Open Q&A Session

You can view this presentation at: youtu.be/V1yEz0eIWy4

[00:00:05] **Dr. Benjamin Greenberg:** Thank you all for joining and for my colleagues who are getting on the call. Hopefully everybody has had a chance over time to look at videos of discussions that have happened both this year and in the past. And you can send in questions that we are happy to take them as they come in and try and group questions by topic. One of the questions we got was how could a diagnosis of viral meningitis fit into the diagnostic flow?

[00:00:37] So, there is an individual who reports having a diagnosis of viral meningitis in 2017 and then in 2020 was determined that they had MOGAD. Dr. Blackburn, you had led us through the diagnostic pathways discussion. Have you ever heard of an anti-MOG associated disorder patient presenting with what looks like viral meningitis.

[00:00:59] **Dr. Kyle Blackburn:** I have. Occasionally patients with MOGAD specifically will have changes in the meninges, kind of that lining of the brain. Occasionally that will lead doctors to think that they have meningitis, and they also occasionally have headaches and vision symptoms and there's evidence of pressure in the ways that we can measure that. So, it is occasionally misdiagnosed as a viral meningitis.

[00:01:28] **Dr. Benjamin Greenberg:** And I don't know, Dr. Graves, if you want to comment on this as well because I know in the pediatric world this is an overlap syndrome that we've seen not infrequently?

[00:01:40] **Dr. Jennifer Graves:** Yes. I think often when people present with MOGAD it presents as an encephalitis in some cases or something that could be interpreted as a meningoencephalitis, having components and symptoms that could look like a viral meningitis or a viral complication in the brain. So, it's quite frequent that when we're initially working up these patients, particularly if they present with seizures or some of the typical pediatric ways in which MOGAD can present, we do a broad work up that tries to rule out infection so we can proceed with immunotherapy and also to look at all the different types of encephalitis or meningoencephalitis actually from autoimmune.

[00:02:27] **Dr. Benjamin Greenberg:** So, the next question we have, I'm going to pose to Michael and it's about the time long it takes for antibody results to get back. And the person asking indicates that they had a daughter who was hospitalized for almost three weeks, not unusual for some of these conditions. And that

spinal fluid testing was sent within the first few days of being in the hospital, but they didn't get a result of a MOGAD test until after she was discharged. Is this the testing process or lack of diagnostic resources? Why is there sometimes this gap between tests and results?

[00:03:02] **Dr. Michael Levy:** I think that the gap is actually the rule and people who get their diagnosis quickly are kind of the exception. I think on average, if I had to guess it would take about 10 days or so for cases that we send from here to be resulted. That's from the blood and spinal fluid is not even a commercially available test for MOG yet. So, if you send that waiting for a result, you might have to wait even longer because that's going to be done on a research basis if at all.

[00:03:33] And a lot of times our patients are already home by the time the MOG antibody test comes back and sometimes there's a drop in the communication between the hospital team and the clinic team and the result is there. And sometimes patients are just wondering what it means before they could even meet their first neuroimmunologist. I understand the question and why it's so important and sometimes this is just how it happens, but it's really up to the inpatient team to make sure that the ball isn't dropped.

[00:04:03] **Dr. Benjamin Greenberg:** Yeah, Jennifer.

[00:04:05] **Dr. Jennifer Graves:** I wanted to add that we're working on ways to maybe speed up diagnosis and come up with more rapid tests. But sometimes there's a bit of a tradeoff between the speed of being able to do a blood test for these disorders and the quality of the test. And since the blood test is the gold standard, I think we're all interested in trying to speed up that process, but we need to do it in a way that doesn't decrease sensitivity and specificity. But I will say that given that this disorder MOGAD is fairly newly recognized, we are making some strides and being able to have a greater clinical suspicion for the disease.

[00:04:43] So, due to the work of lots of groups around the world, we're starting to better define how a MOGAD patient might present in comparison to the things that look like MOGAD. I do think we're getting better at having early suspicion that that will end up being the diagnosis confirmed by the blood test, which does allow us to take some steps very early on and acutely to at least cover our bases that it could be MOGAD before someone leaves the hospital. I don't know if my colleagues agree, but as we learn more about the disease, we'll be able to have some better clinical and MRI indicators that MOGAD might be the diagnosis while you're waiting for the blood test.

[00:05:25] **Dr. Benjamin Greenberg:** Carlos, please comment and then I've got a question for you.

[00:05:30] **Dr. Carlos Pardo:** Yeah, I have a comment about the previous question about viral meningitis, diagnosis of viral meningitis and meningoencephalitis is really challenging in the acute setting. Particularly because in many centers around the country and community centers, there are limitations for diagnosis of viral diseases, and we are basically able to diagnose only herpes virus in the lab as a real validated assay. But we are missing a very large amount of viral diseases that may trigger meningoencephalitis. Recently, we are finding actually that some viral diseases are able to trigger a transitory MOG antibody response.

[00:06:20] For example, there is evidence of some flavivirus that are basically a virus transmitted by mosquitoes that are able to trigger a transitory MOG immunoreactivity. And again, that is unfortunately a research test but finding a viral disease is an interesting aspect in the future for understanding the biology of MOGAD and triggering factor for MOGAD that is again work in progress. But the second thing that I like to emphasize is there is a lot of emphasis in doing spinal fluid analysis of MOGAD. But actually, the money is in blood. And in the community, some neurologists pay too much attention to the CSF assessment of MOGAD, but the reality is that initially the first layer of assessment of MOGAD is in the blood.

[00:07:19] **Dr. Benjamin Greenberg:** So, in this setting, while somebody may have had spinal fluid testing in the first four days, the MOG blood test might not have been sent till later in the hospitalization, which would also explain why the result didn't come on till some day later because it is the blood that's most important. I'm going to switch gears on you Carlos and there's two questions that have come up relative to vaccinations and they're really good, very pragmatic questions.

[00:07:48] So, the first one was a person who's on CellCept and IVIG for their condition and that the neurologist recommended not receiving live vaccines. Can you explain the reasoning behind avoiding live vaccines for somebody in particular who's on CellCept? Because in our talks, Michael and I have advocated for vaccination in general but why would we hold off on the live? And then I'll have a follow up question for you after that.

[00:08:18] **Dr. Carlos Pardo:** So, live vaccine is a very interesting topic at this moment. The good news is we are evolving, and the technology is evolving in the way that very likely some of the live vaccines are going to be modified to MRNA vaccines or protein-based vaccines. The problem with the live vaccines is that patients that are immunosuppressed like in the patient that you are describing with medications like Mycophenolate or medications like the Tacrolimus or other type of immunosuppressive treatments there is a potential that some live vaccines may turn to be pathogenic.

[00:09:08] In other words, the virus that is attenuated to produce the vaccine may replicate and evolve in a virus that may be pathogenic. And that is a topic of discussion because there are many vaccines that are attenuated and fortunately in the United States the number of those vaccines is decreasing. But around the world, we have a problem with polio because polio vaccination in the United States is an IPV that is basically an injectable rather than the oral is the main way to control polio.

[00:09:45] But in other areas of the world, like in Africa and Asia and in some Latin American countries, there is still use of oral vaccination for polio. It turns around that it started in some of patients that are immunosuppressed, that vaccine may have the potential to produce a pathogenic effect. I think that other vaccines that use live attenuated virus actually may have potential to revert to pathogenic. And that is the problem in patients that are severely immunosuppressed.

[00:10:21] The good news is fortunately that's not a common denominator and many of the virus that are attenuated and used in vaccines, the likelihood of transforming to pathogenic viruses is relatively low. It's a note of caution. We need to provide the right advice to patients who may need the use of attenuated vaccines.

[00:10:50] **Dr. Benjamin Greenberg:** And so, along those lines a separate question from somebody else was specific to whether or not an immunocompromised patient can receive the RSV vaccine which is not live. It's not a whole virus or live. Would you have any particular comments unique to the RSV vaccine?

[00:11:10] **Dr. Carlos Pardo:** So, the RSV vaccine or the two versions that has been produced is basically to improve immunity, particularly in the pediatric population and particularly in patient population above age 65. The good news is this new version of the vaccine is not live or attenuated and the likelihood of producing potential problems in patients that are immunosuppressed is very, very low.

[00:11:43] And I think that the current guideline from the CDC is to provide vaccination particularly to adults over age 65 that may have a big factor for infection because RSV is a very dangerous virus and the circulation of RSV increased dramatically in 2022 producing a quite important increase in the incidence in many areas of the United States as well as the world. And the amount and the impact of RSV last year in the period population was very, very high to the point that many hospitals enter emergency situations because the number of patients.

[00:12:26] So, I believe that there is a rational for using the RSV. The rational is there, is extremely important particularly for the pediatric population and for the patient population above age 65 that may have potential for immunosuppression.

[00:12:42] **Dr. Benjamin Greenberg:** So, along the lines of other things that our patients may take that can either help or harm in the same conditions. Paula, I'm going to combine several questions that we've received relative to the use of supplements in the world. So, there are two types of questions where we're being asked. One is just around safety.

[00:13:04] Are there contraindications to taking certain supplements and believe it or not more than one person is asking specifically about Lion's mane and Turkey tail, which are mushroom extracts? And is it okay to take it? And in your opinion, does it work relative to symptoms? And do you have general guidance when it comes to literally the hundreds of different supplements that are out there that people talk about in different chat rooms?

[00:13:31] **Paula Hardeman:** Yeah, that's a very complicated question to answer. But in specific to, I guess the overall approach to it is what does the evidence say for these different supplements and that's the challenge. There's not much evidence to support the use or not use of these different supplements. And so, it's going to be something where it's going to truly have to be individualized. Looking at a patient's condition, the other medications they're on. Why do you want to take the supplement?

[00:14:04] Are you using the mushrooms as an extract to help with inflammation or are you using the mushrooms as part of your dietary changes because you're wanting to live a more plant-based diet? I think it's a conversation that should be had with your health care provider looking at the different supplements. Why you're trying to take the supplements and just to see if there's any evidence on the different supplements as stuff we need to take for that patient.

[00:14:31] **Dr. Benjamin Greenberg:** Does anyone else want to comment in terms of just supplements in general in their clinic? I agree completely. I know it's a topic though that comes up frequently.

[00:14:40] **Dr. Jennifer Graves:** The one thing I would add is that depending on the supplement, and there's a huge variety of things that could be referred to as a supplement, is to keep in mind some of them act like drugs and are processed by the liver. One thing that anyone with any medical condition using them to supplement their medical care is that occasionally it can cause lab abnormalities to take some supplements. Keep in mind that a lot of these things are acting potentially medically and could impair some blood testing for you.

[00:15:12] So, it's very important to report it to your doctor that you're using it. So that if we know that some of those supplements could cause for example problems with your liver testing or sometimes can interfere with other blood tests it's important to be aware of that. And if you're taking certain supplements, your primary care physician or your neurologist should periodically check your labs.

[00:15:35] **Dr. Benjamin Greenberg:** So, we've got about a half dozen to a dozen anti MOG related questions in the chat that cover the entire story arc in the setting of this condition. So, we're going to do the jeopardy round. I'm going to go around the screen. I'm going to start with Kyle and I'm going to take us through the evolution of individual with MOGAD and I believe we will answer all of the questions as we go through this. So, the first question that comes up Kyle which is specific to an individual who has a CNS inflammatory event. They're found to be anti MOG antibody positive on a reliable assay. And the question is, do you subscribe to

the wait and see approach, or do you treat even though there's only been one event even in a situation where the person is left with disability, would that be a reason to say well, let's go ahead and treat even though there's only been one event?

[00:16:33] **Dr. Kyle Blackburn:** Well, that's always a really good question and maybe one day we'll have better ways to predict who's at risk and needs treatment. But in general, right now, I think a lot of us and myself included are prescribing to the idea for a wait and see approach. So, if you've had a single event, even if it's left you with disability if it was effectively treated in the acute setting, I generally don't advocate for any kind of immunosuppression at that moment. But hopefully, we'll have better tools to differentiate that in the future.

[00:17:04] **Dr. Benjamin Greenberg:** So, the next question in this evolution goes to you Jen and that is the individual who has the MOGAD diagnosis, they've had one or more events, but now they're calling with symptoms that raise the possibility of a relapse. And the question that was poised to us is some providers insist on MRI findings to confirm a relapse before treating it. Is this required to confirm relapse or not?

[00:17:32] **Dr. Jennifer Graves:** So, it's very helpful to get imaging to confirm a relapse, but a lot of clinical features can be used. And particularly if you can examine the patient in addition to hear about the symptoms, to strengthen the suspicion that it's a true relapse and to begin efforts to start treating that relapse even while you're waiting on the imaging. And to clarify that point, as you know, an example for optic neuritis is there are ways to verify based on your symptoms, if you're truly having a new episode or not, there are some exam findings we can use, there are aspects of your symptoms.

[00:18:10] I think maybe I can sneak in an answer to another question, which is about why you have reactivation when you're sick or overheated or exercising. And we can answer that question in more detail in a moment but there are ways we can ask you questions about your symptoms, even to distinguish between one of those exercise induced pseudo-relapses versus a relapse. So, the answer is it is very helpful to us and the reason it's so important for us to confirm that relapse is not only to take good care of you now and get you steroids or IVIG or plasma exchange and try to get that patient treated quickly.

[00:18:49] But it's important for the long-term course because we are not only going to be making decisions this week about these symptoms, but how we confirm this relapse and determine its severity and extent might impact a decision we make two to three years from now about whether to continue immunosuppressive therapy. So, we do like to get as much data as possible, not because we want to delay treatment, but because it has an impact long term on how we assess someone's disease course.

[00:19:19] But that being said, most of us who are familiar with the condition can ask you questions or examine you in a way to confirm that relapse. And one clarification on a relapse versus a pseudo relapse is if you've never had that symptom before and it's on a new side or a new eye or a new location, it's very unlikely it's a pseudo relapse because a pseudo relapse by definition is recurrence of an old symptom. So, we absolutely can do a lot before you get on the scanner. But the scanner could help us not just this week, but it could help a couple of years down the road in how to take care of you.

[00:19:55] **Dr. Benjamin Greenberg:** And so, along those themes of useful information for the long term, Michael, there's a question about MOG titer and it's about is the value of the titer just relative to diagnosis or is there any research that says, looking at the titer over time is of value? And they give an example of an individual who had a 1 to 1000 titer diagnosis where they had optic neuritis. They started on IVIG preventative therapy because they had a relapse at one point. And the titer is remaining 1 to 1000. Does it matter or not?

[00:20:29] **Dr. Michael Levy:** I don't know the answer to that. I would like to say that it does matter because that's something that everybody is looking for and nobody has yet found. But we're still looking because we believe that the titer should matter. I think it does matter in two ways for sure. One is in making the diagnosis 1 to 100, 1 to 1000, 10,000, anything in that high level gives you confidence in the diagnostic process. But even people with low titer can still very well easily meet the diagnostic criteria for MOG. It's not a rule out.

[00:21:03] So, if you're 1 to 20 and you have recurrent optic neuritis and no oligoclonal bands, you probably still have MOG antibody disease. So, that's the first and the second is that people who go from positive. So, you have 1 to 1000 you're treated for a long time and then we check you six months, 12 months, 18 months later and you go negative where your MOG antibody is no longer detectable.

[00:21:28] That gives us some confidence that your immunity to MOG is going away, which is a good thing. It doesn't mean you're not going to relapse, but there's some good data out there suggesting that if you convert to negative, that your risk of a relapse is lower than if you sustain a positive. But that data is still coming in. We're not 100% sure about that.

[00:21:50] **Dr. Benjamin Greenberg:** Yes, Carlos.

[00:21:52] **Dr. Carlos Pardo:** I'd like to make an editorial comment in the history of neuroimmunology using antibody titer for falling Neurological Disorder has tend to be not necessarily a good approach. In general, the concept is that we as clinicians and patients shouldn't rely too much in a number. I think that what matters is the clinical profile and what is going on. And basically, the assessment by the neurologist to determine if the disease is really exacerbated or not, but I don't believe it need to be relied too much in antibody numbers.

[00:22:32] **Dr. Benjamin Greenberg:** On the next level of MOGAD questions, Carlos, there's a question on the treatment side. So, for an individual who's had multiple relapses, they've been on a combination of IVIG and CellCept for what they say are many years and they haven't had a relapse in over two years. Would you ever consider taking them off the medications? One or both medications?

[00:22:56] **Dr. Carlos Pardo:** I think that we don't have a good answer to that question yet. I think the future studies led by Dr. Michael Levy and collaborators will provide some information about that. I believe in my experience I am a little bit on the conservative side and basically, I rely very much in number one is the clinical profile of the patient. Number two is the magnitude of the disease that has been determined by MRI studies or optic nerve assessment by OCT.

[00:23:32] And number three is basically the evidence that there is an active immunological problem. But again, I think that we still are a little bit behind in understanding that concept when to stop the treatment. And I think that that should be based on an individual basis.

[00:23:53] **Dr. Benjamin Greenberg:** So, Paula, Jen had gotten into the notion of Uhthoff's phenomenon, the worsening of old symptoms that can be misunderstood of a relapse. And we've got a few different questions that are all interrelated here and two of the questions in particular was why does exercise cause these? In the question, they say fake relapses. I'm going to say pseudo exacerbations or worsening of symptoms even when there isn't a new lesion.

[00:24:22] What's happening you think physiologically? And then related to that an individual who's had transverse myelitis indicates that they actually now have heat intolerance, and they feel like they're not sweating. Is this something we've seen before? And could that relate to controlling core body temperature?

[00:24:42] **Paula Hardeman:** So, with the first one it's always a difficult concept to understand of what's going on in the body for Uhthoff's or worsening. So, I try to get patients just to understand you've had this neurologic event, this demyelinating event in the spinal cord or optic nerve and so your body has to learn a new baseline. So, it has to learn a new way of communicating the signals to the brain and through the spinal cord and optic nerve. And so, your body gets pretty good at compensating and now you have this new baseline and that means internally, everything has to be kind of what we'll say perfect, not 100% perfect, but pretty close to it.

[00:25:21] And so, when you skew it in a different way, so if you start exercising and your body starts to heat up, your body now has to use more energy stores to cool itself down. Therefore, it can't focus on, or the focus has shifted from being 100% at its new baseline. And as a result, the return of these old symptoms can come temporarily and usually if it's heat related or exercise induced as soon as you stop the exercise and cool off, you go back to your baseline.

[00:25:53] And so, I try to just to give an example or just help patients just to understand the thinking of like the spinal cord is the information highway. And then if you get a detour, how that slows you down if you're trying to travel from one city to the other and you have to find a different way around it, but eventually you can get back on your path again. And then I forgot your second question.

[00:26:17] **Dr. Benjamin Greenberg:** The second question was around heat regulation. In our clinic for myelitis patients, particularly ones who have higher spinal cord lesions, they can have changes in their sweating pattern.

[00:26:29] **Paula Hardeman:** I do hear that frequently. Either patients will notice, will say from their chest below that they don't sweat as much or something different compared to the rest of the body. It is one of those things that I think it's just sometimes hard to predict when that's going to occur, and it can cause a lot of anxiety around it. And so, it's just different strategies whether it's coming to exercise from the temperature regulation. And this is where when you work with rare disorders, you have to really sometimes think outside the box and listen to the patient to see what's going on, when does that occur and then approach finding a solution from, from that way.

[00:27:12] **Dr. Benjamin Greenberg:** So, Kyle, one of the questions that comes in is around recommendations for “double negative NMOSD.” So, I'm going to read into this question and assume this is an individual who's had more than one event that phenotypically looks like a neuromyelitis optica but is testing negative for the anti MOG and AQP4 antibodies. How are you counseling those patients relative to treatment?

[00:27:39] **Dr. Kyle Blackburn:** Well, that's always a tough question too. The good thing about these biomarkers is they've given us a lot of information about how best to treat people based on the evidence that we have available. So, we now know certain therapies seem to work really well for anti-Aquaporin-4. We're developing strategies around anti-MOG. So, the double sero negative patients, we're still trying to sort out the best way. I always like to start and kind of take a cognitive step on evaluating these patients and make sure we're not missing an alternate diagnosis being the number one thing.

[00:28:14] Rarely, there are things that can mimic NMO, and we need to consider it in those situations for sure. The next thing I'd say is making sure that it isn't a treatment effect. So, if somebody's gotten plasma exchange or Rituximab, we know that that lowers systemic antibody levels and just making sure that isn't the reason that you are double sero negative and you indeed do have Aquaporin-4 MOG. But if all of those things have been ruled out and we're dealing with a double sero negative person who has had more than one event and I've done everything that I can to rule that out and I'm convinced this is an immune mediated disorder, at that point, it's really an individual discussion.

[00:28:55] If somebody's already on a treatment and they seem stable, I would probably advocate for staying on that. If somebody is not on a treatment and we're convinced they've had relapses and need treatment, I would probably lean toward a treatment that would offer a slightly broader coverage because in these situations we can't really quantify or is this a "B-cell mediated process or T-cell mediated or a mix." So, I tend to lean into maybe older therapies that offer treatments that would cover the immune system more broadly. So, things like Mycophenolate, which has come up already, for example.

[00:29:36] **Dr. Benjamin Greenberg:** So, along those lines, Carlos, I'm going to pose this next question to you. It's an interesting situation. So, an individual who tested positive for the Aquaporin-4 antibody in 2015 was put on Rituximab therapy with an every six-month infusion. Since been relapse free and the neurologist said, why don't we just recheck your AQP4? And what came back was positive for anti-MOG antibody but negative for the AQP4 antibody. Have you seen this happen? Does it happen often? Should they continue to monitor? Should they ask for their money back on the test? How would you advise them to handle the situation?

[00:30:18] **Dr. Carlos Pardo:** Yeah, actually I haven't crossed with this situation. I need to make sure. So, in 2015, we were still using Aquaporin-4 testing that was not necessarily very well standardized and it is possible that there was a false positive and their problem was really a MOG. Again, this is a speculation. The cell-based assets became a standard of care just before the pandemic. So, 2015 was not that time yet. So, it's very possible that we still have some uncertainty about the real diagnosis of the antibody.

[00:31:00] But if the antibody came now to be MOG and is positive and it is done in a very well-established lab with a cell-based assay, obviously that is important. Now, the decision is if a patient that has been very stable and is on Rituximab, I'm very curious why is it still positive for an active antibody. But I believe that again, as we discussed in previous questions, it depends on the magnitude extension of the disease at the beginning to make decisions about what to do now. And if the patient has been stable and the burden of the disease by clinical assessment and MRI is relatively low, it's basically a discussion between the patient and the clinician to determine what is the risk and benefits for continuation of Rituximab treatment.

[00:31:41] Michael, I don't know if you agree with me, but I think that in those particular situations there are many factors involved including the age of the patient, the potential risk for continuation of Rituximab. Importantly, what is the status of the patient and the magnitude of the disease that they experienced before?

[00:32:11] **Dr. Michael Levy:** Yeah, I've seen those low positive AQP4 tests, the borderline 3 to 5 levels and people carry that diagnosis for a couple of years and then the MOG antibody test comes out and everybody's testing positive. I've definitely seen that and that tends to be more MOG disease for sure.

[00:32:29] **Dr. Carlos Pardo:** Would you continue Rituximab?

[00:32:34] **Dr. Michael levy:** I'm not a huge fan of Rituximab for MOG. It's hard to argue if a patient's been on Rituximab and has been stable for years and years, it's hard to argue that it's not working. But if I'm looking forward and thinking about a new start, I probably wouldn't use Rituximab very much.

[00:32:50] **Dr. Benjamin Greenberg:** Michael don't go away yet because there's a question specific to a study that you were doing that both the author of the question and myself found this to be a fascinating study. It was the Scrambler Therapy Study. I'll ask you to explain it to the audience who may not be familiar with it. The question that's being posed is the person was motivated to seek out the treatment and had an experience similar to the outcomes you reported of three months with little to no pain. They asked has anybody in your study continued to take this treatment several times over a longer period of time? Do the outcomes continue to improve? Do you want to give people a little background about it and then address the question?

[00:33:31] **Dr. Michael Levy:** Yeah, Scrambler Therapy is something we pursued for treatment of pain. It's very much like any transcutaneous electric nerve stimulation or even acupuncture, they all work on the same principle and that is if you zap the nerves of the body or stimulate them with a needle or however you want to do it, that signal going into the spinal cord distracts the spinal cord from pain signals due to the lesion. That's the basic principle. And this one device called a scrambler claims to do some sort of stimulation that lasts beyond the period of time that you have these electrodes on.

[00:34:10] So, most transcutaneous electric nerve stimulators you turn it on, you immediately feel some relief and you turn it off and sometimes the pain signal comes right back. But the scrambler, the whole stick, the whole reason that they charge so much money is because they feel like they can cause some durable benefit that lasts beyond just the time that the electrodes are on like a week or two or three. So, we did a trial in Aquaporin-4 NMO, and we found that it does indeed if you do 10 days, one hour a day.

[00:34:41] And you do that consistently without missing a dose, without missing a treatment, you can get a benefit that lasts for two or three more weeks after that, no more requirement to put the electrodes back on and it seems to be durable. So then what we tried to do is we said, well, okay, that scrambler device costs $250,000. Who could possibly afford that? Even when you have access to it in a clinic somewhere, it's still a very expensive treatment and most insurance companies don't cover it. So, could we replicate that success with a transcutaneous electrical nerve stimulator that's a little bit cheaper.

[00:35:19] We found one that you could use at home for $100, $200. And what we found in that study that was also sham controlled is that everybody responded, whether you turn the device off or on, you had a fake device or real device. Everybody seemed to get a little bit better. And so, it wasn't a convincing result that it's better than just putting on electrodes without any electrical stimulation. So, it's an evolving science. I'd say we still have a lot of work to do. If you find a benefit from the treatment, then it works for you. And that's basically the results for everybody.

[00:35:58] **Dr. Benjamin Greenberg:** Great. Thank you. So, Jen, there's a question here relative going back on the MOGAD side of things around symptom evolution. So, a person who had a diagnosis in 2016 had a recovery, 2019 had a relapse, excuse me in 2016 a relapse, but they've had fatigue and seizures worsening over the last three years without any other obvious MOGAD symptoms. So, is this something that you see in anti MOG? Can somebody have ongoing fatigue or even seizures without MRI evidence of a new inflammatory event?

[00:36:39] **Dr. Jennifer Graves:** The classic description of MOGAD similar to Aquaporin-4 positive NMOSD is that it is a relapse-based disease. Unlike MS, there's less pathology happening between attacks. Our knowledge of that is very preliminary and we're all still trying to understand what might be happening inter event, inter relapse in both Aquaporin-4 positive and MOG positive neuromyelitis optica spectrum type clinical presentations. Those specific symptoms of fatigue and seizures are interesting as inter event symptoms because if the initial attack or initial lesions from MOGAD injured certain structures in the brain, they could set you up for seizures even without having new inflammatory activity. I would say if I were treating a case like this, I'd be curious to better understand if I could prove in any way that there's ongoing inflammation that would help me make decisions about immune therapy.

[00:37:45] But I would also be very interested to look at the structure of the brain to see if there could have been injury from the beginning of the disease that has now set this individual up for seizures. Having seizures that are not well controlled could make a person fatigued on their own. So, I guess when I look at this case, there's a possibility that there was injury that set this individual up for seizures which are now causing more fatigue and it may not mean there's new inflammation or there could be some type of new inflammation that's breaking through whatever treatment.

[00:38:18] Or if the patient is not on treatment that's breaking through and needs to be addressed with immune therapy. So, I think in this particular case, there could be two explanations and it would be very important to try to explore those two to better treat this individual. And I do think we need a lot more research to understand if there's something happening, inter event, inter attack in MOGAD and NMO.

[00:38:44] **Dr. Benjamin Greenberg:** Great. So, just to switch gears, Paula, there's a question that comes up quite a bit and I'm going to lump it into the category of just symptoms and rehabilitation management. The specific question that's being asked is around stamina and endurance. And so, this individual is using probably like forearm crutches for getting around.

[00:39:04] And they're asking, is there any reason they shouldn't be working to increase their stamina by continuing to walk longer distances even if they end up tired the next day? So, if they're going to the point that they're exhausted, is that safe? Is it okay? How do we counsel people on balancing these issues?

[00:39:26] **Paula Hardeman:** Yeah, it's very tricky and it has to be individualized. So, on the first aspect of it, from a safety standpoint, it is safe to do you're not going to cause a relapse or anything of that or do further damage to the spinal cord or the optic nerve or wherever the injury is. But the challenge is, do you push yourself so much today that tomorrow you're completely worthless.

[00:39:57] So, meaning that you're so fatigued the next day that you can't even get up and participate in daily living activities. And so, I would say no. While I want my patients to continue to push themselves, it's finding that right balance of how much do I push myself today where I'm not going to cause myself to be totally out of it the next day. I try to focus on just getting people to convey. Can you do 1% better tomorrow? To me that's a really realistic way of looking at things. If just, even if you're doing your timed walking, you're up to walking five minutes, perhaps, maybe you just go five minutes and 10 seconds.

[00:40:38] And then each day if you're just adding on an additional 10 seconds before you know it you've added on a full minute and now, you're walking six minutes. So, sometimes it's just looking at the progress of moving forward and not focusing on while I'm only doing two minutes or whatever the case may be, but just challenge yourself to say, what can I do today that's 1% better than yesterday? And I think that is a more reasonable and balanced way of pushing yourself without over pushing yourself.

[00:41:11] **Dr. Benjamin Greenberg:** No, it's great and that's a question that comes up for us all the time. I want to be mindful of time. We're entering the last two minutes. And so, I'm going to end with a question about neuromyelitis optica that's come up in a few different ways and this is specifically around AQP4 positive NMO and it has to do with starting and stopping medications. So, the question was specifically about Eculizumab or Soliris and is there a danger to starting the drug and later stopping it and whether or not to use it in combination?

[00:41:47] And when I go through this question and others, it's really about comments about how to use Satralizumab, Inebilizumab, and Eculizumab in NMO and the considerations for when to start or when to stop. It was a very broad question and I know we have a short amount of time. Michael, I'll pose it to you first and then Jen second. Do you have general guidance about starting and stopping medication and which one?

[00:42:09] **Dr. Michael Levy:** I think Eculizumab is an easy one to start. It works quickly. A lot of people choose that because of the initial benefit there. You could use it for six months, 12 months, it's an every two-week infusion. So, it is burdensome, and a lot of people do eventually switch off and there's no harm in doing that as long as the timing fits 17 days after your last infusion, your complement levels are coming back. So, you don't want to risk taking too long in the transition period but otherwise switching is fine.

[00:42:41] You can't use though, you can't use Eculizumab and Rituximab at the same time because Rituximab depends on complement for a lot of its activity. So, that won't work. You'll have to stop Eculizumab and then start Rituximab if that's going to be your transition. Whereas with Inebilizumab, I think you can use them concurrently if you want to try to transition like that, that should work and same with Satralizumab. If you're going to transition to Satralizumab you can overlap a bit.

[00:43:13] **Dr. Jennifer Graves:** So, I guess.

[00:43:15] **Dr. Benjamin Greenberg:** Jen, the last word? I know we're in our final seconds.

[00:43:24] **Dr. Jennifer Graves:** I think the other part of this question is, do you have to be on therapy indefinitely? And I think to answer that question, it does depend on which disorder you have but anti-MOG antibody disease, it's not clear if it's lifelong or not yet. Neuromyelitis optica disease many of us would be hesitant to stop therapy altogether. But to echo what we said earlier as we continue to learn about these diseases, these decisions have to be made on an individual basis. Which drug would be the best match for an individual patient in front of us looking at their needs for efficacy and their needs for safety?

[00:44:03] The age of the patient, the comorbidities of the patient, the pros and cons, I don't know if my panel co-panelists would agree that there's lots of individualized decision and we don't like to say we're committing you to one drug for the rest of your life. We get smarter and invent new drugs and there's always an opportunity to do better over time. But for right now it's a very difficult decision that has to be individualized to stop therapy.

[00:44:27] **Dr. Benjamin Greenberg:** Great.