefelar:** Right. And so they're in that section on our website. Yeah.

[01:09:04] **Audience Member 27:** So, great. We have it on our website.

[01:09:06] **Julia Lefelar:** Yeah. It's in that section on our website. There are the three papers that you wanna submit when you, with that appeal when you get it. And, maybe down the line, after these clinical trials hash through, we'll all have a lot better time getting treatment. So it's sort of work.

[01:09:23] **Audience Member 28:** If someone's currently taking subcutaneous Ig, will they qualify for the clinical trial?

[01:09:29] **Julia Lefelar:** You have to have relapsed but probably -- I don't know the answer to that but I think there would be a relapse that (inaudible)

[01:09:43] **Dr. Grace Gombolay:** Any other questions? We've got about three minutes left.

[01:09:58] **Audience Member 29:** So, we're still pretty new to all of this. Two years. My daughter was diagnosed at 17. She's 19 now. Double seronegative NMOSD, but she presents herself more as MOG. The more I hear, I'm like, "Oh, maybe it is NMO. Oh, wait. Maybe it is MOG." But you know, it's very confusing. I'm also confused, is a relapse, does that mean your disease is not under control? I mean, is that correct?

[01:10:30] **Audience Member:** That is correct.

[01:10:31] **Audience Member 29:** Okay. So, it's usually a year in between relapses. April to April, no optic neuritis. Now, November to October, no optic neuritis. Now, optic neuritis, and that's on CellCept and IVIG. So, does that mean a drug has failed? Does that mean we need to increase it? Just it's all very confusing.

[01:10:59] **Dr. Grace Gombolay:** Yeah. So, generally, if a patient relapses, there's usually some timeframes that people give. They're kind of arbitrary time windows. We talked about the ADEM. Everything within that three-month timeframe. For MS and MOGAD, we're saying it was within one month. But, again, I've had patients who had a true, true new relapse within two weeks of their initial onset, and I'm like, "Meh," and it was severe enough I was like, "Eh, I'm gonna call this a relapse," even if it wasn't that definition. But, yeah, if you have a relapse on treatment, that means your treatment isn't working, and so either the dosage needs to be changed or you have to switch the treatments in of itself, so.

[01:11:37] **Audience Member 30:** And really no studies for seronegative, right?

[01:11:42] **Dr. Grace Gombolay:** In terms of clinical trials specifically? No, not specifically, but we do try other treatments. So, I didn't talk about it in this slide, but there's other treatments that we do consider in MOGAD for patients who fail the traditional thing. So, IVIG is a common one if you can get it. I know it's super-expensive, but it does work pretty well. CellCept or mycophenolate mofetil is also a common one that seems to work. People tried rituximab in MOGAD. It doesn't seem to work as well in MOGAD as it does for Aquaporin-4 NMOSD. Tocilizumab is another one that people will try whether it's NMOSD or in MOGADs. That would be another option too.

[01:12:24] **Audience Member 30:** So, she's on CellCept and IVIG for a while. I'm not gonna say (inaudible) in that. So, if you were a MOG patient and you actually had NMOSD or vice-versa, and you were taking that medication, could that hurt you? Like, someone who has MS and was taking --

[01:12:42] **Dr. Grace Gombolay:** I'm sorry. Can you repeat that question?

[01:12:43] **Audience Member 30:** So, she is seronegative. So, if she actually had MOG and they were giving her medication that works better for NMOSD, could that hurt her? Could that cause her lifelong deficits?

[01:13:01] **Dr. Grace Gombolay:** So, that's unfortunately a risk right now that we don't know. We don't know what treatment works. We say, "Oh, this treatment works for most people," but we don't know if it's gonna work for you personally. So, we trial what we think is the safest and efficacious treatment. I can't answer that, unfortunately. It's one of those things where if you're on something and you're having more relapses, I would consider switching to something else versus changing the dosages because that was not working.

[01:13:29] **Audience Member:** I feel your question is specifically regarding to child support, right?

[01:13:33] **Audience Member 30:** Yes.

[01:13:34] **Audience Member 31:** Like, if her daughter went on rituximab, would that potentially cause harm if she doesn't actually have NMOSD or MOGAD?

[01:13:43] **Dr. Grace Gombolay:** It depends on what's causing her underlying things, which are underlying, which sounds like could be seronegative. And then mostly, it's hard for me to comment because I don't know all the particular details.

[01:13:54] **Audience Member 30:** Seronegative ADEM, to begin with, next diagnosed with MS, and there's ADEM, and then optic neuritis multiple times, and now they are saying NMOSD double-seronegative presents itself as well. But then, the lesions in the spine, hers have been at the top, not at the bottom.

[01:14:20] **Audience Member 30:** It's just like she's both, but she's not either one.

[01:14:25] **Dr. Grace Gombolay:** Yes. Yeah. We definitely have some unfortunately, some patients who do fall in that bucket. And, again, I can't comment on your particular situation because I don't know all the details. But in general, for seronegative NMOSD, rituximab can work for patients.