The Latest in Treatments from an Adult and Pediatric Perspective

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[00:00:02] **Julia Lefelar:** Hello, everyone and welcome to a collaborative MOG cast with the Siegel Rare Neuroimmune Association titled, “The Latest in Treatments from an Adult and Pediatric Perspective.” Today, we're speaking with Dr. Elias Sotirchos and Dr. Grace Gombolay.

[00:00:16] My name is Julia Lefelar. I'm the Executive Director and Co-Founder of The MOG Project. We're a U.S. based nonprofit organization devoted to raising awareness, advancing research, and providing support and advocacy for the MOGAD community in the hopes of finding a cure. We'd like to thank our guests, the SRNA and the MOG Squad for their contributions to this MOGscast. So, I'm really excited to introduce GG deFiebre of the SRNA as our special collaborator. GG?

[00:00:50] **Dr. GG deFiebre:** Hi, thanks Julia. I'm GG deFiebre, Director of Research and Programs at SRNA, the Siegel Rare Neuroimmune Association. SRNA is a nonprofit focused on support, education, and research of rare neuroimmune disorders and you can learn more about us on our website at wearesrna.org. This MOG cast is being recorded and will be available on both our and the MOG Project's websites, Facebook pages, and YouTube channels. If you want to submit questions, feel free to do so by submitting in the Q&A area of this webinar.

[00:01:26] **Julia Lefelar:** So, we're going to be answering some community questions, time permitting and any other questions that are unanswered are going to be answered in a follow-up MOG Blog.

[00:01:36] **Dr. GG deFiebre:** And so first, we'd like to introduce Dr. Elias Sotirchos from Johns Hopkins. Dr. Sotirchos is an Assistant Professor of Neurology at Johns Hopkins University and Director of the Johns Hopkins Neuromyelitis Optica Center. He earned his medical degree from the National and Kapodistrian University of Athens. Sorry, if I did not pronounce that correctly. Subsequently, he completed his Osler internship and neurology residency training at the Johns Hopkins Hospital, serving as chief resident in his final year. He then pursued advanced clinical and research training in neuroimmunology at Johns Hopkins as a National Multiple Sclerosis Society Sylvia Lawry Fellow.

[00:02:14] Dr. Sotirchos specializes in the diagnosis, management, and treatment of neuroimmunology conditions that involve the central nervous system including MOG associated disease, neuromyelitis optica spectrum disorder, and multiple sclerosis. His research involves the application of imaging techniques including retinal optical coherence tomography and brain magnetic resonance imaging to study these conditions. His work especially focuses on visual pathway involvement in neuroimmunology conditions and aims to characterize mechanisms of neurodegeneration and to identify novel biomarkers for predicting and monitoring the disease course and therapeutic response.

[00:02:54] **Julia Lefelar:** Thanks GG. And we're also really excited to welcome Dr. Grace Gombolay who is an Assistant Professor at Emory University and the Director of the Pediatric Neuroimmunology Clinic at Children's Healthcare of Atlanta. She attended medical school at Johns Hopkins, pediatric neurology residency at Mass General, and a pediatric neuroimmunology fellowship at Harvard including at Boston Children's and Mass General Brigham. She serves as a part-time CDC consultant for acute flaccid myelitis surveillance. Her research interests include rare neuroinflammatory diseases that can affect children, including MOGAD.

[00:03:35] So she's in a co-leading in multi-center prospective Patient Neuroinflammatory Registry called CONNECT, which stands for CONquering Neuroinflammation and Epilepsies ConsorTium. Welcome. And thanks everybody for joining. GG, thank you and we'd love to have you kick off this discussion.

[00:03:57] **Dr. GG deFiebre:** Sure, thanks so much. And thank thanks so much, Dr. Gombolay and Dr. Sotirchos. So, to start, Dr. Sotirchos, can you give us a definition of acute treatments versus preventative treatments in MOGAD and why it's important for patients to know and understand the difference between these two?

[00:04:16] **Dr. Elias Sotirchos:** That's a great question. And so, I think that in MOGAD, we generally think of MOGAD as being a relapsing disorder. So characterized by discrete attacks that can lead to neurological dysfunction. And depending on the area of the central nervous system that the attacks involve the manifestations will correlate to that. So, if it's the optic nerve, it can lead to vision issues. If it's the spinal cord, it can lead to issues with limb weakness, sensory dysfunction, gallbladder dysfunction, it's the brain, it can have a whole host of manifestations.

[00:04:49] And so with these discrete attacks, the mainstay of the treatment approach is to try to use treatments that will rapidly address the inflammatory process that is going on in order to limit the amount of damage that can accrue from a single attack. And so generally, when we think of acute attacks and treatment, the first line therapy in general is going to be high dose corticosteroids. So typically, intravenously, although often we can use bioequivalent doses orally. So, it's very high doses of prednisone that have been shown in some studies to be equivalent to the high doses that are used that would be typically over 3-5 days.

[00:05:39] And then there are other treatments including plasma exchange and sometimes intravenous immunoglobulin. Those are really the main ones. These second ones are typically used as second line treatments if it's a severe attack or if there's an inadequate response to steroids. Now, one thing I think though is that sometimes acute and maintenance treatment, there's not necessarily a hard line dividing them. One can morph into the other because for example, with the attack, as I said, we do these high-dose pulse steroids for 3-5 days. But then we often do a prednisone taper which might even be prolonged for months. And that's a combination of -- it's a bridge essentially to both treat the attack and the tail end of the attack as inflammation is coming down, but also to prevent an attack from occurring during the recovery from the attack and potentially also bridging over to a longer-term maintenance therapy.

[00:06:35] And so longer-term maintenance therapies are those that are used continuously. In general, somebody may be on them for years in order to prevent an attack from even happening in the first place. And there are several treatments. And I think that there are questions today where we're likely going to go over a lot of these treatments. But this is another area where there's a bit of an overlap because intravenous immunoglobulin, which can sometimes be used as rescue during an acute attack because it does have a relatively quick onset of action can also be used with maintenance infusions typically every few weeks or every month for relapse prevention as a maintenance therapy. And so those are, I think if we grossly try to distinguish the two, but I think it's a point to bear in mind also that it's not black and white, there is a bit of a gray zone where some of

the acute treatments can become a maintenance treatment and there's a bit of a gray zone between them.

[00:07:33] **Julia Lefelar:** Thanks. That's a great answer. And so, I want to hear from Dr. Gombolay and then actually both of you. So, I'll start with Dr. Gombolay. So, first of all, does that hold true what he said in pediatrics? And also, how does one go about this if you're a physician treating somebody? How are those choices made? And so, I'd like to hear this from a pediatric versus an adult perspective. So, Dr. Gombolay, please?

[00:08:05] **Dr. Grace Gombolay:** Yeah. So, a lot of the data that we have in MOGAD, fortunately, we are having more data in kids, but a lot of it is from the adults. We learn a lot from treating an adult. So yes, we do the same thing in the acute phase during the acute attack of doing the steroids versus intravenous immunoglobulin (IVIG) versus plasma exchange. And then if they're really severe and they are refractory to those, then I may add in another agent, something like tocilizumab which blocks IL-6, which is an inflammatory cytokine. And sometimes I've used that in the acute phase if they're really sick.

[00:08:09] This is different between different practitioners and different physicians of how they'll decide. For me personally, everyone gets steroids. And then I will consider if they're really severe, I might do plasma exchange first before doing the IVIG and the reason for that is that even though IVIG does work, if you're thinking about doing plasma exchange, plasma exchange actually removes the IVIG, it removes the immunoglobulin. And so, it seems to somewhat negate the effect. And so, what I personally will do is if they're really severe - and so my definitions of severe can be, "Are you in the intensive care unit because you have flaccid weakness in all four extremities. Do you have brain stem involvement? Are you completely blind in an eye from optic neuritis?" And I would consider doing plasma exchange first and then once the plasma exchange is done, then do the IVIG. But I'm curious what Dr. Sotirchos does, how he decides.

[00:09:46] **Julia Lefelar:** Yes, please, Dr. Sotirchos.

[00:09:49] **Dr. Elias Sotirchos:** It's tough because there's not a one size fits all and there's a lot of individual provider end of preference for these things. I mean, generally, we will start with IV steroids, and I think that that's important that steroids really are the cornerstone. I would pretty much never skip steroids because I have seen that happen sometimes. But there are some situations where you might need to skip steroids. Adults who have very bad, let's say diabetes or people who have severe osteoporosis, I've seen situations like that, and people have had prior what's called avascular necrosis where they can have bone issues occurring due to chronic exposure to steroids. So, you might reach that and be in that situation, but it's rather rare.

[00:10:40] So steroids are typically going to be first line. I think to some extent, it might depend also on the patient's history. Sometimes patients have already had multiple relapses and you can use their own history to guide it because you might have a history of a patient who did respond well to PLEX or responded well IVIG in the past. That's something that can sometimes be used to inform. I think that plasma exchange definitely is something that we often depending on the severity on how people do with steroids we end up using.

[00:11:16] But I think that one thing is that there's a lot of uncertainty here and there is no right answer I have to say because sometimes we see people with just steroids respond very nicely and it might take a few days and all you have to do is wait. But one situation is that often we don't want to have the regret afterwards of saying, "Oh, we waited for the steroids, and they didn't work. And what if we had done plasma exchange earlier?" But I do think that this is something that there is some utility for further studies to actually assess what the optimal timing of plasma exchange is in which cases might benefit more as well. But there are multiple things to take into account.

[00:11:53] And then just one last thing I wanted to mention regarding plasma exchange also is that there are some considerations. Overall, it's a relatively safe procedure, especially people who are otherwise healthy. We have to bear in mind that sometimes the people who have bleeding risks and things like that, there might be some risk for potential adverse effects from the plasma exchange itself.

[00:12:16] **Dr. GG deFiebre:** Thank you. And so, you mentioned some comorbidities that might exist, that might preclude someone from getting--that they wouldn't be able to get steroids, for example, or plasma exchange. Are there any others that sway your decision away from certain treatments? And then Dr. Gombolay, I'd love to hear if there's any considerations on the pediatric side about this.

[00:12:38] **Dr. Elias Sotirchos:** I mean, it's tough to go through an exhaustive list. I have to say some of the issues with IVIG, are that it can increase the risk of clotting, for example. So especially in somebody who has issues, let's say atrial fibrillation. Although often these people might be on an anticoagulation, you have to take into account a little bit that their maybe their risk is higher. Patients have had prior deep venous thrombosis in the legs, you might have to think twice about putting them on IVIG because that can potentially increase their risk of clotting. So that's I think one situation where we might consider. PLEX, as I mentioned, severe uncontrolled diabetes with steroids which can elevate blood sugar levels in other situations.

[00:13:21] And then other situations sometimes that might occur is patients where sometimes the diagnosis is not entirely clear when MOG at first presents. And sometimes there's often with MOGAD especially occurring sometimes as a post infectious or parainfectious disorder. So, somebody's sick and they have a fever and then they develop their first attack of MOG. Sometimes there's a little bit of uncertainty regarding the diagnosis and there are sometimes some might lean more to using, for example, IVIG rather than plasma exchange because theoretically you're giving people antibodies against viruses and bacteria to boost the immune system. So that's a conundrum that we sometimes will encounter at the same clinical practice as well.

[00:14:04] **Dr. GG deFiebre:** Thanks. And then Dr. Gombolay, any specific pediatric considerations there?

[00:14:09] **Dr. Grace Gombolay:** Yeah, I mean, it's pretty similar. I mean a lot of our kids fortunately are not at risk for atrial fibrillation, for example, and also rarer to have diabetes although that can occur. But it's pretty similar in terms of the risks. I unfortunately did have a patient not with MOGAD, it was a different inflammatory condition who again was bed bound for a while, which also increases your risk for clots that had really severe pulmonary emboli, so blood clots in your lungs around the time of IVIG. So again, I will never be able to know if it was cause and effect versus other. And when you're very sick, you also have increased risk for clotting in general. So, there's lots of other factors.

[00:14:50] But for that patient, I will not give that patient IVIG ever again, probably. And then the only other consideration, which is more common, which Dr. Sotirchos alluded to is if there's any concerns for infection, I might not give steroids right off the bat depending on if the diagnosis is really uncertain and start off with the IVIG. And then once you've ruled out infection or encephalitis or an infectious meningitis, then give the steroids after that.

[00:15:21] **Julia Lefelar:** That's all really great information. So, I want to go to side effects and if they're different between pediatric and kids and adults, I'd love to hear about that. So, Dr. Sotirchos could you please tell us about some of the side effects, even the worst ones that might come around with some of these acute treatments?

[00:15:44] **Dr. Elias Sotirchos:** Yeah, definitely. So, I mean, with steroids, steroids can have a whole host of side effects. I have to say one of the things with steroids is that most of the side effects are with long-term

administration. That's why we typically try to limit the amount of time that people are on steroids. And we don't like using steroids for many, many years because of the whole host of side effects that can occur. But a lot of them are things that came up previously. So, steroids can first of all increase blood sugar, even people who are not diabetic. So generally, these patients have to monitor their blood sugars.

[00:16:13] Especially when they're in the hospital, we might need to give insulin. When we're giving the really high doses that people might have prediabetes and then it's on a mass by being on high dose steroids. Other things that can occur with steroids are, one is very disrupting sleep quite a bit actually because of the effects of steroids. And it can lead to a lot of mood dysregulation even result in acute psychosis in people actually. So that's something to be aware of that can occur with a very high doses of steroids.

[00:16:44] Otherwise a couple of the relatively common things that we have to be able to look for. One is a bowel irritation and stomach irritation. And so sometimes people can develop stomach ulcers. And so that's something to be aware of. Typically, patients who are on high dose steroid will receive acid suppressing medications in order to mitigate that risk.

[00:17:07] The other one is effects on the bones. Typically, this is more with long-term administration. But again, even acute high dose steroids can sometimes with the main concern being this avascular necrosis, which is essentially an issue that can occur in the hip bone leading to bone damage there. And then other things that are generally to be aware of is that steroids can impair especially long-term wound healing. They can cause issues with increased risk of infection; they can lead to weight gain. But again, these are more with long-term administration. In the concept of an acute attack, high dose steroids including the clinical trials that have been done are actually relatively safe, even though these are pretty massive doses. But at least for the short periods of time that we use them for acute attacks, they're generally pretty well tolerated I would say.

[00:18:08] **Dr. Grace Gombolay:** And I would say in children quite similar where there's increased risk, especially behavioral problems, sleep can be an issue which younger kids, especially toddlers sometimes have sleep dysregulation in of itself. And so, you're making it worse and then they get really hungry. And so, they just are eating all of the time. But once you taper off the steroids, so side effects including the weight gain can go away.

[00:18:30] And then in terms of the intravenous immunoglobulin (IVIG), we alluded to some of them already, the increased risk for blood clots. That's rare. It's 1%, but still there. The more common ones are going to be headaches. Sometimes you can get reactions during the infusions where it looks like an allergic reaction where they might feel flushing or get a rash or feel like trouble breathing or throat tightening, that thing. But if you give treatments or you slow down the infusions that usually prevents that from happening, it's pretty rare to get an actual allergic reaction to it.

[00:19:05] That's why usually with IVIG, people often give pre-medications and that includes Tylenol, Benadryl, and/or sometimes a small dose of steroids depending on the situation. And then a lot of people can develop headaches are probably the most common after IVIG. And then you can get what's called an aseptic meningitis where patients will get fevers, severe headaches, sensitivity to bright lights, nausea, and vomiting. So, it looks like they are having an infection in their brain, essentially an encephalitis, meningitis, but it's also related to the IVIG.

[00:19:41] And so there's other ways to mitigate those reactions by either slowing down the infusion that usually helps, giving extra fluids, giving as needed treatments, whether it's treating the headaches or the nausea, vomiting. And I think we already talked a bit about the plasma exchange reactions. In addition to that just because there's a lot of fluid being moved around with plasma exchange; you can get fluid shifts

and electrolyte balances. But those are the biggest side effects.
[00:20:08] **Dr. GG deFiebre:** And then moving from acute treatments to preventative treatments, what are the choices in medication for patients who are in need of a preventative treatment? Dr. Gombolay, do you mind starting?

[00:20:23] **Dr. Grace Gombolay:** Yeah. So, I think what I will try to get depending on insurance. Well, also that can sometimes limit what we do or availability. So, a few years ago, there was actually a national shortage of IVIG. So that actually caused some issues in terms of this. But generally, if I can, there's some small studies but I think there's some evidence showing that maintenance IVIG or SubQIg, subcutaneous immunoglobulin, may be one of the more efficacious treatments. I know there's some clinical trials out there that are looking at other ones. But currently that's what I'll often use, especially in children.

[00:21:00] I have used mycophenolate mofetil or CellCept in some cases and the rituximab, but I'm not using that as much just because it seems like the IVIG does work better. But I know some people still use that. And then depending on just talking to some of my colleagues who are more resource limited, they may not have access to some of these including IVIG can be quite challenging to get in a lot of countries. They may use something like azathioprine or Imuran would be another option.

[00:21:35] **Dr. GG deFiebre:** And Dr. Sotirchos, what about in adults?

[00:21:39] **Dr. Elias Sotirchos:** So, an adult, I mean, it would be the same options, what Dr. Gombolay just mentioned. And I mean, there would be -- sometimes we use tocilizumab also or satralizumab off label chronically in patients of maintenance therapy as mentioned previously as an acute treatment as well as azathioprine or mycophenolate. And then sometimes even more rarely, I've encountered patients who might be already on an immunosuppressive treatment for another disease. And there are some older school immunosuppressants, things like methotrexate or things like that, that I've seen in some situations, but generally those are the main currently available options that we're using.

[00:22:22] **Julia Lefelar:** Thanks so much. So just to press a little further with both of you. So, for these preventative medications, how are some of these choices made? What we asked for the acute treatments, can you go a little deeper into that Dr. Sotirchos?

[00:22:42] **Dr. Elias Sotirchos:** Yeah, that's a tougher question I have to say than for the acute treatments because there's more options and there's not a lot of data, it's all off label, it's all experience and observational study. So, there are no clinical trials really examining head-to-head these medications. So, it's a little bit challenging. I mean, I have to say there can be a number of issues that we just need to take into account. So, to some extent, it depends on - first of all, I mean, it's a sheer decision making. So, it's not just what I think is best or, I mean, it's what the patient also values in terms of do they want to be getting an IV every few weeks to get IVIG? Do they want to do SubQIg which can involve self-infusing the medication? Do they want to just take a pill every day? Do they want to self-inject once every couple of weeks, tocilizumab for example?

[00:23:38] So there's a number of issues there that need to be discussed. And then other things that came up such as access to the medication and insurance wise. And just in general in the United States, I mean, something we have to take into account is things like the copay which might be cost prohibitive because IVIG is actually quite expensive. And so, if we are not able to get some financial support and a patient has a high copay and they're not able to afford it, then we have to think about other options as well. Are they able to take off work in order to get these infusions, for example? So, there are a lot of things I have to say that

go into this. And so, it's not a straightforward decision to make, but it has to be individualized for each case. [00:24:25] **Dr. Grace Gombolay:** I would agree that the same thing would be discussed with a family. Especially because I do have a few children who are very needle phobic and so that can also cause some challenges.

[00:24:39] **Dr. GG deFiebre:** Thank you. And so, in terms of preventative treatments, are there any comorbidities that might exist that would sway your preventative treatment choice one way or another, Dr. Sotirchos?

[00:24:55] **Dr. Elias Sotirchos:** Yes. That is something that can definitely come up. Comorbidities are something that has to take into account. I think that for example, we already discussed for IVIG the potential clotting risk. So, in patients who have some prior history of clotting, have significant vascular risk factors, are immobile, things like that. I mean, you might need to think about that a little bit more. With some other medications such as CellCept and mycophenolate, mofetil, and azathioprine that were mentioned, one thing to bear in mind is that these medications potentially may be associated with an increased malignancy risk long term.

[00:25:28] And so sometimes in patients, for example, who have had a history of malignancy or your blood or skin cancers, especially with mycophenolate, that might be a situation where you might need to consider not using that sort of medication. Other things that come into play are if people have had a history of exposure, for example, to hepatitis B or tuberculosis, those are things that would need to be addressed and considered if they're going to go on something like rituximab or tocilizumab, or actually, CellCept,or mycophenolate to some extent because those medications may potentially allow these viruses to just sit dormant in the body and wake up when somebody becomes immunosuppressed. And so that's another consideration. So, there are a number of these factors that need to be taken into account to some extent. Yes.

[00:26:27] **Dr. GG deFiebre:** And Dr. Gombolay I know kids tend to have less comorbidities. But is there any consideration in addition to what Dr. Sotirchos said?

[00:26:35] **Dr. Grace Gombolay:** I mean, those are the biggest things and then usually, we'll get screening labs including looking at the white blood cell count, for example, and if it's very low and then we're considering an immune medicine that's going to lower it even more. IVIG would be an exception to this. I would reconsider not giving one of them until they get better because sometimes, you'll get changes in your white blood cell count. They fluctuate all the time, even every hour they can fluctuate. And also, if you're sick, they can fluctuate too. But that would be the other consideration. And liver enzymes, everything can affect the liver. Very rare. But I always check those too.

[00:27:12] **Julia Lefelar:** Well, that's some good information and it really paints a good picture of the patient experience as they're trying to select and with your health preventative medication. So, I guess we should probably talk about the side effects that patients might experience with some of these medications that could make them change and I realize they change maybe if it doesn't work. But could you describe some of that? And I'll start with you Dr. Sotirchos.

[00:27:43] **Dr. Elias Sotirchos:** Yes, definitely. So, I mean, we went over immunoglobulin. So IVIG I think pretty extensively previously. Other ones that we'd have to discuss would be mycophenolate, really, the main one that would - apart from the malignancy risk that we already discussed is that sometimes people can have GI upset, especially when they're first starting the medication and that can sometimes be dose limiting. And so that's definitely a consideration there.

[00:28:09] Other things that we do is we monitor the white blood cell count and if it drops too low, that can

be consideration, we also monitor liver enzymes for liver issues that may occur on treatment and that might be also an indication to stop or reduce the dose. So generally, there's these monitoring labs that we'll do in people on mycophenolate. Azathioprine is overall pretty similar in terms of monitoring blood, liver function. Tocilizumab or satralizumab which are similar medications also require monitoring of liver function as well. But sometimes that can be an issue as well as sometimes they can elevate cholesterol a little bit. And so that's something to be aware of. And we often monitor, this is more of an issue in adults, I would say.

[00:28:59] And then with all of these ones that we discussed. So, we talked some mycophenolate, azathioprine. These are all immunosuppressive to some extent, pretty much every single one that we've discussed except for IVIG and SubQIg. And so, we have to be aware that these patients may be at a higher risk for infections. And so that is something that we may encounter when these patients have been on these medications chronically. And sometimes we may encounter a situation where people are having a recurrent infection on these medications. And that might lead us to have to consider switching or discontinuing that medication as well.

[00:29:32] **Dr. Grace Gombolay:** I would say that's pretty similar in children also.

[00:29:38] **Julia Lefelar:** So, nothing else to add, Dr. Gombolay about that?

[00:29:40] **Dr. Grace Gombolay:** I mean, not too much. Dr. Sotirchos went through it pretty extensively. I think the one thing would be for patients who I have who are on a rituximab or something that is a similar CD20 agent. About 10% of those patients can get low immunoglobulin. So, if they happen to not be on immunoglobulin and then they're getting recurrent infections, then I'll add in a replacement immunoglobulin for them. And that's because the rituximab targets B cells, which B cells make immunoglobulin.

[00:30:15] **Julia Lefelar:** I think that's a great answer. And there is a community question. I'll just read it here. They said, "Can you talk about behavioral side effects in young children with IVIG?" They've noticed that their daughter's cognitive behavioral issues got worse in the fourth week or get worse in the fourth week leading up to her infusion and she's receiving those infusions every four weeks. Is that something you can speak to?

[00:30:44] **Dr. Grace Gombolay:** Yeah. So, I have some patients who have additional symptoms. Some of these symptoms we talked about in terms of the acute relapses, they're more quantifiable. The weakness or the vision changes, that thing. And then some of these symptoms can be a little bit harder to assess and that's going to be cognition, thinking, behavior in a young child. Fatigue is another huge one I hear from a lot of patients, it's really hard to know. We know that patients with neuroinflammatory diseases, not just MOGAD, that's true for multiple sclerosis and other related disorders that all of these can be quite challenging symptoms to treat. And it's hard to know how much of it's purely neuroinflammation versus neuroinflammation plus other things happening.

[00:31:38] And so for this situation, I hear this a lot quite commonly from my patients who they'll realize that there are some things, and they can't really describe it very well. But the first few weeks, right after IVIG, they feel like their child or themselves are doing well, but then right when they're due, they know that they're due because they'll have these increased symptoms again, slightly harder to quantify. And the one thing to note with IVIG though is even though I do think that it takes effect pretty quickly, the peak effect IVIG is actually not the first day. It's somewhere between roughly about a week after being given.

[00:32:19] That's one thing to also keep in mind because when we're giving IVIG, we're also sometimes giving other things such as a small dose of steroids. And so that can make people have more energy too. People

are attributing to IVIG. But if they're getting some steroids that could be also affecting the symptoms or they're getting a lot of fluids. So, it's hard to know, is it particularly - long story short, it's hard to know if those symptoms are directly correlated with inflammation or directly correlated with IVIG, which I realize is a vague answer to the question, but there's a lot of factors into play that could be contributing to the symptoms.

[00:32:55] **Julia Lefelar:** So, having said that, I guess maybe this is a quick question for both of you and the use of subcutaneous IG. Is there a thought that maybe once per week dosage of the subcutaneous IG versus the IVIG, which is once a month might have a difference in how that disease is controlled? And Grace, I'll let you answer and then I'll ask Dr. Sotirchos from an adult perspective.

[00:32:28] **Dr. Grace Gombolay:** So, I would love to see more data on the differences because I don't think we have that much data so I can just speak from the patient experience. And so, most of my patients with MOGAD are getting IVIG if they're getting maintenance treatment at all. But I only have a few who are getting the Sub-Q. And so far, I'm not seeing a difference in terms of the fatigue and energy levels. But I'm curious from Dr. Sotirchos what your experience has been. If you see a difference in the patients who are getting Sub-Q versus the IVIG.

[00:34:04] **Dr. Elias Sotirchos:** Great question. I mean, we haven't really examined this systematically and I do use a combination of IVIG and SubQIg. One thing that I often do with IVIG is actually dose it every two weeks rather than every four weeks in order to avoid higher peaks and lower trough levels so that you get them build of a more consistent concentration. And also, because sometimes I think the headaches are better for giving a smaller dose every two weeks rather than a higher dose every four weeks. I mean, it's tough to say, I haven't seen, I think necessarily a huge difference. Although I have to say the wearing off, I haven't seen as much in adults in general, I would say.

[00:34:49] **Dr. GG deFiebre:** Thank you so much. And so, there's a lot of research happening, a lot of emerging data on medications like IVIG, tocilizumab, rituximab, mycophenolate, which medications are more effective in MOGAD, and which ones don't seem to be that effective? Dr. Sotirchos, if you could start and then if you can see what similar in pediatrics, Dr. Gombolay?

[00:35:16] **Dr. Elias Sotirchos:** That's a great question. So, I mean, first of all, again, we don't know. I think is a short answer. I would say that I really do think that all of them work to some extent based on my experience, I have patients on all these medications, essentially, some have been on them since a diagnosis of seronegative NMO before MOG was even recognized as a disease. And so, they were being treated with things like mycophenolate or rituximab.

[00:35:46] And, I mean, we've looked that the relapse rate has clearly gone down and patients have been treated with a variety of medications. Now, I do think though that the existing data has been pretty consistent in a pattern that IVIG or SubQIg, especially when you're on the higher end of dosing over one gram per kilo per month. It's very rare to see attacks once you get on the higher doses of immunoglobulin. So, I would say that that's the most consistent pattern that we're seeing if you take all the literature into account.

[00:36:26] But it's pretty clear that all these medications work to some extent and a lot of people you'll hear swear by rituximab as being very effective their experience or they swear by mycophenolate, or they swear by tocilizumab being their medication that they have the most experience with and they're very satisfied with. I think looking at the literature and totality, in my experience, I feel like immunoglobulin. If you had to choose one especially at higher doses, it's very rare to see true relapses occur.

[00:36:57] **Dr. GG deFiebre:** Yeah, go ahead.
[00:37:03] **Dr. Grace Gombolay:** Yeah, I was just going to say same thing is that if I had to pick one without considering all the other factors we discussed, then immunoglobulin would be my first choice.

[00:37:17] **Julia Lefelar:** Thank you for that. Those are all great answers. Really great information. So, I want to switch it up and just talk a little bit about the advancements and the understanding of treatments and the treatment protocols. And I guess this MOGAD is understood more and more in the advancements in data collection happen. Research has shown that only about 50% of the MOGAD patients relapse. How does this affect your decision to put one of the newly diagnosed patients on a preventative treatment? And could you both talk about this from an adult and pediatric perspective? So, I'll start with Dr. Sotirchos.

[00:38:03] **Dr. Elias Sotirchos:** That's a great question. Also challenging question again though, I mean, first of all, I think that my general practice, I would say for the majority of cases is that after a first attack, I usually will not recommend initiation of a chronic maintenance therapy. Given the fact that's as a proportion of patients may remain monophasic and have a single attack. I have to say that the estimate of how many remain monophasic, I think we still need more time to tell because a lot of these 50% figures that get quoted quite a bit it's from studies that followed people for four years, let's say as a median follow up for four years.

[00:38:45] And I've seen patients who had an optic neuritis 15 years ago. MOG wasn't available to test then. And now they're back with the second optic neuritis 15 years later. And it took 15 years to get a second attack, but they weren't necessarily monophasic, although you would have said they were monophasic up to 14 years after the attack. However, one could argue that in that case, had you put them on maintenance therapy for 15 years, you would be patting yourself on the back and saying, "Look, the patient's not having a relapse," but you really probably weren't doing much for them. You were just subjecting them to all of the potential side effects and inconveniences of treatment without necessarily actually preventing a single attack. And so, is it worth putting somebody on treatment for 15 years to prevent a single attack? I would say probably not, especially if they're going to recover well from it, which you can't necessarily know in advance.

[00:39:38] So, I mean, I would say that generally just to summarize my general practice. If it's a single attack, somebody has recovered well from that attack, then I often will not recommend maintenance therapy. If there's incomplete recovery or the attack was very severe, sometimes we will put people on treatment after a single attack but say, "Okay, we're going to do this for now, potentially do this for a couple of years to cover a vulnerable period while you're recovering from this attack. And then we can revisit and taper you off in the future." So, I think that it's a complicated discussion. And again, there's shared decision making, and you have to take into account what the patient values, but it's a complicated discussion to have. And I think that we really need markers that can help us to predict the risk of relapse so that way we can put people on treatment for the highest risk for potential future attacks.

[00:40:33] **Dr. Grace Gombolay:** I agree with what Dr. Sotirchos says, it's a hard question to answer just because we don't have good predictor markers at this point in time. But, I mean, what my personal practice has been if somebody had a very, very severe attack or they didn't recover very well, despite us giving us a lot of treatment, I might consider more likely to put them on a maintenance therapy after the first attack and then generally after the second attack, then I would. But like Dr. Sotirchos said, it's one of those things like if it's so far apart, what do you call that? So, it can be challenging. But I think it goes back to the discussion with the patient and the family of this is the data that we have and the risk versus benefits because like we said, even though we use these medications a lot and generally they're pretty well tolerated, there are some risks that are carried with them. And so, we have to keep that in mind.

[00:41:29] **Dr. GG deFiebre:** Thank you. And so, if there's someone who is on a preventive medication and

then they have a period of time that they are in remission, would you ever consider taking a patient off a preventative treatment? And if so, under what circumstances might you consider this Dr. Gombolay?

[00:41:50] **Dr. Grace Gombolay:** I think this is even harder than deciding to start somebody on maintenance actually. I think some of the data suggests is waiting two years sufficient, is waiting four years sufficient? I think again, we don't have any good markers to predict that. So, until we have that, it's again an individual discussion and it's one of those things where some people, which I do this too will actually recheck antibodies. We'll check the MOG antibodies because we know that if your titers become undetectable or lower than what the assay can detect that decreases your risk of relapse. Unfortunately, it's not zero. Unfortunately, nothing in medicine is zero.

[00:32:30] And so it's one of those things where it's a discussion with the family. And again, with the severity of the attack, the age of the patient, the recovery and what everything else looks like. I do interval imaging. There's a lot of data to show that having new brain lesions on MOGAD is pretty rare. And if it does, it probably doesn't predict an attack, it doesn't mean a relapse or other consequences. And which is different from, for example, the multiple sclerosis literature. But I don't think we have enough follow-up data to look at that quite yet. But generally, I will do interval imaging to repeat the MRIs to make sure there's no new spots or lesions and then recheck the antibodies but it's a hard decision.

[00:43:18] **Julia Lefelar:** Yeah, I'm sure it is. And just talking about taking people off, is there - I guess, hopefully I formulate this question right. Is there a precautionary measure that doctors can take to avoid the situation of taking somebody who's relapsing that has this milder disability off of a preventative treatment due to being in remission or whether they call remission and then they go into a relapse causing more disability? I mean, unfortunately, we've heard from patients that this has happened. And so, if that would be a choice that you would make, what precautions would you take to make sure that they didn't get worse disability? Does that make sense? So, Dr. Sotirchos I'll ask you that question.

[00:44:09] **Dr. Elias Sotirchos:** Yeah, I mean, I think the first and most important thing is to educate the patient regarding what attacks may occur. So again, let's say that somebody's had optic neuritis, they know what optic neuritis is, they've experienced it. If it happens again, they will likely recognize it early on. But if they might have not had other manifestations of MOG like transverse myelitis or brainstem involvement ,or things like that. So, I try to educate my patients for what symptoms should raise alarm bells.

[00:44:39] Because we've seen this, especially when people are having their first attack, they have optic neuritis and they think that maybe something got in their eye, they wait on it, for a few days go by. They think it'll get better on its own. So, I think that it's important to make sure that people are aware and can recognize early symptoms of an attack that would prompt them to seek medical attention early because we do think that earlier acute treatments may improve outcomes. So earlier steroids, plasma exchange, IVIG potentially. So, I think that's the first thing.

[00:45:12] Sometimes one thing that we have been doing is this steroids in the pocket approach, which patients will have a high-dose prednisone prescription on hand. Now, it's something that we have to be careful about because prednisone, high doses of steroids can have significant side effects and the patients are instructed to not take it without consulting with a physician first. But if you speak with them on the phone, it's very clearly very typical. There's nothing else going on. There's no concern for active infection. You could potentially try to get the steroids in very quickly when let's say the attack is first developing in order to nip it in the bud before it blossoms into a full attack. And that's something that we have been implementing to some extent.

[00:46:05] But you have to be careful to not overdo that because steroids can have significant side effects

and often patients may have things that are called pseudo relapses in the context of an infection, stress, other things, just old symptoms are emerging and you don't want to be giving steroids repeatedly to do that because that can lead to more harm than good.

[00:46:28] **Dr. GG deFiebre:** Thank you.

[00:46:29] **Julia Lefelar:** Dr. Gombolay do you have any thoughts on that from that pediatric perspective?

[00:46:34] **Dr. Grace Gombolay:** Yeah, I do something similar. It's a conversation and it can be quite nerve wracking when you're taking people off. And it's one of those things where we unfortunately don't have any good predictive markers yet. There's a few that people are studying, but if we had a predictive marker for when the relapse was going to occur, that would be awesome because then we could treat you before that happened. But until we have that, I think just having discussions about the symptoms, what to look out for and then the steroids in the pocket are the ways that I approach it too.

[00:47:10] **Dr. GG deFiebre:** Thank you. And so, are there any steps that may be taken to get more healthcare facilities to move towards subcutaneous IVIG this came from the community question, Dr. Gombolay?

[00:47:23] **Dr. Grace Gombolay:** So, it's one of those things where for me, it's by experience. So, I started off with more familiarity with using intravenous immunoglobulin and then seeing more people using subcutaneous for inflammatory conditions, not just for replacement because that's when it was more commonly used that more people are using it. I don't know about other steps in terms of whether it's insurance or other political moves to make it move towards Sub-Q. But so far, I've had a pretty good success with getting either covered, it takes a little bit in terms of insurance, but it can get either covered by insurance for MOGAD specifically.

[00:48:14] **Dr. Elias Sotirchos:** I agree, and I think again that they're pretty similar overall, I mean, I do use quite a bit of subcutaneous IG and in my experience, patients quite like that because of the fact that they can be more independent and self-administer, they're not dependent on a nurse and coming to their home to administer, it can be self-administered. Also, some of the side effects that we were discussing previously seem to be less. So, the risk of headache and blood clot seems to be less. That makes sense because you get more of a steady state level of the antibodies in the bloodstream. Whereas with IV you give a huge bolus into the bloodstream of antibodies and that can increase the risk of clotting and a headache.

[00:48:55] And so, I mean, things that we've tried to do is, first of all, just publish our experience and that I would say has been quite helpful, something to cite when we're arguing with insurance companies and things like that. Then I think the next step would be a clinical trial in order to definitively demonstrate the efficacy of SubQIg because that would definitely be very helpful to convince payers to cover it.

[00:49:23] **Julia Lefelar:** Thank you. That's a great answer. I think before we go on to our next section, we want to grab one of the community questions. And this person's asking which medication is best for breastfeeding mothers? Dr. Sotirchos, I'll let you answer that.

[00:49:41] **Dr. Elias Sotirchos:** It's a great question and definitely one of the things that comes up quite a bit when counseling patients for maintenance therapies, is it is important to consider pregnancy and breastfeeding. A lot of our patients are of childbearing age. So, if we're referring to maintenance therapies, I mean, I think that importantly with breastfeeding, generally, often people will have either been treated during pregnancy and then continue during breastfeeding or maybe stop for pregnancy. So that's something that I think needs to be taken into account. This needs to be preplanned before potentially preconception, ideally. So going into pregnancy with a plan for what we're going to do with the maintenance therapy and what we're

going to do during the breastfeeding period.
[00:50:31] Importantly, IVIG and SubQIg are fully compatible with breastfeeding. There's a little bit less known about the biologics, for example of rituximab. But there's been a lot of evidence emerging that rituximab, the amount that may get into breastmilk are minimal, that the amount that would get absorbed essentially by the baby is very, very low. And so generally, there's been a move, for example, in multiple sclerosis to recommend that it's probably safe to treat. Now, that doesn't mean that the FDA label has necessarily been updated to say that.

[00:51:08] The FDA label, if you read for some of the medications like rituximab will continue to say that it's unknown what the safety is in breastfeeding. But I think that things have been evolving overall but it's really an individualized decision. Other medication like CellCept, mycophenolate, azathioprine, those are generally of avoided. Although azathioprine may be compatible with pregnancy, but it's complicated discussion and a lot of factors may be taken into account.

[00:51:37] **Dr. GG deFiebre:** Thank you. And so, moving on to what's in the pipeline, let's talk a little bit about the two clinical trials. What hope lies in these medications and in your opinion, will we get there and achieve FDA approval at least in the U.S.? Dr. Sotirchos?

[00:51:56] **Dr. Elias Sotirchos:** I'm sorry, could you repeat the first part of the question? I think I missed something.

[00:52:02] **Dr. GG deFiebre:** Sure. Of course. So, the two clinical trials that are happening in MOGAD, what hope lies in these medications? And do you think we might get FDA approval at least in the US?

[00:52:15] **Dr. Elias Sotirchos:** That's a great question. I think that, I mean, again, just to summarize. So, there are two ongoing phase three clinical trials that are international, the two molecules that are being examined are satralizumab and rozanolixizumab. So satralizumab is a medication that's already FDA-approved for the treatment of aquaporin-4 IgG seropositive neuromyelitis optica. And it works very similar to tocilizumab on the same immunologic pathway. And so, the trial is ongoing. So, we won't know until the end when we are unblinded and the data are analyzed for the result. I mean, we're hopeful that based on the existing experience with tocilizumab, that the trial will demonstrate efficacy and that that could lead to FDA approval of satralizumab for treatment of MOG antibody disease. And it would be really nice to have availability of an FDA-approved therapy.

[00:53:10] The other medication, rozanolixizumab, is a medication that mimics to some extent some aspects of plasma exchange and IVIG by preventing recycling of antibodies in the body. And so essentially dropping the levels of MOG antibodies as well as just antibodies in general in the bloodstream. And while this is not--we don't really have experience with off label use in MOG antibody disease, this specific one that's being studied is actually FDA-approved for the treatment of myasthenia gravis, which is another neurological autoimmune disease that is associated with the presence of auto-antibodies. And so, there's a strong biological rationale that this may also work in MOG antibody disease.

[00:53:54] And so I'm hopeful that at least one or both of these trials will be positive and will lead to FDA approval. However, I think it's important to bear in mind that both of these trials are still recruiting and still ongoing and they have to recruit, they have to have a sufficient number of relapses in order for the analysis to be done and that entire process will likely take a few more years. For the trial to end is what I'm saying to be completed and for the primary analysis to be done.

[00:54:30] Then after that, the data needs to be submitted to the FDA, FDA needs to review and write approval.

So, we're likely a few years out even if these trials are positive to FDA approval. And so, we're still, for the next few years, definitely going to be in a similar situation in terms of off label therapies issue with payers. But overall, I'd say that this is getting better overall in terms of approvals are a little bit easier in my experience, each year, it's getting a little bit easier because MOG antibody disease is becoming a little bit more well known. There's more data, more literature on the topic. And so overall, I think that there is clearly a positive outlook even without the clinical trials at least for the off-label therapies right now in the meantime.

[00:55:23] **Julia Lefelar:** That's a great question and a great answer. And I think a lot of people are hoping for that. Dr. Gombolay, what hope are there for parents with kids who have MOGAD in the future in the way of new therapies?

[00:55:38] **Dr. Grace Gombolay:** So, it's harder to do trials in children. I will say the satralizumab trial is actually recruiting patients 12 and older. So technically pediatric, although it's harder to know about the younger kids. But generally, and this is true for many studies, we test adults first and make sure it's safe and tolerated and works well in adults. And then there will be potentially a pediatric trial versus off label. And so even though this may not be technically including younger children, or the other study is mainly adults, at least these could be options available. And like Dr. Sotirchos has mentioned, just having increased awareness for the insurance companies and the people who work there realizing that MOGAD exists and that there are effective treatments for it can be helpful in terms of the approval process.

[00:56:31] **Dr. GG deFiebre:** Thank you. And then is there an age group, socio-economic status, or ethnic group that seems to have more difficulty getting access to preventive medications for MOGAD, Dr. Gombolay?

[00:56:49] **Dr. Grace Gombolay:** Yes, I would say this is true, not just particular to MOGAD but for many of our conditions. So unfortunately, patients who are of lower socioeconomic status and then if they don't have health insurance, that can cause a huge barrier and then on top of that language can be also a barrier. And then just a level of education and understanding. Then there're lots of other life factors. We have a lot of, unfortunately, some patients and families, they're single parents, they have multiple children in the home and they're working multiple jobs. And so, there're lots of other factors that can get in the way.

[00:57:27] One of the things I've been trying to work on and work with--I'm based in Georgia--is that the Georgia Department of Public Health has an emergency insurance coverage in certain situations if you have an approved diagnosis. But I will say right now, neuroinflammatory diseases are not on the list, whereas other things like cerebral palsy, for example, or epilepsy is. And so, if you are a child in Georgia and you have epilepsy, cerebral palsy, and a lot of other disorders, you can get some emergency coverage in the meantime, while you're waiting for your health insurance to kick in. But neuroinflammatory diseases are not on there. So, we're working on that. So, if any of you are in Georgia, talk to the public health office and see if we can get that on the list.

[00:58:16] **Julia Lefelar:** Thanks, Dr. Gombolay. And we're running out of time. And one thing we really like to ask both of you, and I'll start with Dr. Sotirchos is that we'd love to hear about your latest work in MOGAD. And just please let us know what you've been working on that you really are excited about that you want to convey to the community? Dr. Sotirchos you can start.

[00:58:40] **Dr. Elias Sotirchos:** That's a great question. I think that, I mean, we're excited about a variety of things. I mean, we're looking at a few things that we've done recently of one which is relatively simple. But, I mean, it's that the diagnostic criteria were only really proposed last year. And so, we looked at validating how well they performed compared to our empiric clinical diagnosis in our patient cohort here, we found that they

performed rather well, which I think is really nice and demonstrated really good sensitivity and specificity for the diagnosis of MOG antibody disease. So, I think that that was something that we were really happy with. [00:59:20] Other things that we're looking at is examining the performance of various assays. So, looking at the more accessible fixed assays that are done on a lot of the commercial laboratories versus live assays and how many patients may be missing potentially only by doing one versus the other. Especially seems to be a problem with some of the fixed assay may be missing some patients.

[00:59:48] And then there are a few other things that we're looking at including imaging studies. Looking at how after MOG antibody disease, optic neuritis, the blood vessels in the retina can become affected using a technique called OCT angiography. So that's something that we're tracking over time in patients and looking and comparing to other neuroinflammatory diseases such as the MS and neuromyelitis optica. So, there are a number of studies, and we have a big biorepository. So, collecting blood and cerebrospinal fluid from patients with MOG antibody disease who are seen here in order to enable additional studies and biomarker development as well.

[01:00:24] **Julia Lefelar:** Dr. Gombolay?

[01:00:30] **Dr. Grace Gombolay:** Yes. So, we're also working on quite a few things but the two main projects I'm going to highlight one is we recently published on the rates of leptomeningeal enhancement in our children with MOGAD compared to, for example, children with MS or aquaporin-4, NMOSD. So, we're expanding upon that, looking at what is the differences? Why do some children with MOGAD get leptomeningeal enchantment versus not? And why is it more common in MOGAD versus, these other neuroinflammatory diseases that can look into that.

[01:01:00] And so as the piggyback on that, we're putting together a multi-center autoimmune encephalitis registry, which will include MOG antibody related autoimmune encephalitis. And that is a multi-center prospective cohort looking at all patients who have autoimmune encephalitis who meet criteria and again doing EEG, MRI, biomarkers patient and caregiver reported outcome surveys with that. And then just a hint of this. But I'm also putting together a treatment consensus and an international treatment consensus cohort expanding upon what the European group has already done in terms of their treatment consensus guidelines and then the international diagnostic guidelines. But now we want to try to see if we can come to any consensus on treatments in an international way.

[01:01:52] **Julia Lefelar:** Well, that's fantastic to hear from both of you. I think it's a good time if you're a MOGAD patient with all of this going on. We're very lucky to have both of you putting all this work into this.

[01:02:05] And so we've come to the close of our time and I really want to thank GG from the SRNA for all the hard work that they put into this MOGcast. And I'd like to thank the both of you for your great answers and just the information that you've passed on to patients. GG does have a little announcement for some exciting news coming up here. So, GG, I want to pass that on.

[01:02:32] **Dr. GG deFiebre:** So, thank you both so much. And to continue this conversation too, we have our "MOGAD Together" Q&A tomorrow actually with Dr. Sotirchos. So, we can answer some of these questions or if that was also a reminder, I guess. But thanks so much for your time and taking the time to answer these questions. We appreciate it.

[01:02:57] **Julia Lefelar:** And thank you GG, that sounds exciting, and we'll certainly be there. So, everyone, please look out for our follow-up MOG Blog with some of the unanswered questions that we just didn't get

to during the MOGcast. And it was a great discussion. I really appreciate everybody coming and we hope to see you again.
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