Deliberations on acute and long-term treatment guidance

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[00:00:05] **Dr. Benjamin Greenberg:** There's a good segue. Dr. Carter has talked, to our last conversation about long-term treatment guidance. Because one of the issues that comes up is for some individuals who've had more than one event of inflammation or at high risk of more than one event, we use medications to prevent new attacks. These medications do nothing for symptoms from old attacks.

[00:00:31] So, we're not trying to correct the past. We're trying to change the future. And then for some of you, you don't need that. You fit into a category where we feel like prevention isn't needed. So, I'm going to run the list and we'll play a little game. Needs prevention. Doesn't need prevention. All right, and so we'll start with acute flaccid myelitis.

[00:00:56] **Dr. Michael Levy:** I would say no, because I've never seen a case of relapsing, acute flaccid myelitis that's due to the infection.

[00:01:04] **Dr. Benjamin Greenberg:** Idiopathic myelitis and I will specifically tell you they have been tested for the aquaporin-4 and MOG antibodies and they tested negative.

[00:01:14] **Dr. Michael Levy:** That's a harder one because it's hard to know that a negative test is truly negative. If there's enough time that has passed after the attack, like say three years where I'm confident that it was truly a one-time transverse myelitis. I'd feel more confident saying, okay, you probably don't need it. If you just came out of the hospital and you had your first attack of transverse myelitis and tested negative for everything, that's going to be a more of a discussion about whether our testing is good enough and comfort level of you as the patient and going home without any treatment. So, that's a harder discussion.

[00:01:54] **Dr. Benjamin Greenberg:** Somebody who has had either optic neuritis, myelitis, inflammation in the brain, any syndrome you want to pick and they test positive for the aquaporin-4 antibody?

[00:02:07] **Dr. Michael Levy:** That's the easiest one. That is an automatic, yes. Everyone who tests positive for the aquaporin-4 antibody is going to relapse eventually and it's going to be bad the next time probably. So, it's in everyone's best interest if you test positive for aquaporin-4, you go on something.

[00:02:26] **Dr. Benjamin Greenberg:** So, I gave you the easy one in order to give you this one. Somebody who's had optic neuritis, myelitis, brain-based inflammation, whatever syndrome you want. And they've tested in that event during that event positive for the anti MOG antibody.

[00:02:42] **Dr. Michael Levy:** So, that's a harder one because we know about half of people with MOG won't relapse that they can go six months, 12 months down the line, you look back and the MOG antibody has disappeared and despite no treatment, they've never relapsed again. And that's always best case scenario. And then there's the other half of people who will relapse and it's really hard to predict who that's going to be.

[00:03:05] And then the harder question is people who test positive for MOG and then a year later they come see you, they're still positive for MOG but they haven't relapsed yet. And so what does that mean? If they've gone a whole year with no relapse does that mean that they're just going to be one time thing? What about that next positive MOG test? Still sorting those details out.

[00:03:26] **Dr. Benjamin Greenberg:** If you had a person with the anti-MOG antibody who has had two distinct events, one year, they have an event and two years later they have another event. Would that individual get from you get a recommendation to be on a preventative therapy to prevent further attacks?

[00:03:39] **Dr. Michael Levy:** Yeah, usually people who have one relapse are more likely to continue to have relapses but they have to be separated. If it's like one attack and then two weeks later after your steroids were done, you're back in the hospital within two weeks that's still probably the same initial attack. So, I'm not counting that. But if you have another attack two years later, that means your immune system is inclined to attack a third time and then treatment might be worthwhile there.

[00:04:10] **Dr. Benjamin Greenberg:** And so, before we get into the preventions, one other situation because we had one person talk about the notion of neurosarcoidosis. There are systemic conditions. Sarcoid is one or others that can manifest with inflammation in the optic nerve of the brain or the spinal cord myelitis. In general, do those individuals need to think about being on a preventative therapy?

[00:04:33] **Dr. Michael Levy:** Yeah, neurosarcoid is a little bit interesting because it seems like that is a condition that persists. It's not an attack that happens over and over again. It's like one really long attack and then you treat it, treat it, treat it, treat it and then in about half of cases, it just finally goes away and then in the other half you're treating on really long term. It's a little bit different from all the other diseases we've talked about.

[00:04:57] **Dr. Benjamin Greenberg:** All right, so what I've heard so far and you guys are keeping track, you're calling balls and strikes here. I heard if you're positive for the anti-aquaporin-4 antibody, don't pass go, don't collect $200. You need to be on prevention therapy. And if you have the anti-MOG antibody and have more than one attack over time, clearly separated in time, not one long attack, but two distinct events, you should be discussing going to therapy that those are on the easy end. And then there's the grey area and then the ones where we say nothing.

[00:05:29] **Dr. Michael Levy:** That's right.

[00:05:30] **Dr. Benjamin Greenberg:** Everyone hearing the same thing? So, now we get to the fun part. What do you want to talk about first? Anti-MOG associated disorder or anti-aquaporin-4 neuromyelitis optica?

[00:05:43] **Dr. Michael Levy:** I think aquaporin-4 is more straightforward. We've spent the past 15 years sorting this out. So, I think we have more answers.

[00:05:50] **Dr. Benjamin Greenberg:** Just to put this in the context, can you tell everybody what the world was like before any FDA-approved therapies?

[00:05:58] **Dr. Michael Levy:** It was bad. I was at Johns Hopkins, we were residents together and we had a lot of cases that were misdiagnosed as MS and they were actually NMO and these people were getting MS treatment and ending up in the hospital saying I did everything my doctor was telling me to do and I'm back in the hospital with another optic neuritis or another transverse myelitis and with aquaporin-4 disease, the healing is very poor.

[00:06:23] And so, these people would have relapses after relapses, clusters three or four a year and we'd see a lot of them in Baltimore and those days were pretty dark. We had about 60% of our patients were blind in one eye or more. About 23% I think were in wheelchairs. It was really bad and we didn't really know how to prevent treatment. We were still thinking maybe NMO was a variant of MS and using all these MS drugs that turned out to be harmful.

[00:06:50] **Dr. Benjamin Greenberg:** So, then when the anti-aquaporin-4 antibody was identified, we moved to using a lot of drugs in what's called off label fashion. So, just to bring everyone up to speed, can you tell us your description of the difference between off label and on label? What does it mean for a patient to hear that they're on a drug off label versus on label?

[00:07:09] **Dr. Michael Levy:** Off label means the FDA has not approved that drug, but we have a sense that it might work.

[00:07:14] **Dr. Benjamin Greenberg:** For the indication.

[00:07:16] **Dr. Michael Levy:** For that indication so that the drug is approved in the US. If it's not approved in the US for anything, you pretty much can't access it.

[00:07:23] **Dr. Benjamin Greenberg:** Except through a research protocol. So, just so everybody is clear that I am not, neither of us are allowed to give you access to a drug that has zero approval. So, the only way to get access is as part of a research protocol. But if we approve a drug for asthma and I want to use it to treat your migraine, the FDA says, well, all right, Greenberg go, you know, just warn people that you're way off the reservation here and using an asthma drug to treat migraine. Yeah, I can prescribe it for anything but then it's considered off label.

[00:07:56] **Dr. Michael Levy:** And there's no guarantee that it would be covered by your insurance if it's off label.

[00:08:01] **Dr. Benjamin Greenberg:** Yeah, insurance I forgot that.

[00:08:02] **Dr. Michael Levy:** We have access to some of the older medicines that are already approved for other rheumatologic diseases that broadly suppress the immune system. So, if we have a new immunological disease and we think we need something off label, what can we use? We look for the broad applicable treatments and then we just try them and then we publish them. We meet together at conferences and we say, hey, how are you doing with this drug? Oh, no, that's a horrible drug. We should put that out there that it's not working.

[00:08:30] Or what's your experience with that drug? And then that turns out to be more useful. Sometimes companies pay attention if there's still some intellectual property behind it. They may want to develop that

drug that you're testing and try to develop it for FDA approval. And we did that with three drugs in NMO. The science was so good these companies were like, wow, you really think our drugs will work? Yes, and then they got approvals 2019 and 2020 in a very small disease population, maybe 20,000 people in the US we now have three FDA-approved drugs.

[00:09:03] **Dr. Benjamin Greenberg:** And so, those FDA-approved drugs. So, and if you remember every drug has two names, the one you can't pronounce and you can't pronounce more. So, for people who have the anti-aquaporin-4 antibody, so you have to test positive for that antibody. The FDA is given approval for Inebilizumab, which is Uplizna. Eculizumab, which is Soliris and Satralizumab which is Enspryng all for antibody positive neuromyelitis optica. So, if you test positive, the FDA has said those for 18 and up for adults because I see both kids and adults. So, they haven't been approved for if you're 17 and a half the FDA hasn't given approval yet.

[00:09:55] **Dr. Michael Levy:** [Crosstalk] Enspryng is.

[00:09:57] **Dr. Benjamin Greenberg:** Enspryng in Europe they, on the US, they recognize the data, the label they still approved was the 18 up. They did the trial in 12 and up, but we still sometimes have to fight to get it in our teenagers. But that would be considered on label if you have aquaporin-4 disease. Now, in your practice, do you still have any patients using a drug off label? So, not one of those three for aquaporin-4 neuromyelitis.

[00:10:23] **Dr. Michael Levy:** Actually, most of them are still on Rituximab. We started using Rituximab off label in 2005 after our colleagues in California published a series of nine patients and they said, hey guys, these nine patients, they did really, really, really well on Rituximab. And so, we took notice and started using it here and there and, wow, it really did seem to help. And since then, there have been probably 30 observational studies of anywhere between nine patients and 100 patients saying, yeah, this drug really does seem to work.

[00:10:56] Now, it's not like we placebo controlled it. There was one placebo-controlled trial of Rituximab in Japan and it is approved there. But in the US, Rituximab is still not approved for NMO, it's approved for other conditions. I would say the majority of NMO patients are still on Rituximab. They love it. It works, it really does seem to work for them. And even when offered new drugs, they'll say no, I'm doing well on my Rituximab, I'm fine with it and then they stay off label on their Rituximab.

[00:11:28] **Dr. Benjamin Greenberg:** And so, when you're meeting with your health care providers, one of the things we do in our clinic is just make everybody aware of what's available. Even if we're not necessarily switching, we feel it's important as these changes come out to make people aware. In the conditions we're talking about it's worth noting only aquaporin-4 positive NMO of all these diseases has an FDA-approved drug available for it. So, as we move to that next category, the individuals who have anti-MOG associated disorder and have more than one event, everything we're doing is off label. So, what are your go to considerations off label and then you want to talk about trials?

[00:12:20] **Dr. Michael Levy:** Our off-label experience comes from kids. Kids who have acute disseminated encephalomyelitis have a form of MOG and people have been using IVIG in this population a lot and it seems to work. For MOG we started using IVIG and it does seem to work. Same type of experience where we're a little bit biased towards. Well, we think this is really working. What do you think? And everybody gets together and says, yes, yes, yes, I think IVIG is the one. And so, we have a positive vibe about it, but it's never been tested.

[00:12:45] **Dr. Benjamin Greenberg:** And does everyone here know what IVIG is? It's a fun story. So, intravenous immunoglobulin, it's a bottle of just antibodies. And each bottle has antibodies collected from approximately

2000 individuals, human blood donors. And so, they take the antibodies if you go to the American Red Cross and donate a unit of blood, which is a wonderful life saving thing to do.

[00:13:05] Some companies will take it and pull out the plasma and pull out the antibodies and package it all together from donors. So, the difference between IVIG, one of the differences between IVIG and all the other drugs that we're used to prescribing is it's the only one that doesn't suppress the immune system. So, IVIG isn't killing off or modulating any immune cell or blocking the immune response, it's flooding your system with antibodies. And I won't be mean and ask Michael how it works because we both agree we don't know.

[00:13:36] **Dr. Michael Levy:** We don't know, but I can give you my sense.

[00:13:38] **Dr. Benjamin Greenberg:** We have an idea. What's your sense?

[00:13:40] **Dr. Michael Levy:** If we take all of the antibodies from healthy people and flood one person's immune system with it, it's going to dilute all of your bad antibodies. And then all those good antibodies are hanging around. The immune system says there's way too many antibodies here. Let's go back to a normal number and it starts chewing up all of the excess antibodies and a lot of those were bad and you just keep doing that every month after every month. And pretty soon you're not going to have any of your old bad antibodies around. That's how we think it works for MOG.

[00:14:10] **Dr. Benjamin Greenberg:** It's just as good a story as any. So, but the key there being that it's not immunosuppressive. And so, for a lot of our patients who say, geez, I don't want to take, who have this disorder. Who don't want to take an immunosuppressant because we use a drug called Mycophenolate, sold as CellCept or even some people have used Rituximab in anti-MOG associated disorder. Of all those choices IVIG is the only one that's not immunosuppressive, but it also opens up an interesting conversation because we've been at meetings and I think we agree there's a sense that IVIG reduces the risk of an attack for people who have anti-MOG associated disorder. Do you think it works for people with anti-aquaporin-4 mediated NMO?

[00:14:48] **Dr. Michael Levy:** No, I don't have a good sense of IVIG for aquaporin-4.

[00:14:53] **Dr. Benjamin Greenberg:** So, why would it work for one and not the other?

[00:14:58] **Dr. Michael Levy:** I think we can all agree that the mechanisms are different, the drugs that work for MOG don't always work for NMO and vice versa and it's okay. I mean, even though we don't understand that our observation I think is still valid, but I don't have a good explanation for why that is.

[00:15:13] **Dr. Benjamin Greenberg:** And so, this is one of the areas and I'll just zoom out the lens a little bit. When you and I were training and the Siegel Rare Neuroimmune Association used to be the Transverse Myelitis Association. But very early on Sandy and Pauline had a view of having a big tent organization. So, even individuals with neuromyelitis optica who had nowhere to go, they said, well, let's all form the Optic Neuritis ADEM. And it was actually a brilliant decision because we learned just as much by comparing individuals with these conditions as we do by everybody living in their own silo.

[00:15:55] And so, there were at the board meetings discussions, I won't say arguments, discussions for years on, we have to change the name. We're not the Transverse Myelitis Association because we offer services to so many individuals. And finally, we're able to not just recognize Sandy and Pauline's contribution but really embrace that big tent.

[00:16:18] And it's only by the comparisons that we realize even though these two conditions, neuromyelitis optica and anti-MOG associated disorder are both autoimmune caused by an antibody, affecting the brain, the optic nerve, the spinal cord, their responses to treatment are very different. And those comparisons become incredibly important. We achieved a lot in aquaporin-4 disease. Do you want to talk about the current trials going on in anti-MOG associated disorder?

[00:16:47] **Dr. Michael Levy:** There are two worldwide phase three trials in MOG going on now. You have to have an attack in the past year and it's placebo controlled, meaning there's a 50% chance you're going to end up in the placebo arm. But this is how science is done. We'll enroll these patients into our study. Half of them will get the drug, half of them will get placebo and then we'll see if the drug prevents relapses better than the placebo does. And if so, then we'll get two new FDA-approved drugs. Hopefully, we'll read out by 2027. One of the drugs is called Rozanolixizumab.

[00:17:25] **Dr. Benjamin Greenberg:** I'm sorry, what?

[00:17:25] **Dr. Michael Levy:** Yeah, I hope they come up with a good name for that.

[00:17:29] **Dr. Benjamin Greenberg:** Could you spell that? Like a spelling? Use it in a sentence, please.

[00:17:31] **Dr. Michael Levy:** No, I can't. And the other one is Satralizumab, which is a crossover from NMO Enspryng that's been developed for NMO aquaporin-4 type is now being tested in MOG type. So, there might be some overlap there. We don't think IVIG is useful in NMO, but we think that Enspryng might be useful in MOG. And so, both of those studies are currently enrolling.

[00:17:55] **Dr. Benjamin Greenberg:** And you're taking the lead on one out of Boston and it's a very different trial design. And I give you and the team credit for approaching a rare disease trial differently. Do you want to comment how you structured the trial?

[00:18:09] **Dr. Michael Levy:** We're still in development phase, but we're taking people who have a single attack of MOG, you know how I told you about half of them won't relapse. But what if we can treat all of them and ensure that nobody will relapse to really push the immune system away from relapsing in any cases? It does mean that we're treating half of patients unnecessarily, but it also means that the other half who are going to relapse maybe will never relapse. So, it's a different sort of trial design.

[00:18:40] **Dr. Benjamin Greenberg:** So, one of the critically important things for everybody to hear is it's important to get an accurate diagnosis because some of you need prevention, some of you don't. We've each experienced patients who come in on preventative where we look at their history and say you don't need to be on drug X and we've had people come to us not on preventative, where we say you really need to consider being on some sort of prevention. And then depending on what your background testing shows would dictate which therapies are worthy of consideration.

[00:19:16] And I want to stress that all of this is about preventing attacks. One of the things I have to remind my patients is that you're going to take drug X or drug Y or drug Z, it won't make you necessarily feel better. In fact, it probably won't make you feel better. It's not going to get rid of a corset feeling, a tightness or a buzzing. It's not going to get rid of those nagging symptoms. The goal if you think about Dr. Tardos talk is not to prevent recurrences of old symptoms, but to prevent relapses and the occurrence of new symptoms. So, we judge the success over time by the lack of relapses if that makes sense. What we call secondary prevention, preventing a future.

[00:19:57] **Dr. Michael Levy:** I think it's very anticlimactic because we talk about these medications in clinic all the time and patients finally get it and they're waiting to feel better, but it's not designed to make you feel better. It's just designed to prevent the next attack. So, a lot of my patients in wheelchairs will say, okay, now that I'm on this drug, how do I get out of the wheelchair?

[00:20:15] **Dr. Benjamin Greenberg:** And that's going to be the after-lunch conversation. So, we're going to get to that but these drugs don't and it's important that we set expectations appropriately. Although I will say prevention is exquisitely important regardless of a person's level of function at this moment, losing more functioning is always incredibly bad. And so, with that in mind, we wanted to leave some time for any questions around these drugs. I will preface this by saying we're always cautious. If there's a very personal specific issue, we may say see us after we'll try and keep this as general as possible. But we welcome questions about your thoughts and questions around the drugs when to use them and the differences. So, I think we have one third row and then we'll come to the front.

[00:21:02] **Audience Member 1:** So, our granddaughter had idiopathic transverse myelitis and we were told aquaporin-4 negative anti-MOG negative. We were never talked to about the possibility of needing preventative medication for her. In fact, we were told just the opposite. Monophasic, never going to happen again. Lightning strike this is not going to be something you have to worry about. Has that changed in the last few years? Is that something that is new because we've never been talked about that?

[00:21:32] **Dr. Benjamin Greenberg:** No. So, my answer and the answer Michael gave at the beginning are slightly different on that. So, if somebody has idiopathic myelitis and they have had a complete work up that's always in the eye of the beholder in terms of what defines complete, but they're negative for those antibodies that you list. There is not an indication to be on a preventative therapy. Depending on the history and the situation, there is always an indication for monitoring over time.

[00:22:03] One of the things we learned in our clinic and I don't see Dr. Carter in here. So, when I moved from Baltimore to Dallas, when I was in Baltimore, we were there together, we were seeing we're adult Board of Neurologists. And we can annoy the pediatricians in the world by saying kids are just little adults and their heads explode and they're like, oh my God, they're not little adults. But in Baltimore, we would see kids with myelitis or kids with ADEM to help with the neuro immunology side of things.

[00:22:31] And when I moved down here to Dallas, there was nobody in Dallas seeing these kids, they were all going to Houston to get care. So, we opened our pediatric center and it just exploded. And one of the rules we set at the very beginning was for idiopathic myelitis or ADEM, which was also considered a monophasic condition. Even when kids had recovered, we wanted to continue seeing them until they were past 18. We're going to see them all the way through. And the history had been 1 to 2 years out. Neurologists were saying there's nothing more for me to do. Just follow with your primary care physician or physiatrist.

[00:23:12] And we realized that's likely a mistake because we were discovering two things. One is in a lot of our kids, we were seeing as they grow new impacts of the deficits into their functioning in life that we needed to intervene on. And when I started this clinic, we didn't have anti-MOG associated disorder. It didn't exist and it was literally halfway through my tenure here where there was a brand new disease we need to deal with. And I literally had kids.

[00:23:40] So, I told this is ADEM, it's monophasic, it's never going to happen again. And then I had to say sorry. Yeah, we got smarter. And so, we really feel keeping that connection with our family is important, but to answer your direct question as of right now, there is not an indication for preventive therapy.

[00:24:03] **Audience Member 2:** So, for NMOSD, if you find that the CellCept doesn't work, then are you saying the IVIG?

[00:24:18] **Dr. Benjamin Greenberg:** Yeah, I want to make one comment and then I'm going to ask Michael. So, did everyone hear the sentence for double negative neuromyelitis optica presenting as MOG? It's a great sentence. It's a wonderful sentence. The translation is the symptoms, the areas of inflammation that a person has experienced looks like what somebody with anti-MOG associated disorder would experience either optic nerve involvement or spinal cord development. It's like walking down the street and saying, I think that's a golden retriever.

[00:24:52] But then you send the blood to the testing and they say we don't know what it is but it's not a golden retriever. It's walking like one, it's talking like one but the testing for the aquaporin-4 and MOG antibodies are both negative. And it puts us in an interesting scenario because we rely on. We love when the test is positive because we get to lump you into like groups and learn from those like groups and for those of you who just decide to be difficult and test negative on both, it causes us pause to decide where should we pull from experience. Because I just heard you say certain things work for aquaporin-4 and not for anti-MOG. So, for somebody who's in that category where they're having breakthrough disease, do you have the next chess move in mind in terms of what you do?

[00:25:37] **Dr. Michael Levy:** That's a tough one. We like CellCept because it's broad and that's our first go to for anything that we don't understand. We know it's immune mediated, but we don't know like what category to put it in. We like CellCept. If it fails and there's a true relapse. As Dr. Taylor mentioned, you really want to be sure that it's a true relapse, a true breakthrough and not a pseudo. Then you do want to consider putting something either adding something or maybe switching all together.

[00:26:06] And then you have to decide, is it MOG-ish in which case, maybe IVIG would be helpful or is it kind of NMO-ish, maybe Rituximab would be helpful and sometimes it's kind of trial and error at that point. You don't really know what it is. You're going to try one thing or the other, maybe based on side effects or maybe cost or maybe other indications you might think, let's add this and then you just got to try it.

[00:26:30] **Dr. Benjamin Greenberg:** And this notion of MOG-ish or NMO-ish, which is a great term. The chair of our department here at UT, Lewis is a specialist in movement disorders, tremors and things like Parkinson's and essential tremor. And he gave a talk this week that was phenomenal on neurology is a field of individuals who can identify patterns. And so, the first part of his talk was putting up pictures of llamas and alpacas and asking can you pick which is the llama or the alpaca? And I was like, seriously, but by the end of the talk, we could all pick a llama versus an Alpaca.

[00:27:06] And that's essentially residency and fellowship and early career literally is when Michael, when you go to see Michael in Boston, he says this is MOG-ish, it's because of the pattern recognition of seeing patient after patient after patient after patient. And that's not something that is yet transferable into a textbook or into a Google search or into ChatGPT or whatever the case may be. And so, a lot of this is in the eye of the beholder the practitioner you're working with. In terms of if you're in that, no man's land of getting a diagnosis, what seems most correct? We're not always right. In fact, we're wrong all the time we're going to be wrong, but the batting average goes up as people see more and more of these.

[00:27:55] **Audience Member 3:** So, I was treated with an off-label therapy which is Rituximab three months ago and I didn't respond well to it. It elevated my liver enzymes and I just recovered from that. So, my question is that out of the three approved therapies that are there, which one of them would you recommend or would you suggest that would work for me?

[00:28:27] Because at the moment I'm a little skeptical and afraid and I'm not quite sure which one to go for. I know that my doctor has recommended Enspryng for me, but I'm just a little scared and I'm not quite sure if I'll manage to like inject myself. And over and above that, I'm just obviously afraid and I don't know how I'm going to respond to that, especially my liver. And you know if it's going to affect me health wise.

[00:29:01] **Dr. Benjamin Greenberg:** I love this question because the answer is ultimately a very personal one. And I can tell you how we would manage this in my office space which is going to be different than all my colleagues but with one. What we share is one common approach of this notion of shared decision making. So, if you turn back the clock, five decades, you'd go to a physician, you'd tell him what was wrong. They do an exam, they take on a pad, they'd write something down and they say take this. And there was no discussion, there was no anything.

[00:29:39] And what we found was if you take that approach today, the adherence rate and compliance rate is like 5%, you know? People are saying, wait, I don't know what I'm taking, why I'm taking it. And we learned in medicine that we really do have to discuss the options, the pros and cons of each. And I'll tell you in this exact situation, I have some patients who tell me Dr. Greenberg, I don't care what you say. I'm not doing an injection. Well, then that makes an injectable therapy a bad recommendation on my part if they're just going to leave it in the refrigerator.

[00:30:12] I have some people who tell me, Dr. Greenberg, I'm thinking about getting pregnant this year. Well, that's a different conversation. One of the drugs we use in NMO is an infusion every two weeks and I have some patients who say I just can't do that in my schedule. So, it really is a very personal discussion. Relative to liver toxicity can we rank the drugs in terms of the percent of people who had changes in liver enzymes? We can. And I'm happy to share that data with you in terms of how frequently it happened. But it doesn't mean we can't predict who's going to have a reaction to any given drug.

[00:30:49] So, just because you have it with one drug doesn't predict you'll have it with another. So, it really is understanding the pros and cons of each. There's not a single right answer for the group. There's a single right answer for you. And then my favorite question I get is Dr. Greenberg if I were your brother, which would you recommend? And I say, well, my brother beat the crap out of me as a kid. I take the chemo, you know. So, it really is my answer for me may literally be very different than your answer for you. I don't know if you have a set answer or?

[00:31:25] **Dr. Michael Levy:** I would agree with that, that the priorities for everybody here are different. And sometimes I look at my patient, I say, why are you picking that? That's not my decision for you, but that's their decision. Everybody makes their own decision.

[00:31:37] **Dr. Benjamin Greenberg:** But the key is making sure you're getting that information, that communication. And for everyone in the audience doesn't matter if you have one of these diagnoses or not. So, there's a question for everybody who has seen a health care provider of any kind in the last year. For how many of you was the face-to-face visit more than 45 minutes? All right, one, two, for how many of you was it less than 20 minutes? Somewhere in between. We've had the whole morning talking so far and we're inching into more and more knowledge.

[00:32:15] What are the odds I'm going to be able to go through three FDA medicines, two off label medicines, the pros and cons of each in a meaningful way in 20 minutes? It's zero, there's zero chance, none whatsoever. And so, it is extremely important for you to listen to your health care providers, for you to come prepared and have strategies for how to engage with them to ask the questions and do the digging, that you not only should do but want to do and that you need to do before making a decision.

[00:32:48] **Dr. Michael Levy:** You do talk a lot then.

[00:32:49] **Dr. Benjamin Greenberg:** I do talk a lot.

[00:32:51] **Dr. Michael Levy:** You could shorten it and probably get through the three drugs.

[00:32:54] **Dr. Benjamin Greenberg:** So, I used to in NMS when we had, when we were at six drugs, we're at 26 now. When we were at six drugs, my rule was I discuss every drug. For a new diagnosis patient I discussed every drug start to finish and then we got a seventh drug and an eighth drug. And I would time my talk and my talk got to 65 minutes of going through drugs. And literally, I think some of my patients were like beating their head against the wall, like, I'll take the shot like just shut up, you know? And literally, but I took pride in the fact that I offered everything. I can't anymore. 26 it'd be mean, it'd be cruel and unusual. And so, we have to find ways to simplify things.

[00:33:35] **Audience Member 4:** I had a question about the IVIG, how can you be confident that when you're taking those antibodies that you were not unwittingly receiving rogue antibodies that have yet to be identified?

[00:33:51] **Dr. Michael Levy:** You are getting those antibodies. In fact, if you're going to be tested for anything on IVIG, you're probably going to test positive, but it doesn't mean that you're going to get those diseases.

[00:34:04] **Dr. Benjamin Greenberg:** So, just having an antibody that somebody else produced that is reacting against the self target isn't enough to induce the disease it turns out. Your own immune system, the cells that make the antibodies have to be present for you to have the clinical manifestation of the disease. So, it's not enough to have the antibody. So, Michael tried for years to get mice to get sick by just putting antibodies into them and tons of antibodies. And the mice were like, hey, I'm fine, I am fine and it was only until you change other parts of the immune system that you get a clinical manifestation of the disease.

[00:34:39] So, one of the issues is if you're on IVIG to Michael's point, if you get the IVIG on Monday and then a health care provider on Tuesday says, oh, I want to test you for autoimmune disease. You're going to have some abnormal results. And we get a lot of referrals from people who say, oh, Celine Dion has stiff person syndrome. I just tested positive for anti-GAD antibody, which is the antibody with it. And we see that positive after IVIG all the time.

[00:35:08] And so, but we don't see anybody get the actual disease. So, it's a safe thing to do. Now, I will say for these disorders, aquaporin-4 in particular groups have gone through testing tens of thousands of healthy individuals and they can't find the antibody. So, it's not out there in the population circulating and you're going to get exposed to it.

[00:35:36] **Audience Member 5:** So, I actually have two, but I think I'll save one for the hallway maybe. I'm aware of several people like me that are aquaporin-4. And pretty much since we started taking Rituxan or biosimilar, we've also had to supplement with IVIG to keep us out of the hospital. I was going in every four to six weeks and this is similar for other people. When would you consider switching drugs from Rituxan and the IVIG to keep people out of the hospital to maybe something else or is that just part of the deal?

[00:36:10] **Dr. Benjamin Greenberg:** So, I'll give you a piece of information and then I'll give Michael the hard question. So, there's about depending on the study you read 8 to 15% of people on Rituximab whose natural overall antibody levels will drop over time. And then of those, there's a subset of patients who will start having recurrent bacterial infections, sinus, pulmonary, urinary tract infections. And when you give those individuals back antibodies, the IVIG their infections clear up.

[00:36:38] So, that's the situation that's being described. And so, we're giving one drug to prevent autoimmune disease. We're now inducing an immunodeficiency leading to recurrent infections and giving a second drug to prevent the infections. At which point everybody agrees. Isn't there a better way to do this? Should we be looking for a switch? Michael, should we switch?

[00:36:59] **Dr. Michael Levy:** So, I would say, yes.

[00:37:01] **Dr. Benjamin Greenberg:** See how I did that?

[00:37:03] **Dr. Michael Levy:** He's setting this up for me. Makes it easy. In our patient population, it's more like 25% who get to that point. But we can see it coming down years ahead. We watch the immunity waning, waning over time. So, we can tell you're eventually going to need IVIG. We looked at strategies to prevent that. Maybe by reducing Rituximab dose or extending the interval, nothing works. If you're going to be one of those people, you're just going to be one of those people and you either have to go on IVIG every month or switch to something else. I've been switching people because if you're taking monthly IVIG, that's a burden in itself. Every three weeks, yeah.

[00:37:43] **Dr. Benjamin Greenberg:** Yeah, we've done it a little, we've played with what's the lowest amount of IVIG we can get away with and keep people out of the hospital. And so, if we can extend that out, not every three weeks and in most of our patients we can and it works. But it really is that frequency we have the conversation about. So, I want to be cognizant of time. We'll do one last question.

[00:38:13] **Audience Member 6:** Are any of them more harmful than others? For instance, I've only had one attack when I was first diagnosed but my antibody count was positive and it was very hot, but I've not had another attack. The only thing I have now is chronic fatigue and then I can't finish for it. Since I haven't had the, just the one attack, I don't have any lesions anywhere. Could I switch from Rituxan to a drug that's maybe not quite as helpful. And would it help with the fatigue?

[00:38:52] **Dr. Benjamin Greenberg:** So, the second part, first, the answer is no. So, I don't advertise any of the drugs as helping with symptomatic management. So, that's a separate management approach other than these preventative drugs. That's my standard answer. Do I have some patients on a drug who say they felt better over time? It's like bonus, but it's not the reason I prescribed the drug. Is one more potent or harmful than the other? In my mind, they each have risks that are unique to each drug and the risks are different. So, it's picking which risks seem most manageable to you and your health care provider.

[00:39:36] I'll give you one example just to point this out. So, Eculizumab Solaris, which is FDA-approved for aquaporin-4 NMO is an every two week infusion. It is a very good medication for preventing attacks. The major risk to it is development of what's called meningococcal meningitis. It varies risky bacterial infection causing meningitis and the way it presents is fever and headache and sometimes the headache comes first.

[00:40:07] So, if I have a person with frequent migraines and I'm having a hard time controlling their headaches, do I want to put them on this drug and then six weeks later they call the clinic and they say, hey, Denise, I'm having a headache and I'm trying to decide, do they need a spinal tap or not? Is it the meningitis or their migraine? So, for each patient the risks may impact them differently in terms of their life. I don't think I have one that I would say is uniquely different in terms of overall risk.

[00:40:39] **Dr. Michael Levy:** They're all fairly safe. I mean, I'm not too worried about meningococcal meningitis that it does happen and we can keep an eye on that, but they're all fairly safe. And as far as side effects, I do wonder though if the Rituximab could be contributing to your cognitive fatigue, but I haven't seen that. But if

you're reporting that maybe immediately after the infusion, you get worse and then it starts to ease up over time. Maybe consider switching just to see if it's a unique side effect that maybe only you have.

[00:41:13] **Audience Member 6:** It's constant.

[00:41:14] **Dr. Michael Levy:** It's constant.