Upcoming therapies for MOGAD and NMOSD

Long-term therapeutics

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[00:00:00] **Dr. Grace Gombolay:** It's my pleasure to introduce Dr. Hutto, who is an assistant professor of neurology at Emory University School of Medicine.

[00:00:10] He also serves as the associate program director for the residency program. He did his training here at Emory and then went off to do fellowship at Mass General Hospital in Boston. And we're very fortunate to be able to recruit him back here. He does have a lot of expertise in rare and neuro immune disorders.

[00:00:25] In particular neurosarcoidosis, which is what he mentioned earlier that have a lot of mimics and overlap with a lot of the conditions we're talking about today. But he also sees patients in the hospital. So, thank you, Dr. Hutto.

[00:00:36] **Dr. Spencer Hutto:** Thank you for having me. I guess the mic's working. Everybody can hear me okay. Yeah. So, thank you for having me. I really appreciate this opportunity to meet with you all. It's such an important opportunity, I think, for us to all come together and to hear from you as well about your experience. And that informs our, our own perspectives on diagnosis and treatment and where our research initiatives should lie.

[00:00:57] Because you all have just the perfect questions. And so, it's been really nice to hear. So, I, I have my disclosures are that I may talk about some medications that are perhaps. Off label, just meaning that not necessarily FDA-approved for treatment. And then I'm here as a volunteer essentially and I have no financial relationships to any of the medications that we're talking about today.

[00:01:21] Just wanted to make that clear. And so, we will be talking about the treatment of NMO. So, we'll briefly just go over what are the currently available treatments. We'll talk about why it makes sense to use those medications. So, we'll discuss really briefly about what goes awry in NMO and why certain medications were developed that target certain issues that have gone wrong.

[00:01:47] And then we will, we'll talk briefly about treatments in the hospital. We'll talk about some long-term treatments. And then we'll move on to just discuss briefly about some of the things that are coming down the pipeline or in development or at least as best as I could tell, through clinical trials.gov.

[00:02:01] And so I want to begin by talking about NMO. And I know that this slide is a little bit more pertinent for medical personnel, but I just, I wanted to have at least one picture besides my face in this talk. So, I've included it here. So, you will notice that this is the this is the antibody in NMO that is pathogenic and causes the problem.

[00:02:20] So this is something called aquaporin four antibody. So, Aquaporin four is actually just a water channel, a small protein in the brain. This antibody targets that water channel and then leads to a lot of the issues that, that we see in NMO. So, we're centrally focused on this antibody. But so, there are some treatments that affect that antibody.

[00:02:39] So if you've been in the hospital, you have NMO, and you have been treated with something called plasmapheresis, otherwise commonly called plex, that treatment actually takes out your blood. And included in that blood is this antibody. And so, you get rid of the antibody. And so that treatment targets that.

[00:02:54] There's another treatment called efgartigimod, which is, which currently being researched in in NMO that helps speed up the elimination of that antibody. So, it's like plasmapheresis except with all the without all the machinery plasma cells or B cells make the bad antibody. So, if you're on a treatment that depletes B cells, this is one of the cell lines that it targets.

[00:03:17] So it can kill B cells, and the B cells make the antibody. So, if you get rid of the B cells, then you don't have as many antibodies. So that's the thought there. This thing called IL six, interleukin six helps to generate B cells that make these auto antibodies. And so, there's a treatment called satralizumab particularly that kind of targets this sort of mal development in the process.

[00:03:39] And then there are some treatments available. Well, the antibody attaches to the water channel, and once it attaches to the water channel, it recruits in some other things that lead to damage and that is something called complement. So, there are some complement inhibitors that we're gonna talk about briefly today that address this piece of a puzzle.

[00:04:00] Okay, so I just wanted to begin by talking about some treatments available in the hospital. So, you all have probably experienced this really, maybe even actually whatever disorder you may have experienced this to some degree. So, I work principally in the hospital. So, a lot of my expertise is in diagnosis and acute treatment.

[00:04:17] And like Dr. Gole was saying I see patients with neurosarcoidosis in the clinic, which is a different disorder, but oftentimes can manifest with optic neuritis and transverse myelitis and a lot of things similar to what some of the other disorders do. But we treat people with steroids and so those are IV typically and it's called intravenous methylprednisolone.

[00:04:36] Usually we give that over three to five days and we give a certain amount based on how people do. So, if somebody returns back to normal after just three days, then maybe they don't really need five days. Like Dr. Kana was saying earlier is, you want to give as much steroids as a person needs, but not more than that because it's likely that they may need additional steroids in the future.

[00:04:55] And the total cumulative burden of steroids puts you at risk for adverse effects in the long run related to steroids. And so, we try to give as much as needed, but not necessarily more than that. And so it may be, typically somewhere between three to five days, but oftentimes not usually more than five days.

[00:05:10] But importantly it affects pretty much all immune cells. So, it yeah, affects them all. So, B cells and T cells and sometimes granulocytes as well. And then the plasmapheresis we talked about is a machine that will exchange your plasma, so it's called plasma exchange. So, it will take out your blood, and they will give you actually new blood, which does not contain the aquaporin four antibody.

[00:05:32] So it's trying to remove the antibody and that's something that's given as a session every other day for five days. When it comes to maintenance treatment and the importance of what we're talking about today in terms of being on a long-term disease modifying treatment to prevent attacks from occurring is oftentimes, it's oftentimes it's better to get ahead of it and prevent an attack or a relapse from happening because a lot of the disability is actually related to the attack itself, and so it's cumulative based on the attack.

[00:06:01] There's not clearly a progressive phase in neuromyelitis optica like there is in patients who have multiple sclerosis who may have a primary progressive phase or even a secondarily progressive phase. But with NMO, it seems to be like you have an attack and you can accrue some disability related to the attack.

[00:06:17] And that sort of stacks on top of each other every time you have an attack, depending on how well you bounce back from treatment. So, we keep that in mind when we think about, we need patients to be on a treatment, a good treatment that prevents attacks and they occur with some regularity here.

[00:06:31] So an average of 0.7 attacks per person per year if they're untreated, and then of course, an individual attack could potentially be severe. So NMO is perhaps one of the disorders that tends to affect people the most strongly whenever they even have a single attack. And so, we bear all these things in mind as we make our decisions about how we select disease modifying treatment, so that is otherwise known as DMT.

[00:06:56] And there are several options for these days. A lot of people have probably been exposed to rituximab or Rituxan. That was the treatment that was used historically from the time that NMO was first discovered. But since 2019 or so, we've got four new drugs that are FDA-approved.

[00:07:11] And so the treatment landscape for NMO has changed substantially. And so, there's a menu of options and patients may choose a certain medication for a variety of reasons. One may have to do with efficacy or how well the drug prevents a relapse from occurring. It's important to say that none of these drugs have actually been compared head-to-head, so it's not ever gonna be a situation where you can do an apples-to-apples comparison to get a good sense of which one is definitively the best in preventing a relapse from occurring.

[00:07:39] You may think about what the logistics behind the medications are. So, some of the medications may be self-administered, some of the medications may require you to go to an infusion center. Some may require you to be treated more frequently or less frequently. And then of course with any medication, there's always a potential for side effects.

[00:07:57] And those side effects are oftentimes different based on the medication and what you experience may be different than what somebody else has experienced. And so, if you go online and you read about medications or if you watch a commercial, even they talk faster than I do in terms of what could happen.

[00:08:13] And so it's just important to realize that, that you're being told about all of the things that have essentially ever been reported. And, it could be something that occurs in 10% of patients, it could be something that occurs in 0.001% of patients. So just bear that in mind when you hear about adverse effects.

[00:08:29] Some of those things can be more or less frequent and they may not happen to you or they might. So just note, note that. And then certain medications also require vaccination before you're treated with them. And so, there are reasons why you might select one thing as opposed to others. And so, I'm just gonna run quickly through the things that that we use currently.

[00:08:47] And so rituximab was the thing that we have always used historically. So, it was developed in 1997, so it was around actually before the antibody against NMO was discovered in 2004. And this targets essentially a certain protein on B cells to identify them for elimination. It's given via IV.

[00:09:07] You receive one treatment two weeks apart as the induction or loading phases and then you get one treatment every six months. The particular thing that we watch for is, we wanna be careful about giving it to patients who have hepatitis B virus because it can increase your risk for reactivation of hepatitis B.

[00:09:25] And we also screen for TB. And the most common side effects would be infections, particularly upper respiratory tract infections. This is not FDA-approved, so I just wanna emphasize that. But it was something that has been used extensively in NMO because it was the thing that was available that made the most sense based on what we just talked about.

[00:09:45] This drug gets rid of B cells; B cells make the antibody. Of course it was, something that we had available as soon as the disorder was discovered. And so, people reach for that kind of first and sometimes people are still on that medication. But now as of 2020, we have a B cell depleting antibody that is actually FDA-approved for neuromyelitis optica.

[00:10:06] It is known as inebilizumab. So, I'm sure you all have had some education and training and funny names. And so, today's another chance to just dive deeply back into that. But this drug also eliminates B cells except it targets a different protein on B cells, which might be present on more types of B cells than what rituximab covers.

[00:10:27] And so there's a thought here that maybe this drug more thoroughly depletes B cells of more different kinds rather than less. It's an IV drug. It's basically given similarly to rituximab. You get a dose once at time zero and then again two weeks later as the induction phase. And then you get a dose every six months thereafter.

[00:10:48] You have to screen for hepatitis B and TB. So, it's very similar in some ways to rituximab except maybe the spectrum of B cells that it eliminates is perhaps greater than rituximab. And that was the thought process there. And it is FDA-approved for NMO. So now I'm gonna switch gears and talk about IL six antagonists.

[00:11:07] So we spoke earlier about how this interleukin six, IL six, will sometimes lead to generation or proliferation of B cells that make these antibodies in a bad way. And so, can you target that specific signaling molecule to, to prevent these things from happening? And so that's what satralizumab does.

[00:11:27] It was approved in 2020. Again, it's FDA-approved, it's a subcutaneous medication, so it is different than IV. You could give this medication to yourself if you are okay with the self-administration of medications and needles and those sorts of things. That's the thing that, that oftentimes holds people up.

[00:11:42] And my own neurosarcoid practice, if people are like a little bit uncomfortable with needles, but if you're perfectly fine with that, then you know this medication that you can administer yourself. And so, you

give loading doses over the course of the first four weeks. And then it's a medication that you take essentially once a month.

[00:11:58] And then there are some side effects that are most commonly are headache, upper respiratory tract infections, nausea and joint pain. And we screen for hepatitis B and TB just like we did with the other medications. But we also have to keep an eye on patient's liver function test. And so, keep that in mind.

[00:12:13] The really interesting thing to note I think about satralizumab is that the present moment, it's a medication that's approved for pediatric patients who are older than 12. And so, there are a lot of medications that are coming down the pipeline. We are examining the possibility of using medications that we have approved for adults in pediatrics, but satralizumab is the one that, that is approved for patients who are at least 12 or older.

[00:12:36] So it's an option in that age group. Now I'm gonna move on to talk about complement. So, these antibodies, once they fix to that water channel molecule that we were talking about, it recruits complement to cause problems and cell damage. And so, the complement inhibitors try to block that issue.

[00:12:54] And so Eculizumab was the first FDA-approved medication for NMO. It was available in 2019. It's a medication that you give IV, you have to have some loading doses every week for the first four weeks or so. And then you get maintenance doses every two weeks. I think the sort of; people will commonly experience a lot of the same side effects that are true for kind of the other medications.

[00:13:15] But the particular thing to be aware of is it could put you at risk for meningitis. And so, we want patients to be vaccinated for meningitis beforehand and sometimes be on antibiotics that would prevent meningitis from occurring. Particularly if there's not an opportunity to get a person fully vaccinated, say if they present into the hospital and for some reason, we have to use that medication sooner rather than later.

[00:13:37] Maybe there's no time to fully vaccinate. And so, we keep that in. So, this medication was given every two weeks which is fairly frequent. But they have since developed a new complement inhibitor that's ravulizumab, that's given every eight weeks. And so, it's nice in the sense, we talked about, how do you think about which drug you're gonna take?

[00:13:58] And logistics may be one of those factors. And this is a medication that's given every eight weeks instead of every two. So, it's much more spaced apart and probably works with everybody has a busy life. And so, it's a factor sometimes. But the risks the side effects and sort of the risk profile include for meningitis are, things that we bear in mind just like we, we have with Eculizumab.

[00:14:20] And so now I want to just talk about some of the clinical trials, and I guess I didn't finish, fully finish this slide with my slides. I've had still on it, but I was busy looking at clinical trials.gov and editing that slides appropriately. But I wanted to bring you all up to speed on some of the things that are currently ongoing in terms of investigations that I've found here.

[00:14:41] And so what I'm gonna do is talk about, what the name of the drug is, what sort of population it's being investigated in. There's a clinical trials ID number here. So, if you have some interest in looking at this in your own time, you're certainly available, you could snap a picture of it or something.

[00:14:57] And with this ID number, you can find the clinical trials webpage. So, this is this was investigated

and it seemed to have been stopped early. Only five patients were enrolled, but they were investigating Eculizumab, which again is a compliment inhibitor in patients between the ages of two to 18.

[00:15:17] You had to be a certain, a certain weight but it's just, I think they weren't able to recruit enough patients. And so that trial was re terminated earlier. Satralizumab, like we discussed earlier, is approved for patients who are 12 years or older, but there obviously is a portion of children who are, who haven't reached the age of 12.

[00:15:39] And so they're doing a clinical trial looking at patients who are younger than 12. So, between the ages of two and 11. Essentially this is a study that, that is actually is more so looking at the pharmaco dynamics of satralizumab. So, we give the person the treatment, we do some testing to figure out, how much drug is absorbed into the system, how quickly it's eliminated those sorts of factors.

[00:16:06] But as a part of this study, they are also assessing for, of course, they're gonna, they're gonna wanna know, like, how often do people have relapses and what was their experience in terms of efficacy? So technically the study is more so looking at, of course kids are very different than adults.

[00:16:22] And they're changing every year. And so how much medication does a person really need, changes year by year. And so, the study is more focused on that, but they'll be looking of course at, how well patients do you have to be positive for the Aquaporin four antibody and at least 10 kilograms.

[00:16:40] And having had one attack in the preceding year to enroll in this trial. Of course, they wanna enroll patients who, who have recently been active with NMO, because when they give you the medication, they can say like, oh, it stopped that. So, if you had been free of attacks for a prolonged period of time, then it may or may not be because you received a medication.

[00:16:58] But if you were recently very active, then maybe that's something that can you, you can say like, oh the drug really had the effect here in stopping the disorder. And so, this is something that's coming down the pipeline. It's 48 weeks and there's an option to extend.

[00:17:13] In Eculizumab, we spoke about this earlier, it's a medication that gets rid of B cells targeting that protein called CD 19. And it's being run in various places across the United States. In California at Loma Linda University and University of California San Diego. It's also being investigated at Massachusetts General Hospital.

[00:17:33] So I'm just saying Mass Gen for short, but that's in Boston. And so those are the sites where this is taking place. And patients who are essentially less than 18 years old down to the age of two who have the antibody and are at least 15 kilograms are eligible so long as they've had two attacks in the last year.

[00:17:53] And this also is a study that is mainly looking at yeah, drug concentrations, how quickly it's eliminated, how safe is it to use in the pediatric population. But I'm sure they'll be interested, of course, to know like how well it works. And so, it's, the timeframe is up to 80 weeks essentially being enrolled in the study.

[00:18:12] And so that's being extended to children. The same is true for ravulizumab. So, we spoke about ravulizumab earlier in terms of like, extended sort of dosing. But in kids it might be different. So, in adults we spoke about how this is a complement inhibitor, it's given every eight weeks.

[00:18:31] And in children it seems like it depends a little bit, I think, on weight in terms of, is it gonna be given to them every four weeks or every eight weeks once they get outside of the loading dose loading doses. And so, this is gonna go on for 50 weeks, but with the option to extend use of the medication for actually 104 weeks.

[00:18:50] And so this will be, this will be interesting on the clinical trials website. I cannot find exactly what ages this pertained to because it said something like children and young adults and older adults. And I don't know exactly like how they define that especially as it relates to the children part.

[00:19:06] But the name of studies actually ravulizumab for pediatric NMO. And be interesting to see how well this works. And of course, the same things that we discussed before apply, patients need to be vaccinated against meningitis. And then finally for kids there's a lot of observational studies ongoing, just getting a better understanding of how these disorders actually affect children and does it affect children in the same way that it affects adults.

[00:19:34] We talked earlier about how MOG, there's oftentimes a dichotomy in terms of how kids are affected versus how adults are affected. We're trying to define that more precisely in NMO. And so, you'll see here there are at least two studies that are investigating \that include multiple clinical visits and obtaining, essentially blood samples to better understand this process.

[00:19:53] And so having these types of studies are important in terms of designing treatment studies because if you don't really know exactly what you're up against, sometimes it's hard to design a treatment that works most effectively for it. And so, these are laying the groundwork for future investigations.

[00:20:09] So now I'm gonna switch to talking about adults. And I would say this is probably, this probably one of the more interesting studies that I think are coming online. And so, when I look at clinicaltrials.gov, I were, I was looking at studies that were either actively recruiting or are being organized and not yet recruiting.

[00:20:31] And at Mass General Hospital in Boston, they are interested in apparently running a trial comparing the medications, all the medications that we commonly use in NMO against one another. And so, we've spoken about rituximab, eculizumab, ravulizumab, inebilizumab and satralizumab; talked about all those drugs.

[00:20:52] And they're gonna be, essentially recruiting patients and then randomly assigning them to one of the treatments and seeing how well they work because this has not been done before. And so, it's always been very difficult to say how well agents compare against one another.

[00:21:06] And so this is for patients who have the Aquaporin four antibody. They're at least 18 and they don't have certain comorbid disorders. And those largely rely on or have to do with infections. So, hepatitis and TB and anything that might cause a person's immune system can be deficient otherwise.

[00:21:24] So whatever disorder, HIV will be included. But this is a study that is anticipated to take at least two and a half years, if not up to four years. And I think they're not recruiting yet, but it's something that is posted and potentially on the docket. Very interesting to me is how do we treat patients acutely in the hospital, and what can we do to treat them more effectively upfront?

[00:21:46] So we talked a lot about how attacks for NMO can be very disabling with just a single attack. And how do we, how do we treat that more effectively from the get-go? And efgartigimodis a medication that sort of simulates the effect of plasmapheresis. So basically, what it does is it prevents the recycling of the bad antibodies.

[00:22:07] So you have antibodies and your body can recycle them and reuse them, which is overall a good thing. If you have antibodies that aren't causing you problems, but if you have antibodies that are causing you problems, you wanna speed up the elimination of that antibody. That's essentially what plasmapheresis does, but efgartigimod prevents the recycling of antibodies including the Aquaporin four antibody.

[00:22:30] And so it would simulate the effect of plasmapheresis, but it's a medication that you just give to a person. So, this is really interesting because not every center has the capability of, hospitalizing somebody for two weeks and giving them plasmapheresis and they don't have the machines, and they don't have the transfusion medicine team to come do that.

[00:22:46] It's a very labor-intensive process, and this is simply a medication. And so, this is something that's also being run in Boston and it'll be very interesting to see how well it works. And importantly, this study is gonna be conducted in a way where patients will get steroids in both arms of the study, except in one arm of the study they'll also get efgartigimod.

[00:23:05] And if either arm, if patients don't do well, then they go on to get plasmapheresis. So, it's not like plasmapheresis off the table. It's just that we're seeing essentially if efgartigimod can prevent the need for that. And that may be good for many reasons, including like reduce, reductions in hospital stay and, the speed with which we are at able to administer a highly effective therapy may be different.

[00:23:27] Because if you've ever had plasmapheresis, you'll probably recall, you've got to get some special type of central line in place. We've got to consult a team; we've got to get the machine to the bedside. It's, there are a lot of steps to work through, whereas medications are oftentimes given more simply.

[00:23:41] This is something of interest. There is a study on ravulizumab safety in pregnancy. And gathering additional data I think is important, particularly in this population where, how safe are these drugs in pregnancy? And so, this is this is another study oriented in that direction that's anticipated to go on through July of 2034.

[00:23:59] So it's a registry. You'll see the number here. If this might apply to you, then it's worth maybe making note of that. And registering yourself if an event, a pregnancy event happens while you're on ravulizumab, essentially. And I will say that, so we talked mostly about studies that are happening in the United States, but right now I'm transitioning to studies that are occurring in China.

[00:24:23] And so China has far outpaced the number of clinical trials that we're performing in NMO in the United States, but they're looking at a wide range of medications to, to use in the treatment of NMO in terms of long-term disease modifying treatments. And so those things include a lot of different drugs than what we currently have employed in the United States.

[00:24:44] So drugs that affect the, something called a Bruton tyrosine kinase. Also, B-cell activating factor is a signaling molecule that sort of activates B cells. So, trying to get ahead of it from that angle. JAK inhibitors, this neonatal FC receptor antibody beta. I haven't practiced the pronunciation of this one yet, but batoclimab is similar to efgartigimod in, in kind of a way.

[00:25:10] And then CD 38 is a protein present on B cells. And so, it's targeting that from a different angle than say, CD 19 and CD 20 antibodies do. And then finally there's a medication called CAR T, which is basically teaching your own immune cells to identify bad immune cells, if you will, to eliminate them from the body to quit causing the autoimmune problem.

[00:25:34] And then finally, in, also in China, they're looking at efgartigimod, which we spoke about we're doing in the United States, but using Eculizumab, the complement inhibitor to treat attacks in the hospital. So, inhibiting complement in the setting of an acute attack. Could that really be helpful? They're looking at that.

[00:25:52] And then finally there's a thing that's different than plasmapheresis called immuno absorption which does not exchange your blood actually. So, it does similar things as plasmapheresis. It filters, it filters

your blood, it filters out antibodies, and so it tries to filter out the bad antibody without the need to give you a plasma donation or if that makes sense.

[00:26:14] And so it's similar. So, they're looking at that. And with that, I will end, I need to turn it over to Dr. Gombolay. But thank you very much for your attention.

[00:26:23] **Dr. Grace Gombolay:** Hi everybody. I have the pleasure to be discussing about the current clinical trials in MOGAD as we discussed earlier, there's currently no FDA-approved treatments, and right now different people are doing different things just because we just don't really know what works best. Here my disclosures, I do part-time salary.

[00:26:41] I get part-time salary support as a consultant to the CDC for AFM review. I'm an associate editor for the Annals of the Child Neurology Society, but I get no honorarium for that. All of this is gonna be some off-label use treatments that might be discussed. And I have no financial ties to any of the companies that are discussed today.

[00:26:56] This has been touched upon already, but this is a schematic, a diagram of MOG of what it looks like. So here on the left you see this blue neuron. This is a brain cell, and these yellow little pockets here are the myelin, the covering of it. I liken it to like computer cords. And there are phone cords, right?

[00:27:13] There's like an insulation of wiring and things like that. And so, what happens is that there's different proteins on the surface of it. So, MOG is this little light purple guy here. It's on the surface. It's only expressed in the central nervous system, meaning only in the brain and in the spine.

[00:27:29] It's not expressed in any of our peripheral nerves, meaning the nerves that come out of the spine into our arms or legs. It only makes a very small proportion of the myelin. You can see there's tons of other proteins in here but it's on the surface, meaning that it probably is more accessible and easier for the immune cells to come in and to restart reacting to it.

[00:27:48] And so what happens is that we have these MOG antibodies that sort of appear that are generated by our immune system that are targeting these surface proteins. We touched upon this already. Dr. Huro did and alluded to this, but there is clinical trials.gov. So, if you're interested, hey, what is the most current clinical trials studies that are ongoing right now?

[00:28:09] You go to this website, and I just have a screenshot here of what it looks like. When you go to the website, you type in your condition and disease. You can type in whatever you want. Here. Here I happen to include type in MOG and the other place just to put a plug in because we are here at the SRNA. the SRNA does a really good job of keeping their website updated too.

[00:28:27] So if you go to the SRNA website, which is we are srna.org or go to the research tab and then go to the clinical studies and trials. They have a really good up to date website also for the study. So, if you want a quick shot looking at that, you can always go to the SRNA website. I'm gonna talk about, focus on the two main clinical trials that are ongoing in the US currently and then touch upon some of the more external trials that are happening.

[00:28:53] The first one is called the cosMOG Clinical Trial. And here's the clinical trials number if you're interested. This treatment is called rozanolixizumab. So, we have lots of "ibs" and "mabs" and things happening today, and this is a placebo control trial. And what that means is that some participants in the trial will get a placebo, so not really the medication itself, and some of them will actually get the rozanolixizumab.

[00:29:17] What happens is it's a double blind. And what that means is that both the participants and the investigators in the study, meaning that the doctors and people who are doing it, they don't know which treatment you are getting. And the idea for that is that as we look at monitoring outcomes and how people are doing, we really wanna know, is this medication working or not?

[00:29:36] And then there's something called an open label extension, meaning once the study is over something you can be eligible for the medication afterwards. Some of the inclusion criteria include being an adult. So, between 18 and 89 years of age you have to have a confirmed diagnosis of MOAD, and then you have to have relapsing MOGAD.

[00:29:55] So this is not for the patients who have a single episode and don't have another episode. This is for those who have had an episode, a relapse, meaning they had a second event over the last 12 months prior to the inclusion being recruited for this study. And then you have to have a positive serum, meaning in the blood MOG antibody test using a cell-based assay.

[00:30:16] And so there's different types of assays out there for MOG antibodies especially at the, we talked about the Mayo Clinic earlier. Again, no financial ties to them but they do a cell-based assay, so you wanna make sure that's where the antibody testing is being done. And then for this particular trial their participants may not be on any other immune treatments.

[00:30:36] Dr. Hutto alluded to this of the mechanism of action of how this works. This is also very similar to what he had talked about earlier. So rozanolixizumab also binds what's called the neonatal FC receptor. And so, this also works very similarly, plasma exchange where it's clearing your antibodies.

[00:30:53] So here what's happening, what we're looking at here is here's a cell, here's your little y, the upside-down Y is your antibodies as they're floating around. And what happens is this triangle, which is this neonatal FC receptor, it binds to the antibodies to help preserve them, to keep them in your body and recycles them.

[00:31:09] However, what happens is the way that rozumab, as I'll call it from here on out, which is here hereby, R. R binds this recycling system. So, then what happens is that the antibodies then actually get cleared by the body. So, it's very similar to the mechanism as plasma exchange. Most common side effects for rozumab include headache, upper respiratory infections, and urinary tract infections.

[00:31:30] And even after the first dose, about approximately 80% of every, your antibodies are actually cleared. But it seems that so far, no major serious infections have occurred with it. So, if you are interested in the list of sites involved, again, go to clinical trials.gov or again, wearesrna.org website to see if there's a site closest to you if you're interested in being part of this study.

[00:31:52] The next study is called meteoroid. This is looking at satralizumab, which again, Dr. Hutto had also talked about earlier, so I'm not gonna go in too many details about this. This is also a placebo-controlled trial, meaning that some of the participants will get satralizumab, some of the participants will get what they think is satralizumab, but there's actually no medication in there.

[00:32:10] This is also double blinded, meaning again, both participants and researchers will not know what medication that they're getting. This age inclusion is actually 12 years or older. So, some of our older children are gonna be included in this study. Again, this has to be a confirmed diagnosis of with relapsing disease.

[00:32:28] So history of at least one MOGAD relapse. So, a second attack in the 12 months prior to being enrolled or being screened for the study, excuse me. And then, or at least two more attacks in the past 24

months. You can be on current certain immune treatments for this particular study. The way that Satra works, which again, Dr. Hutto had a very beautiful slide earlier.

[00:32:48] But just to remind you this sort of targets that interleukin six or IL six is a very common pro-inflammatory cytokine, meaning the cytokine a chemical in the body that sort of like revs up your immune system. And both satralizumab and tocilizumab, which some of you might be familiar with because we have used that in certain diseases, including in MOGAD target this IL six signaling.

[00:33:13] So IL six is important for B-cell. And activation B cells are what makes antibodies. So, the thought is that the, by blocking the IL six, you're actually affecting the B-cell, so you're not making the antibodies. And also, IL six is thought to be really important for what's called disrupting the blood-brain barrier.

[00:33:30] Your brain and your blood vessels and your astrocytes, all these different cells in your body protect different things from getting into the brain. When you have inflammation, you have increased IL six, it pokes holes in there and then that's how you start getting a lot of your immune cells and antibodies to get in there.

[00:33:49] More common side effects for this medication include headache, fatigue, rash, again, increased risk of infection, but that's true for all of our immune treatments that we give with maybe exception of intravenous immunoglobulin, IVIG. And it affects the liver enzymes. And again, if you're interested in which sites are involved with the study, go ahead and go to clinical trials.gov or the SRNA website and you'll be able to know which sites are enrolling if you're interested in that.

[00:34:16] I was gonna take a few minutes to talk about some other studies that are happening outside of the US. This is an azathioprine, which is actually a very old medication. It's a medication used by mouth often used in other it has been used in the past in other neuro immune conditions. It used to be in the past for multiple sclerosis before we had other options available.

[00:34:35] And it's a very cheap medication. So, in other countries that don't have access to the same medications that we do here in the US, this will be an option for them. Like I mentioned, it's used in neuroinflammatory diseases. And so, this is a clinical trial occurring in France. And this is actually to see this medication prevent relapses after the first attack.

[00:34:56] This is the big million-dollar question that a lot of you have talked about. Who gets a relapse? Why does a relapse occur? Do we need to treat everybody? And currently the thought is no, we don't treat everybody after the first attack with a few exceptions. because the thought is only half of you are gonna have a second attack in MOGAD, so we don't need to give you a lifelong treatment for that.

[00:35:17] But this particular clinical trial is that if we put people on azathioprine, does that prevent a second attack? This is also a double-blind study, meaning that both the participants in the study and the researchers don't know if they're getting azathioprine or something else, or just basically no drug.

[00:35:35] It's a placebo control trial. So, speaking of China, this is one of the studies occurring in China. This is looking at safety and efficacy of tocilizumab in MOGAD. Tocilizumab is a similar action to satralizumab like I talked about earlier and interfering with the IL six pathway by blocking IL six receptor.

[00:35:54] And this study is looking at tocilizumab plus steroids or prednisone or steroid only. You have to have a confirmed diagnosis of MGOAD to be enrolled in this study. And again, have a history of relapsing disease. So, this is, if you've had relapses, does this help you or not? This is randomized, meaning that the computer basically picks who gets which medication.

[00:36:16] It's open label so people actually know if they're getting the tocilizumab versus not. And then, like I mentioned, this is in China. Finally, I was gonna touch briefly about this. This is CAR T-cell therapy. This is an immune cell therapy. I get questions about this quite frequently in the clinic or when I'm out and about, about, what kind of immune cells, what kind of stem cell treatments are available.

[00:36:39] Long story short, there's no stem cell treatments available for our neuroinflammatory diseases with the exception of MS. There has been stem cell transplant, but that's a different talk. So, this is something called CAR T cells. So, CAR T cells have been developed, especially for treating cancer.

[00:36:55] And what they do is, this is a very fancy diagram and that T cells are part of your immune system. We talked about B cells that make antibodies. T cells are like the active infantry men that actually go out and do the killing. And so, the B cells help provide a signal and the T cells actually go out and attack the tissue.

[00:37:13] So what happens in CAR T-cell therapy is that they actually remove the T cells from the patient. And then they in the lab will actually change the target of what the T cells will target. And so, the thought is that if in this particular case this is talking about cancer cells, if you target have the T cells target cancer cells, it can bind to the cancer cells and kill them at a microscopic level.

[00:37:33] There's talk and interest in if you do T cells against your MOG B cells, can they go out and kill the MOG B cells. There is actually a trial in China looking at CAR T-cell therapy in that. This is short and sweet. The biggest takeaway is that there's a lot of studies in a lot of clinical trials ongoing in MOGAD I didn't mention.

[00:37:56] There's another studies that people have been talking about that are, that they're interested that are gonna hopefully come out and then, and start enrolling in the next few years. But if you're interested in the latest research clinical trials.gov and then go to the wearesrna.org website. Thank you for your attention. And we have a couple of minutes for questions for either myself or Dr. Hutto. So, thank you.

[00:38:19] **Audience Member:** Thank you. So, my daughter has MOGAD. She was diagnosed at three, she's now almost 10. At the time I know research has changed and it was two years treatment. Now it's four years treatment. But is the thought process, as you said, lifelong treatment now for relapsing MOGAD?

[00:38:39] **Dr. Grace Gombolay:** Yeah, that's a great question. And hopefully we'll have some more time to explore that later on in the panels. But something that I talked to my families about is that we're still learning more. And for me it's about how severe were your attacks in the past. because if there is a little bit milder and you had multiple, and you recovered pretty well in between, I might consider you weaning off a little bit sooner.

[00:39:00] But if you had more severe attacks where you're a bit sicker, you're required some more stays in the hospital, you haven't recovered back to your normal self-prior before, I might keep you on a little longer. So, two to four years-ish, maybe longer. And if you're an older, like an adult age, they tend to do more longer term. But I'm gonna defer to my adult colleagues for, to answer that question.

[00:39:22] **Audience Member:** I noticed you were talking about the French study that they're doing. Could you explain the thinking behind adding in prednisone with the tocilizumab?

[00:39:33] **Dr. Grace Gombolay:** Yes. I wasn't part of the clinical trial design, so I don't know for sure how they decided on doing that. But we know that, let me backtrack here. So, we talked about how steroids are quite effective in MOGAD. There are certain places around the world, especially if they don't have access to, for example, IVIG or it's harder to get, they'll advocate for a longer steroid course. So, there's certain countries

we've had lots of discussions about them where sometimes people where will be on steroids for six months or even longer if they have MOGAD or to prevent that early relapsing phase.

[00:40:08] And so my yes, of why they're doing to tocilizumab plus steroids versus steroids alone is to say, I'm wondering if that practice in that country, because it's I think that one is China. But anyways, I think their practice may be that they do steroids longer, so they're trying to see does adding to Tocilizumab help prevent relapses better? But I don't know the exact answer to that. That's a good question.

[00:40:30] **Audience Member:** Thank you. I it's a good follow up is that, there's also the UCB clinical trial for rozanolixizumab, so they're here to answer any questions about that. But thank you. Yeah, thanks.

[00:40:45] **Dr. Grace Gombolay:** Okay. We have a question over here.

[00:40:49] **Audience Member:** Thank you. Acknowledging that clinical trials or it's important because that's how things get advanced. Can you provide, I don't know, tips and guidelines for us to consider if we think about participating in a clinical trial?

[00:41:11] **Dr. Grace Gombolay:** Yeah. That's a really important thing because clinical trials, while they're important, they're really involved and I think a lot of the study design and a lot of the companies and the investigators, the people who are running the trials, I think they've been trying to be thoughtful of that. because I think in the past, we some that sometimes you have to do it this way, right? Because certain clinical trials, you check in with the participants.

[00:41:33] So the people who enroll in the clinical trials called the participant. So, participants, they have to come in for every so often for assessments, for blood draws, because we wanna explore, are there things in the blood that we can look at to help us guide and treatments and things like that.

[00:41:49] But it can be cumbersome, it can be hard to travel. Just our experience here in Atlanta, right? Traffic, I live less than two miles from here, but sometimes traffic, it can be, it takes me 20 minutes to get home. Like I could walk faster than, drive sometimes. because traffic here in Atlanta can be horrendous.

[00:42:06] And so I just think about people who are coming from further away. Like, it just makes it hard. So, I know some studies have thought about, what is look looking like remote monitoring, meaning like remote check-in, meaning that you don't have to travel. A lot of studies do provide, accommodations for transportation and they'll provide, give, giving you money for being part of the trial because we understand it takes a lot of time and energy and all of that.

[00:42:32] And so, I think weighing, what does your time look like? What are the, all the things of the trial look like? Is this something that you can or cannot do? But just take a look, talk to the person who's enrolling you. Talk to the companies that are, see if there's a way to work around these.

[00:42:48] You're like, oh, this little piece is the thing that would make it hard for me. Let them know. because even if it, that makes it hard for you to enroll in this particular trial, they'll keep that in mind. Okay, the next trial we had, a lot of people said this was made it really hard for them to enroll. What are some creative strategies?

[00:43:03] We can go around it. They have it where some trials, they, the nurse will come to your house to come do the blood draw, for example. So, there's lots of different creative ways that we can do it. I hope that helps in answering your question.

[00:43:15] **Dr. Spencer Hutto:** I'll just add one other thing really quickly. I think there's a big difference almost in talking about like MOG antibody disease versus NMO for instance because with NMO we do already have, four FDA-approved treatments. And so, there's been a lot of really good research in terms of long-term, disease modifying treatment in that disorder. But if your disorder is perhaps something where there's not quite as much known about it and what we know about treatments that we have repurposed to treat this rare disorder that are not FDA-approved.

[00:43:45] If those things are known to perhaps like not work super effectively, then that may also kind of factor into your decision. because one of the things we've learned about MOG is that, a lot of the medications that we have attempted to repurpose that are used in other disorders may not be quite as effective in MOG, even when you compare.

[00:44:04] Like it, it should make sense that certain medications should work well in MOG because they've worked well in other disorders that have a similar underlying cause. But may not actually, like we have noticed, have not worked too well in, in MOG. And so, you may also just keep that in mind.