ABCs of NMOSD Podcast Series
Choosing a Long-Term Treatment Option

The audio of this podcast is available at: https://youtu.be/gA4AOUwV018

Intro: [00:00:00] ABCs of NMOSD is a 10-part education podcast series to share knowledge about Neuromyelitis Optica Spectrum Disorder, or NMOSD, a rare relapsing autoimmune disorder that preferentially causes inflammation in the optic nerves and spinal cord. ABCs of NMOSD podcast series is hosted by SRNA, the Siegel Rare Neuroimmune Association, in collaboration with the Sumaira Foundation for NMO, the Connor B. Judge Foundation, and Guthy-Jackson Charitable Foundation. This education series is made possible through a patient education grant from VielaBio.

GG deFiebre: [00:00:59] Hello, everyone, and welcome to the ABCs of NMOSD podcast series. Today's podcast is entitled "Choosing a Long-Term Treatment Option." My name is GG deFiebre from the Siegel Rare Neuroimmune Association. For today's podcast, we are pleased to be joined by Dr. Benjamin Greenberg, Dr. Brian Weinshenker, and Dr. Stacey Clardy.

[00:01:22] Dr. Benjamin Greenberg received his Bachelor of Arts degree from Johns Hopkins University, and his Masters Degree in Molecular Microbiology and Immunology from the Johns Hopkins School of Public Health in Baltimore, Maryland. He completed his residency in neurology at The Johns Hopkins Hospital, and then joined the faculty within the division of neuroimmunology. In January of 2009, he was recruited to the faculty at the University of Texas Southwestern Medical Center where he was named Deputy Director of the Multiple Sclerosis Program and Director of the new Transverse Myelitis and Neuromyelitis Optica Program.

[00:01:58] Dr. Greenberg is recognized internationally as an expert in rare autoimmune disorders of the central nervous system. His research interests are in both the diagnosis and treatment of transverse myelitis, neuromyelitis optica, encephalitis, multiple sclerosis, and infections of the central nervous system. He currently serves as the Director of the Neurosciences Clinical Research Center and is a Cain Denius Foundation Scholar.

[00:02:23] Dr. Brian Weinshenker is a Professor of Neurology and Consultant at Mayo Clinic in Rochester, Minnesota. Dr. Weinshenker's major research interests are directed at the understanding of inflammatory demyelinating diseases of the central nervous system, including multiple sclerosis, including the natural history of multiple sclerosis, defining clinical and radiologic differential diagnoses of inflammatory myelopathy, classification, diagnosis, and treatment of severe inflammatory demyelinating syndromes of the central nervous system, including neuromyelitis optica and McArdle's sign, a recently rediscovered clinical sign that is highly specific for multiple sclerosis. He was awarded the John J. Dystel Award for multiple sclerosis research in 2011 by the American Academy of Neurology and National Multiple Sclerosis Society.

[00:03:13] Dr. Stacey Clardy is both clinical and research faculty in the Division of Neuroimmunology within the Department of Neurology at the University of Utah. Prior to joining the University of Utah team, Dr. Clardy furthered her training with a fellowship in Autoimmune Neurology at the Mayo Clinic for training and experience focused on the evaluation and management of autoimmune and paraneoplastic disorders of the nervous system. The spectrum of autoimmune and paraneoplastic neurological disorders intersects all traditional neurology subspecialties, including movement disorders, epilepsy, behavioral/cognitive, neuromuscular, autonomic, demyelinating, and neurooncologic.

[00:03:52] Welcome, and thank you all for joining us today.

Dr. Clardy: [00:03:57] Thank you.

GG deFiebre: [00:03:58] So, to start, if we could just have kind of a brief overview of what the most common long-term treatments are for NMOSD, and why these treatments are given. Dr. Clardy?

Dr. Clardy: [00:04:16] Sure. So this is evolving, right? As you know, the three pivotal trials for NMOSD wrapped up over the last 12 to 18 months. And so the answer to that question was quite different two years ago compared to where it's moving now. I think we all try to stay away from steroids outside the acute period or for relapses. And so, if we go back 10 years, people used things like, mycophenolate mofetil and azathioprine quite commonly.

[00:04:47] At that time, it was difficult to get, CD20s like rituximab, as we know, approved. That's become much easier, fortunately. And if we go back even further, it's a bit more relevant, but it used to be treatments like methotrexate and things like that. So, if we look at today, some people still continue on commonly azathioprine, mycophenolate mofetil, and rituximab.

[00:05:10] And then there are the three newly tested medications, one of which is already approved, eculizumab. The other two are wrapping up their FDA review process. That's inebilizumab and satralizumab. So, those will probably come more into the conversation over the next six to twelve months. I guess the other piece of that is acute relapse treatments or acute treatments at the time of first attack. And for that, I think many of us still consider using a high dose methylprednisolone and/or plasma exchange or plasmapheresis to get the antibodies out quickly. And then we move to the other treatments I mentioned first to prevent future relapses.

GG deFiebre: [00:05:54] Okay, great. Thank you. And then, Dr. Weinshenker, how do these treatments work that Dr. Clardy just talked about? You know, the three most commonly used, and then the three that are potentially, you know, the one that is recently approved, and then the two that are coming out. And how are these treatments given?

Dr. Weinshenker: [00:06:13] Well, thank you. It's nice to be here. Basically, neuromyelitis optica is a disease of the immune system, and we think that the majority of patients have antibodies, and 70% directed to aquaporin-4. So, the goal of treatment is to suppress these levels of antibodies, which we think are directly responsible for the problem, and this involves suppressing the immune system.

[00:06:43 The common treatments that are being utilized now, azathioprine and mycophenolate mofetil, work on DNA metabolism and purine metabolism. And because of the way immune cells replicate, they're relatively more sensitive to these medications than other cells in the body. So, basically, these result in a diffuse immune suppression. Rituximab, which is an antibody that's infused and is directed to B cells, is somewhat more specific. It depletes, almost completely, B cells in the blood, and to some extent, in the tissues. And, this would be predicted to result in a decrease in antibody production.

[00:07:34] The antibodies don't necessarily disappear completely, but there seems to be enough of an effect on production of antibodies that we see a very substantial clinical effect. So, yeah, it's an antibody. All of the new drugs that Dr. Clardy talked about are also antibodies. They have somewhat varying targets. Inebilizumab, which is a drug that's not approved yet, also targets B cells like rituximab, but a somewhat broader swath of B cells. And, we're all hopeful that that more, somewhat more extensive spectrum of B cells that are targeted, by doing so, the drug may even be more effective than rituximab. Although strictly we do not have good data comparing rituximab with inebilizumab.

[00:08:28] Eculizumab or Soliris, which is a drug that was just recently approved last June in the United States and also was approved in Europe and Japan, works by targeting a protein called complement. And when these antibodies interact with aquaporin-4, they activate complement. Complement, in its own right, causes a lot of damage in tissues. And it can also attract other cells like eosinophils and neutrophils. And so, it has a lot of downstream consequences.

[00:09:02] And eculizumab blocks one of the key proteins in complement called C5 and prevents that activation in tissue damage that occurs. So, that's how that one works. And satralizumab targets a receptor for a cytokine, which is a chemical that circulates and is generated by a number of different inflammatory disorders called IL-6. And IL-6 has a number of effects, one on B cells. It promotes survival of B cells, but it also has effects on T cells. It has effects where the blood brain barrier becomes leaky and allows antibodies to get into the brain. And by these actions on IL-6 and blocking the effects of IL-6, there are a number of different mechanisms by which we think satralizumab seems to interfere with the NMO process.

GG deFiebre: [00:10:06] Great. Thank you for that overview. And then, you know, in terms of how these treatments are given to a patient, you know, are they pills, infusions, injections? Dr. Greenberg, do you mind just giving an overview of that?

Dr. Greenberg: [00:10:20] Certainly. So, the medications that have been mentioned by Drs. Clardy and Weinshenker involve all different forms of administration. So, the use of, historically, mycophenolate mofetil sold as CellCept, or azathioprine sold as Imuran and prednisone were all pills. The currently used drugs rituximab was an infusion, an IV, where you'd go to an infusion center usually twice a year to have it administered.

[00:10:50] With the newer medications, the eculizumab, whose name brand is Soliris, is an infusion that is currently every couple of weeks and is a much shorter infusion time than rituximab. And satralizumab, which is not yet approved and is under consideration, is an injectable medication. It gets injected into the skin, and after the first few doses, people wind up on a once a month injectable schedule. The assumption is that people will be trained to do injections themselves at home, and that you will not have to go to a physician's office in order to get the injection. But we are awaiting FDA approval and guidance for that.

[00:11:39] And then finally, inebilizumab, which is the medication Dr. Weinshenker was just referencing that kills off B cells in a more expanded way than rituximab. Inebilizumab is an infusion, and similar to rituximab, the plan is to give it every six months.

GG deFiebre: [00:11:59] Okay, great. Thank you. And then are there any particular side effects of each of those treatments that are commonly seen, Dr. Greenberg?

]**Dr. Greenberg:** [00:12:08] So, for the new medications, we track the negative things that could happen in two different categories: side effects versus risks. Your question is specifically about side effects, meaning could people feel bad taking these medications? And in general, the answer has been no. That's a broad statement based on the publicly available information for the two drugs that have not yet been FDA approved.

[00:12:38] And then, for eculizumab, from the experience prior to neuromyelitis optica and from the trials with neuromyelitis optica, the side effects are relatively few. For any infusions, we worry about infusion reactions - people feeling itchy or feeling as though they're having changes in their breathing. Those have all been either nonexistent or mild and have not proven to be an issue.

[00:13:04] With injectable medications, we worry about injection site reactions, either stinging or burning, or issues in the skin. And for the publicly available information for satralizumab, again, we haven't seen the final product approved by the FDA. But for what's been available, this has not been a big issue. Thankfully, for all of these drugs, we do not see side effects that people see with things like chemotherapy. So, whenever we're suppressing the immune system, people use cancer treatments as kind of a litmus test. And a lot of cancer treatments have obviously gotten a bad name because people can have nausea or vomiting, or feel tired, or have diarrhea, or loss of their hair, and those types of things we do not see with any of these medications.

GG deFiebre: [00:13:55] Okay, great. Thank you. And then, in terms of efficacy, so if someone is trying to figure out what medication to use, are they all kind of seen as equally effective or do some work better than others, or is it based on some factor in the person who's diagnosed with NMO? Dr. Clardy.

Dr. Clardy: [00:14:15] This is the million-dollar question. [laughs] We're never gonna be able to fully answer which one is better than another one because there probably will never be head-to-head trials. Meaning, you would compare, say, Imuran to mycophenolate mofetil. These won't happen, right? This is just something that really no one's going to pay for, at least on the pharmaceutical side. It's just not a wise business decision to compare your compound head-to-head to another one, unfortunately. We would love that data as clinicians.

[00:14:52] So, the best we have to go on tend to be studies that are done by institutions or our colleagues in Europe where they can collect data from the entire country and sort of do a retrospective head-to-head or even sometimes a prospective one. So, it's a tough question. There's a lot that goes into that.

[00:15:10] I will say we have a general sense. So, let me give you the general sense, and then we can ask Brian or Ben what their thoughts are too. From the retrospective studies and those other studies I alluded to in Europe, we have a sense that perhaps if we're just looking at straight efficacy and preventing relapses, that maybe the infusions are a bit better than the oral medications. There's a big caveat there because, you know, with the oral medications, for example, we don't know if somebody is missing doses, and that could affect how well it works. You know, we're all human. If something is dosed once or twice a day, we're bound to miss a dose.

[00:15:44] Whereas when we look at the infusions, we can track that, and we know that people are 100% compliant because as physicians, we get reports back from the infusion center and we get the labs back, so we know if someone has missed an infusion. So, all these things make it difficult in terms of which one works better. And so, ultimately, the decision for which medication to start is a very personalized one.

[00:16:06] And I know from training under Brian, and I'm sure Ben does the same, that this is a discussion you have one-on-one with the patient. You lay out all of the options, all of the available medications, and then you consider any number of variables. Very often in Utah, we have a younger population, and so, one of the first things I'm asking is, you know, "Are, are you gonna plan to have children? When would you like to do that?" That's one that we have to address right away based on safety and pregnancy.

[00:16:33] But many, many other variables. Do you travel a lot? Can you get an infusion? Are you afraid of needles? You know, do you absorb well from your GI tract? You know, all sorts of things like this play into the discussion. It absolutely has to be a very personalized... I

mean, this discussion takes usually at least 30 minutes if that's all we focus on in terms of choosing which one. Now, having said that for the three new trials, and Ben and Brian can elaborate here too, they do look to be... All three of the drugs that just completed trials, the eculizumab, the satralizumab, the inebilizumab, all look to be very effective.

[00:17:08] So, you know, there's a lot of good options. That's the really exciting part. There are so many options and choices now just in the last couple of years. So, it really opens things up for a lot for our patients, which is very exciting for us. We love to offer them options.

[00:17:25] One other piece I will add in there is, and then we're going to get to this later, I think too, it is hard to know when we're just looking at one or two years of data or comparing just short term because what we know about NMO, especially the aquaporin-4 NMO, is that you can go a decade in between attacks. Even natural history-wise, back before we had treatments, some people will go a decade, some people will go three months. And so, you really have to look at the long-term when you're trying to decide which one is more effective.

GG deFiebre: [00:17:57] Got it. Thank you. Dr. Greenberg, Dr. Weinshenker, do you have anything to add to that?

Dr. Weinshenker: [00:18:03] I think Stacey gave an excellent answer, and she pointed out the various things that we can do to try to assess the relative effectiveness. Certainly one of the best approaches are head-to-head. And there have been a small number of studies that have tried to compare one with the other. For example, there was a recent study from China comparing tocilizumab with azathioprine. Tocilizumab is very similar to satralizumab. And they, tocilizumab and satralizumab, both antagonize that IL-6. And it seemed like tocilizumab maybe looked a bit better. Similarly, there being, there was one uncontrolled, open label comparative study between rituximab and azathioprine that suggested rituximab is better.

[00:18:55] But, all of these are really pretty imperfect studies, small numbers of patients, and short follow-up. So, I think, you know, we put together a number of factors including how much experience we have with the drug over what period of time. I think we certainly look at safety issues. Ben talked about side effects. I think he just didn't have time to get to the next issue that he had mentioned is what is their safety?

[00:19:27] And fortunately, most of the treatments we've looked at have been very, very safe. But on the other hand, I think, you know, now we're in the time of COVID, and none of these studies were really conducted, say, at a time like this. And we have to ask ourselves, if we were in such a situation, or if this ever came up again, would the safety look as good? Because we know that all of these drugs do suppress the immune system. And would they have differences in terms of susceptibility to COVID, say, for example? This is a big issue

that's come up now. And these are largely unknown, but issues that I do think that we have to consider.

GG deFiebre: [00:20:14] Yeah, I think that's a really good point, especially with, you know, everything that's happening now. And I know we've gotten a lot of questions from our community about that as well. Dr. Greenberg, do you have anything to add?

Dr. Greenberg: [00:20:27] I think the points that Dr. Clardy and Weinshenker made are dead-on. This is gonna be a tough thing to do, a very scientific comparison between these agents relative to efficacy. But one of the reasons it's tough is because at least from the data we're seeing, the medications seem to be working for a large number, if not the majority, of patients. And while there'll be responders and non-responders to any drug, at a population level, I think we have a number of tools in our tool chest to put patients into remission.

[00:21:08] And so, ideally, what we would come up with as a community of scientists, clinicians, and patients are ways to predict responders and non-responders because each of these drugs have proven to be, of significant value at the patient population level. It's really a matter of figuring out who should start with which first. And at this point, we don't have a way to predict responder or non-responder status. And so, to me, more valuable than knowing drug A is 5% more effective than drug B, I'd really wanna know which patient population would benefit from each individual drug the most.

Dr. Weinshenker: [00:21:53] I think that's an excellent point that Ben made, that all of our treatments that we use, all of the ones that were mentioned have been really very, very effective. And, you know, many of us also care for MS patients. MS, in a way, is a less severe disease. The attacks are less severe. But in terms of our ability with any of the medications we use with MS to achieve the degree of attack suppression we've seen with NMO, we just haven't seen it. We're actually much better, especially in the aquaporin-4 positive most severe kind of NMO, we're really pretty good with our current armamentarium at suppressing attacks.

[00:22:37] And one thing that's been clear is if one of the drugs is not working, switching to another drug often will help. It's not as if, well, if you're not responding to one of them, none of the drugs are gonna work for you. There's actually a lot of opportunity to get much better suppression of the disease by switching to another drug. So, I think it is a very hopeful message for what's being achieved over the last 20 years in terms of all these treatments.

GG deFiebre: [00:23:08] Thank you. And then just to follow up, in terms of when you're speaking to someone diagnosed with NMO, what factors should they consider when choosing a long-term treatment? Do you consider things like age, gender, the severity of their previous attacks or their number of previous attacks? What goes into that discussion and the decision-making process there? Dr. Clardy?

Dr. Clardy: [00:23:32] Yeah, I sort of alluded to this a little bit. It's a very personalized discussion, and a lot goes into this. And the elephant in the room, too, that I really try to make the effort to discuss more is also cost. You know, I have to bring that up to every patient as well. Azathioprine is pennies on the dollar for most, and so that is a very easy medication to get ahold of with costs.

[00:24:01] The rest of them, I'm trying to do a better job talking with patients and trying to predict what their actual out-of-pocket costs will be, to see if in some of these cases the pharmaceutical company can pitch in to help, all those sorts of things. Because with all these therapies, we haven't necessarily really touched on this yet. My approach at this point, I think the approach of most is that you remain on these therapies lifelong, because we know that you can have an attack at any point, a relapse at any point. And so, I tend to leave patients on these for the long-term. And so, cost is a huge deal. I don't want to medically bankrupt my patients. So, I talk about that at some point in the discussion, usually not first, but it has to come up. [inaudible 00:26:22] pregnancy, absolutely.

[00:24:49] You know, this condition disproportionately affects females and young females. And, you know, as I tell them in the office, "I want you to live as normal life as you can and for this to be, hopefully, an inconvenience, while we're preventing attacks, and go on, build your family, you know, work if you can," things like that. So, all of those things are factors. I don't know if you want us to get into specifics of which ones we recommend in each situation. Do you want us to do that?

GG deFiebre: [00:25:18] If you think it would be helpful if, if there are kind of those distinctions that you're able to make, if, you know, I leave that up to you.

Dr. Weinshenker: [00:25:26] Stacey, does being aquaporin-4 positive versus not influence your recommendation?

Dr. Clardy: [00:25:36] This is a leading question. [laughs] So certainly I think aquaporin-4, everybody who's here today knows that we have a lot more data on that, much of it from the Mayo. But, you know, aquaporin-4 is pretty clearly pathogenic and we know, from a lot of Brian's work honestly, that you can go a decade or more and things seem to be going fine and then you have a devastating attack. So, that is the rationale on which a lot of us operate when we say, "Look, we're going to recommend lifelong therapy here."

[00:26:07] I think MOG is still very much in the learning phase, and Brian and Ben will talk about that more. We don't have the evidence base yet for MOG. I know one of the questions that's been typed up is about that, you know, what are you doing for MOG? What are the trials for MOG? MOG is several years behind aquaporin-4 right now because we're still very much, I think, in the small series, the data gathering, and organizing perhaps trials larger scale, high quality trials for MOG.

[00:26:37] So, I think a lot of the answers I'm giving are focusing on aquaporin-4. Right now for MOG, I tell patients, I'm very frank with patients, I say, "We're gonna come up with a plan today and we're gonna revisit that plan in 24 months because we're gonna know a whole lot more in two years." [laughs] You know, it's just the truth. And so, that's what I tell the patients.

[00:26:56] And then that plan tends to depend on the severity of that first MOG attack. If it's, you know, the entire spinal cord with some eyes, then I'm gonna be more aggressive and treat it more like I would in aquaporin-4, at least for these first two years. Versus, if it's a mild optic neuritis, that discussion maybe has more of a focus on do you want to do a watchful waiting? Do you want to treat for a period of six months and then stop and recheck titers.

[00:27:23] But back to the aquaporin-4, you know, I will tell you, as time is going by, I'm tending to favor the oral medications less. And I think this is being informed by the studies that Brian was alluding to. Other studies as well. There was just one recently, I think it was Lancet Neurology about rituximab that came out last week. And we're doing a deep dive into our data here at the University of Utah as well, and it seems so far, preliminarily, like the rituximab patients are doing better over the long term.

[00:27:53] There's a couple of, you know, it's also more affordable now. I can get it for patients, so it takes that money discussion out. And, for many of my patients who are fortunate to be, you know, partially or largely recovered, you know, these are folks who we try to get back to working full time and maximizing all their activities of daily living. They also tell me, at the end of our discussions, they prefer the option of a rituximab because in that sense, then they only have to really deal with their NMO head-on four days a year. And those are the four days of the infusion. So, that's one take on it. Brian, tell me yours.

Dr. Weinshenker: [00:28:32] No I think that's excellent. In general, in the aquaporin-4 patients, are ones that we worry about more because they have more severe attacks and are less likely to recover. And patients, as you said, with MOG disease were less clear about how things might go with them. And some of them, the antibodies seem to go away and there seems to be less of a chance of a relapse. I point out that for the new medication that's been approved, Soliris or eculizumab, the study was done exclusively in patients who were positive for aquaporin-4.

[00:29:09] And one of the messages that seems to have come out from the other studies of satralizumab and inebilizumab, is that patients who do not have a positive test may not respond as well. I don't think we have definitive evidence because, certainly in the inebilizumab study, there were only a small number of patients who were negative. But a third of the patients who were in the satralizumab studies, the two satralizumab studies, were negative for aquaporin-4 antibodies. And they didn't seem to show any response at all to satralizumab.

[00:29:47] So, I think we don't have definite answers, but it does seem like there is a difference in how patients respond and struggle for the new medication, which is very expensive, eculizumab in the range of a half million dollars per year. Especially in a patient who was negative for aquaporin-4 antibodies, I'd be unlikely to recommend it.

GG deFiebre: [00:30:09] Thank you. And then, Dr. Greenberg, are there any different considerations for pediatric patients with NMO?

Dr. Greenberg: [00:30:18] So, there are. It turns out that the majority of pediatric patients who meet the clinical criteria for neuromyelitis optica spectrum disorder, a large number of them have the anti-MOG antibody that Dr. Clardy was referring to. And so, I think it's gonna become very important for us to separate out our patients based on which antibody they have or if they have none detectable.

[00:30:44] And so the aquaporin-4 antibody positive patients, as Dr. Weinshenker was just mentioning, responded differently to certain drugs in clinical trials. So, [inaudible 00:33:15] the lens in pediatrics to just consider them a unique population, there are several factors that have to be put into context when treating them. The first is that these children are still developing, not just neurologically but immunologically. And the impacts of immunosuppression or immunomodulation in a pediatric population, especially for a condition that may require very long-term immunosuppression or immunomodulation, is not fully understood in the same way we can track adults.

[00:31:33] Changing the way a preteen or teenager's immune system develops may have implications for them much later in life. Unfortunately, we do not yet have treatments that can reprogram the immune system without suppressing it. So, it is definitely an evil that we are aware of, a risk that we are aware of. But I think the consensus is, especially in children who have the anti-aquaporin-4 antibody, that the benefits of immunosuppression outweigh the risks of changing a developing immune system.

[00:32:16] Some of the other unique issues that have come up in that backdrop is around maintaining a vaccination schedule if, depending on the age of the patient, they haven't completed their vaccinations. Because we definitely do want our kids getting vaccinated for preventable diseases. And then watching for any unique exposures that can come up in kids more than adults. Things like mono caused by the Epstein-Barr virus and managing complications in an immunosuppressed child.

[00:32:45] Luckily, what we found is complications in these patients, albeit we have small numbers, have not been different or higher than what we see in the adult population. And so, while we have theoretical concerns about the long-term impact, thankfully so far the data we're seeing is the children tolerated quite well. The one other consideration I would just put out when talking about the pediatric population is the mental and the emotional aspect of things. A lot of these kids have gone through hospitalizations, procedures, testing,

invasive testing, and they have not yet developed the coping skills that we hope adults develop. And not all adults do. We- a lot of us develop, poor and/or unhealthy coping skills.

[00:33:37] But children are particularly vulnerable to developing anxiety or mood changes or poor coping skills due to stress, because they're being thrust into these situations at a young age before they've had a chance. And so, for any of our kiddos who are dealing with these chronic conditions that require treatment, we put a high priority on making sure they all get evaluated relative to the mental, cognitive, emotional, and psychosocial aspects that come with a chronic disease.

GG deFiebre: [00:34:07] I think that's a really good point about considering the emotional consequences as well of having this diagnosis and what goes into that. So, thank you. And then, Dr. Clardy, you did mention a little bit about insurance considerations and not wanting to medically bankrupt your patients. Can you just talk a little bit about are these treatments used off label? What's approved for NMO and what isn't, and how that factors into what gets covered and not?

Dr. Clardy: [00:34:40] Yeah, absolutely. That's an important part of this. So, for the three medications; inebilizumab, satralizumab, and eculizumab, and I did type them out in the comments, if you want to see the spelling, someone wisely asked. You know, presuming that all of them ultimately get FDA approval, that means they will be on label. And so, at least in that sense, then insurers are forced to consider them if a physician recommends them.

[00:35:09] What we're seeing already with eculizumab, owing to the price tag that Brian mentioned of half a million dollars a year, is that some insurers are instituting what's called step therapy. Meaning, as a matter of their sort of templated policy of what they will cover, they will try to say that eculizumab will not be covered until a patient has "failed" in other therapy.

[00:35:35] This is sort of a slippery slope. Sometimes you'll find this, you know, you'll find insurers mentioning that this is what they're doing. Sometimes it will be more of a covert thing that we discover as we're going through the approval process for our patients. You know, these things are intentionally made quite opaque, not only to patients but also to physicians. And so this is a hurdle that has to be crossed.

[00:35:57] But at the very least, when things are FDA approved, the insurance companies do have to acknowledge that and they do have to consider the request. When you look at what we went through over, say, the past decade when trying to get rituximab approved. Rituximab has always been and will continue to be off label, right? There's no incentive for the pharmaceutical company to try and obtain labeling for rituximab at this point. This gets into the business of medicine a bit where satralizumab is actually, similarly... it, it's basically the same drug company that manufactures rituximab, right?

[00:36:32] And satralizumab would theoretically be on patent, and so they're not going to compete against themselves. And so, rituximab will not get labeling, likely. So, in the past decade when rituximab was favored for some of our patients who, say, failed one of the oral therapies and we would try to get it, we could immediately be told no by the insurance company because it was not FDA approved, right? So, these are sort of the behind the scenes shenanigans that we go through to get our patients the right therapy for them.

[00:37:01] So, what has happened though with rituximab, the cost has come down over time. And that same pharmaceutical company, I've had great success in them giving us, per se, the drug for free. Of course, we all know nothing's for free, but discounting it significantly one way or another, often by asking sort of nosy financial questions to the patients or other mechanisms. But it's appreciated. You know, at the end of the day, if my patient and I want rituximab and we can get it somehow discounted, you know, we'll do whatever we can to do that.

[00:37:32] What that does not account for, as many people will realize, is, so you get the drug for free, but there are significant infusion costs, right? So, one can still incur a significant financial burden if you're only on the hook for the infusion costs. And so we try to do other things to leverage that. So there's many, many pieces to this. I think most of us physicians who treat any number of NMO patients or the rare disease patients have a pretty good protocol in place to advocate for our patients.

[00:38:00] But at the end of the day, often after, you know, sort of the first visit where the patient tells me what therapy they want to pursue, I say, "Okay, well, we're gonna be in close touch with you over the next month as we will march through all of these sort of processes to get approvals and to try and minimize funding." And, you know, just to make it further complex, it's different for every single payer, right?

[00:38:20] So, yeah, this is a huge burden administratively on our practices. One that's necessary. And I don't know that it's gonna get any simpler with the three FDA approved drugs because, again, they may not be the right choice for patients. You know, there's still going to be a discussion, you know? For example, eculizumab is an infusion every two weeks. Even when I show some of the great, compelling relapse prevention data to my patients, they say, "Look, I've got a life to lead, and I'm not interested in an every-two-week infusion."

GG deFiebre: [00:38:50] Thank you, Dr. Clardy, for that overview. I know it's a very complex system and can be very difficult for patients to navigate. And I know it's an important factor in, unfortunately, how treatments get decided sometimes. And then, if someone has a relapse on one of these medications, so they're on a long-term medication and they have a relapse, do any of the acute treatments have an effect on these medications? Or how does the relationship between the acute treatments and the long-term treatments, you know, what is that relationship? Dr. Weinshenker?

Dr. Weinshenker: [00:39:21] Well, the decisions are pretty much not dependent on one another as far as acute treatment. So, a patient who has an attack, regardless of what treatment they are receiving to prevent attacks, if they do experience an attack, generally, we would treat with intravenous steroid treatments, typically methylprednisolone or solumedrol, for five days. And particularly, if the attack is severe and if the recovery is poor, it's not occurring fast enough, and the patient has a pretty significant neurologic deficit, plasma exchange is widely accepted, based on fairly substantial evidence to be beneficial.

[00:40:06] It doesn't help every patient, but it's a fairly safe treatment. It's a bit cumbersome, that's maybe to say the least, but we think worth doing. And about 50 to 60% of patients can result in a substantial salvage from the neurologic deficit.

GG deFiebre: [00:40:27] Great. Thank you. Sorry, I think my connection is cutting in and out a little bit. But that's what happens when you're on the internet. [laughs] But then, so Dr. Greenberg, if, people are on these medications, or if they were diagnosed with NMO, are these medications that they have to be on for the rest of their lives? How does that get determined? And then, if someone's been on a medication and they haven't had a relapse in years and years, is there a point where you recommend stopping medication, or is this a lifelong thing? Dr. Greenberg?

Dr. Greenberg: [00:41:01] Well, it's a great question, and it's one we get all the time. And my answer is, I do not think these are lifelong medications because I believe we're gonna come up with something better. So, it's a nod to the fact that until we come up with something better, my belief is patients will require long-term management. And we frequently get asked the question, “if I've been in remission for X number of years, five years, 10 years” - and we have a lot of patients, thankfully, who've been in remission for a decade on medication – “is it okay to, stop?”

[00:41:38] And my answer in general is no because, statistically, the remission is likely being mediated by the medication, and when going off, we increase the chance for a relapse. And that can be frustrating to patients understandably. It's frustrating to us. We would like to get people off all of these medications, but until we come up with either a way to definitively fix the immune system or be able to accurately predict who's at risk for a relapse through some sort of testing versus not, then we're stuck recommending blanket therapy for everyone.

[00:42:16] And it's worth noting this is a rough and great problem to have. I'll defer to my colleague and friend, Dr. Weinshenker, to remind individuals, before we had all of these therapies being routinely used for patients, and frankly, before we could accurately diagnose patients based on the blood test, patients who were either not on therapy or who were on the wrong therapy were doing poorly. If you read the literature prior to 2005, it's a scary place to be with neuromyelitis optica. And now I've got a large clinic of patients who haven't had a relapse in a decade and are asking me if they can go off therapy.

GG deFiebre: [00:43:01] Great. Thank you. And then, Dr. Weinshenker, you did talk a little bit about if someone doesn't do well you can potentially switch medications. Is there an advantage to switching medications every few years, or when does the decision to switch come into play?

Dr. Weinshenker: [00:43:17] No, I wouldn't say there's any advantage to just switching. There's really not a lot of evidence that a drug loses its benefit over time. So, as long as the patient is doing well, then I would continue them on the same treatment. I really only consider switching if there are problems.

[00:43:36] Now, a very good question would be how much problem does there have to be before you switch treatments? A patient who'd been on azathioprine for 10 years, was free of attacks and then had a minor attack. Would you say that drug is not working for that patient, or would you say that, "Oh, they did really well. I would have expected that they would have been having one or two attacks per year, and they went 10 years without. Just continue."

[00:44:06] So, it's a difficult decision to say that a switch needs to be done. And again, I think you have to individualize it. If there's a bad relapse, certainly if there are more than one relapse. And with NMO, often when the disease becomes active, you can sometimes get attacks occurring in clusters. If you're seeing that, I think there's a clear need to switch treatments. But if things had been fairly stable and there's a minor breakthrough, I think it's a controversial thing, whether we could do better by switching to another treatment or not.

[00:44:43] Hopefully, as we get more head-to-head comparative studies and more long-term real-world studies, we'll feel more confident about making those decisions. But right now, it's really, a lot of it is by feel and there are no exact answers.

GG deFiebre: [00:45:02] Great. Thank you. And I see that Dr. Clardy is back. So, what are the chances that someone has an attack while on a long-term treatment? And is there anything else they could do besides, you know, any supplementary non-medications that can be used to prevent new attacks? Dr. Clardy, if you're there.

Dr. Clardy: [00:45:20] [laughs] I'm here. Can you hear me? I got the Zoom boot. It was like, "Hey, thanks for being in the meeting. It's over now." I was like, okay, I guess I said something wrong. [laughs]

[00:45:30] So, yeah, those are a couple of tough questions. I'll start with the second one, right? From the non-pharmacologic point of view. So, outside of what we consider the disease-modifying therapies long-term here, I think there's a couple of things there. One, it's just like with any chronic medical condition, the more you can do to stay healthy and so that you don't require other medications. You know, for example, I do worry sometimes about our patients developing things like diabetes from the periodic on and off corticosteroids we have them on. Anything you can do to stay healthy is huge.

[00:46:05] And in that vein, it's really two things. One, you're avoiding other chronic medical conditions that will affect your overall health and quality of life. But, you know, we, more anecdotally, there is some soft data too. Staying healthy and exercising, keeping your stress levels down, this starts to get a bit abstract, but the more you can avoid stress and, by that I especially mean emotional stress, the better you're gonna be. You know, we know things like chronic stress states increase sort of inflammation broadly. So I do really try to talk to my patients a lot about that. I mean, life is life, but the more you can do that way, the better.

[00:46:46] You know, many of my patients also ask about vitamin D because it comes up so much in multiple sclerosis. I tend to just say we just need to make sure you're replete. I am not in favor of the super therapeutic vitamin D levels that we have evidence to support in multiple sclerosis. So, I do not recommend the high levels of vitamin D in NMO patients. I just want them to be replete and not deficient. So those are some big things. Remind me again, so getting back to the subtleties of the first part of your question.

GG deFiebre: [00:47:16] Sure, yes. So, what are the chances that someone might have an attack on a long-term treatment? Do we see people have well-controlled, not having attacks? Or do people still have attacks? And, you know, what are the chances of that happening?

Dr. Clardy: [00:47:30] Oh, yeah. So, yes, people do have attacks. People have attacks on almost all of the therapies that we've discussed. You know, and that's again, part of what we do when we do these retrospective series, looking back at given populations. We're doing it now, long-term, with the patients at Utah. And people have had attacks on all of these therapies, I will say, so far, except eculizumab. But we only have two patients on eculizumab. And it hasn't been, you know, the over decade experience we have with some of the other therapies. So, too soon to say there.

[00:48:03] So, there are attacks. And, again, it comes back to figuring out what happened around the time of the attack. We can't, just like Brian said, we really can't accurately predict who's gonna have an attack when. We certainly know the chances of having an attack are much, much higher if you're not one of the therapies long-term. But again, Brian did these studies before we really had any good therapies looking at the natural history of the condition untreated. And untreated, it's bad. So, we know that the natural history is you'll have attacks. It's not, for most patients, it's not a matter of if, but when, if you're not on a therapy.

[00:48:42] The therapies, all of them seem to reduce that, for sure. I don't think we have the perfect therapy yet though.

Dr. Weinshenker: [00:48:49] And I think, Stacey, that was an excellent answer, but optimizing the dose and the frequency of treatment, you know, there are certainly patients

who are doing everything perfectly and get breakthrough attacks. But all too often, I'll get things that happen like, "Oh, I stopped my azathioprine because I had a white blood count, and my family doctor told me that my white count was a bit low." And they told them to stop azathioprine, and then they get a breakthrough attack.

[00:49:21] That's not really a failure of azathioprine. And a very common thing that I tell my patients is, "Before you stop or change the dose of any treatment that you're on, make sure that anybody who recommends that calls me and discusses it with me so we can..." Because often, slightly low white count is really nothing to worry about, and it's part of the expected side effects of the drug. We'll see this when patients have insurance issues and their rituximab dose gets delayed by several months, and then they have a breakthrough attack. It's really not a failure for rituximab, it's sort of a failure of the system.

[00:50:01] So, you have to really look at all those details before you switch treatments or propose switching treatments. Is it something that we could optimize by just making sure the dose is right or there were no interruptions in treatment?

GG deFiebre: [00:50:18] Great, thank you. And then, are there any current trials for long-term treatments right now happening? And if there are, how does someone join them? Dr. Greenberg?

Dr. Greenberg: [00:50:28] So, it's a great question. There are extensions of the trials going on right now for the drugs that we've discussed, where people who were enrolled in the original trials have been invited for several of them to keep being followed long-term. Those, in general, don't accept new enrollments, but they do follow people over time. There will be new trials with different agents coming, and the two best ways to track this are, one, at clinicaltrials.gov. It is a website where clinical trials in the United States and from around the world are listed. And you can go in and search by your zip code, your diagnosis, all sorts of different criteria and see if there are any trials enrolling in your area. And it's a great resource.

[00:51:14] And then, the SRNA website does a great job of listing open trials that are looking for individuals. I will say, beyond drug trials, I encourage everyone, if possible and feasible and not too much of an inconvenience, to look for opportunities to take part in research studies that are observational. I know here at UT Southwestern, I know Dr. Clardy and Dr. Weinshenker's institutions, all look for patients who are willing to share either specimens or data. And those are great opportunities to be a part of a research opportunity.

GG deFiebre: [00:51:54] Great. Thank you. And then, just as we're towards the end of our time here, I just wanted to open it up to all of you and see if you had any additional thoughts or things we didn't chat about that you think are important to bring up in how to... choosing a long-term treatment option. I'll start with Dr. Clardy.

Dr. Clardy: [00:52:12] Sure, more of the same. It's really, really customized. Let me give you a couple examples. So, as many know, sometimes you have other co-morbid autoimmunity in NMO. So, if a patient has problems with absorption, oral absorption, I will tend to say, "Hey, let's think about that because if we give you an oral med, are we concerned about your absorption levels? Do we need to follow markers of how well you're absorbing more closely? Likewise, are you gonna get pregnant? Do you wanna get pregnant? In that case, let's look at the medications that are safer, and let's come up with a plan in advance."

[00:52:51] I often will talk to my young women, and, an example of, say, if they're on rituximab, you know, they'll get their dose, and I'll say, "Okay, go get pregnant." [laughs] You know, in an ideal world, that's how it happens. But, you know, coverage for the 10 months, I'd like to plan that in advance. You know, again, cost, I discuss it very frankly all the time, and I think we all should. All of these things. Are you working full time? You know, do you travel a lot? You know, I'm excited about one of the therapies coming down the pike because of subcutaneous administration. So, theoretically, my patients who like to travel could just take that with them on vacation. So, lots of things like that.

GG deFiebre: [00:53:29] Great. Thank you. Dr. Weinshenker?

Dr. Weinshenker: [00:53:33] And, and I'm sorry, you're asking about how we select which treatments?

GG deFiebre: [00:53:39] Oh, just any last thoughts, you know, as we're at our end of time.

Dr. Weinshenker: [00:53:45] Well, I think this was an excellent webinar. We covered a lot of important issues. Bottom line is that these days, our treatment of NMO is really quite good in terms of preventing attacks. We can't stop all of the attacks. But I think one of the messages that is coming through from some of the clinical trials is not only did we reduce the number of attacks, but the severity of clinical attacks in people who are on treatment seems to be less. So, even if you do get an attack, very likely, it'll be less severe and may respond better to the acute treatment like steroids or plasma exchange if you've been on one of these long-term agents.

[00:54:29] And it’s very important to take the drug exactly as prescribed. I know one of the questions that was listed is, can we cut down on the dose of rituximab? I probably don't have time to do justice to that question, but I know Dr. Greenberg did a study where he looked at a much lower dose of rituximab, which seemed to be much less effective. And in particular antibodies, they don't have the dose-related kind of complications that if you take twice the dose, you get more nausea, more liver function abnormalities. The drugs are very targeted at a specific mechanism, and we just want to make sure that the drugs are administered at the dose that needs to be done to do the job.

[00:55:17] We're not gonna get a lot more side effects by being extra cautious and making sure there's adequate medication. So, I'm a strong personal believer in not trying to do any

ad hoc adjustments that might reduce the effectiveness, especially when we're dealing with these monoclonal antibodies that don't have a lot of dose-related toxicity. And those are my thoughts.

GG deFiebre: [00:55:43] Great. And Dr. Greenberg, any last thoughts as well?

Dr. Greenberg: [00:55:47] I think my final thought would just be for, one, for everyone to take stock and really see what incredible things have occurred in a really short period of time, scientifically speaking. Two years ago, five years ago, ten years ago, we had a rare disease that had the potential to be devastating. No FDA-approved therapies, no clinical trials looking for therapy for patients five years ago. And we're on the heels of having three, potentially having three FDA-approved therapies for a rare disease. It's a tremendous testament, frankly, to the community, to organizations like the ones sponsoring this call, the SRNA and Guthy-Jackson Charitable Foundation.

[00:56:30] It's a testament to the patients and families who banded together, the different clinics who work together in a very collaborative fashion. And it really is remarkable to see these opportunities. We are not done. Clearly, from this call, we know there's a lot more work to be done to get to a point where we don't need therapies, but it is an amazing story, an example for other communities on how coming together and collaborating public, private, with biotech groups, patients, et cetera, a lot can be achieved in a short period of time. So, I've just been really impressed to see where we've gotten to over what is relatively a short period of time in clinical research.

GG deFiebre: [00:57:12] Great. Yup. That's good to hear as well. So, thank you all so much for joining us today. We really appreciate you taking the time to do this. It's been great. So, thank you so much.

