Long-Term Therapies in NMOSD

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Intro: [00:02] "ABCs of NMOSD" is an 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, and in collaboration with the Sumaira Foundation for NMO and Guthy-Jackson Charitable Foundation. This education series is made possible through a patient education grant from Horizon Therapeutics.

Dr. GG DeFiebre: [00:59] Hello and welcome to the "ABCs of NMOSD" podcast series. Today's podcast is titled "Long-Term Therapies in NMOSD." My name is GG deFiebre and I'm from the Siegel Rare Neuroimmune Association. "ABCs of NMOSD" is made possible through a patient education grant from Horizon Therapeutics. Horizon is focused on the discovery, development, and commercialization of medicines that address critical needs for people impacted by rare autoimmune and severe inflammatory diseases. They apply scientific expertise and courage to bring clinically meaningful therapies to patients. Horizon believes science and compassion must work together to transform lives. For this podcast, we are pleased to be joined by Dr. Dean Wingerchuk. Dr. Wingerchuk is Professor and Chair of the Department of Neurology at Mayo Clinic in Phoenix and Scottsdale, Arizona. He obtained his medical degree at the University of Saskatchewan and completed a neurology residency at Mayo Clinic in Rochester, Minnesota. He completed successive fellowship programs in Clinical Neuroimmunology at Mayo Clinic, Rochester, Minnesota and at the University of Western Ontario in London, Canada. He also holds a master's degree in Clinical Epidemiology and Health Research Methodology from McMaster University in Hamilton, Canada. His clinical and research interests focused on neuromyelitis optica spectrum disorder and multiple sclerosis. He is the principal investigator for two NMOSD therapeutic studies and leads international collaborations that aim to improve NMOSD diagnosis and evaluation of outcomes.

Dr. GG DeFiebre: [02:26] Thank you so much for joining me today to talk about long-term treatments for NMOSD. So, to start, do you mind just talking about what the difference is between acute versus long-term treatments? We hear these terms being used in relation to NMOSD.

Dr. Dean M. Wingerchuk: [02:44] Sure. So acute treatments are treatments that are used to intervene for a clinical attack or relapse. So, if somebody is having new symptoms, new activity of the disease optic neuritis or inflammation in the spinal cord, transverse myelitis, then we would try to shorten and limit the effects of those attacks or relapses with an acute treatment. That would usually be IV steroids to start with and sometimes plasma exchange, especially for more moderate or severe attacks or attacks that aren't responding very well or very quickly to the steroids. That's distinct from long-term treatments. Long-term treatments, the inference there is that we're thinking about therapies that one would take on an ongoing basis to prevent attacks or relapses from occurring in the first place. So, one is an acute therapy for an attack that has happened recently or is happening, and another is a preventative therapy.

Dr. GG DeFiebre: [04:00] Got it. Thank you. And so why are long-term treatments needed in a condition like in NMOSD?

Dr. Dean M. Wingerchuk: [04:08] Well, for people who have NMOSD, who are antibody positive, so by this, I mean people who have the aquaporin-4 antibody detectable in their blood, we know that they're at very high risk of relapse. Almost everybody who has that antibody and presents with their first event is going to be at risk of having a second or subsequent events in the future. Other people by the time they're diagnosed have already had more than one event and we determine that they already have relapsing disease. So, in those instances, long-term treatments are needed to prevent those potential future attacks. For people who don't have the antibody, it's a bit more challenging because after the first presentation, a single attack, we think that the risk of relapse is low. It may not be zero, but it's low and probably not sufficient for us to actually begin a long-term treatment. So, for people who are antibody negative, most times we would initiate a long-term preventative therapy only after they've established that they have a relapsing course that is two or more attacks.

Dr. GG DeFiebre: [05:29] Got it. And so, what are the most common long-term treatments for NMOSD? I believe there are three that are used, maybe-- that are not FDA-approved for NMOSD, that are used off-label, three FDA-approved and then if there are any others that are used maybe less frequently in NMOSD.

Dr. Dean M. Wingerchuk: [05:49] Right, that's correct. So, there are three approved therapies in the United States for NMOSD with aquaporin-4 antibodies. So, the FDA has approved these medications only for people who have the antibody. And those drugs are eculizumab, satralizumab, and inebilizumab. There are several medications, as you say, that are off label, not formally approved in the United States but still commonly used and especially before the FDA-approved therapies were available. The three most common are rituximab, which is given intravenously typically every six months. And then two oral therapies, pills, azathioprine, and mycophenolate mofetil. There are other medications that are uncommonly used, things like Cytoxan or cyclophosphamide or methotrexate. And some of these are used in other regions of the world more commonly than they are in the US, but they are not approved therapies in any countries.

Dr. GG DeFiebre: [07:04] You mentioned how the older treatments are given, so an infusion versus oral pills. How are the newer-- the FDA-approved treatments given?

Dr. Dean M. Wingerchuk: [07:16] So the drug eculizumab is given, which was the first drug approved in the United States, is given intravenously and it's given every two weeks. There's a sort of a longer-acting version of that drug called ravulizumab, which is not yet approved but which would allow people to do the same kind of therapy but with infusions much less frequently, every eight weeks. And there's another drug that's given intravenously, that's inebilizumab. That's the B cell depleting drug and that is given every six months once it's fully on board. And then satralizumab is different. That drug is given as a subcutaneous, under the skin, injection. And once that's onboard, it's given every month.

Dr. GG DeFiebre: [08:16] And so you mentioned that one of the medications is a B cell depleter. Are all of these treatments B cell depleters or do they work on different pathways or mechanisms of the disease process? You might talk to me a little bit about how each of them works or how we understand them to work.

Dr. Dean M. Wingerchuk: [08:33] Yeah. So historically, the older medications that were used prior to any approved drugs, especially the oral medicines like azathioprine or mycophenolate, those are sort of broad-spectrum immune suppressants. They have effects broadly across different arms of the immune system. Rituximab, which became much more commonly used over the last 10 to 15 years, even though it was

never formally approved for NMOSD, is a B cell depleting drug and looked like it was probably better than those general immune suppressants. And as we gained experience with that, it occurred in parallel with recognizing that those B cells are very important in NMOSD as well as other conditions such as multiple sclerosis. So that became, before the approved therapies, the sort of treatment of choice, I would say, in the United States. The other medications that are approved though are different. One of them, inebilizumab, is quite similar to rituximab, but has a little bit more broad effect on those B cells. And so, in theory at least, it may be more effective than rituximab, because it depletes a bigger population of these B cells. The other medications though that are approved are more targeted. So satralizumab, the self-injectable one that's given every month, that targets a protein that's secreted by immune cells called Interleukin-6. Interleukin-6 is a key part of a signaling pathway that we know is important in many autoimmune conditions and by inhibiting the receptor for that protein, it appears that we can shut down the activity of aquaporin-4 positive NMOSD quite effectively. And then, the first drug that was approved, eculizumab, is a complement inhibitor. So, complement is a very important component of the immune system, important for protecting us against certain types of infections but it's also pivotal in what's happening in NMOSD when the disease becomes active. We think that compliment becomes active very early in the process of an attack. And so, preventing that from happening seems to be extremely important as a mechanism of shutting down inflammation and the disease. So, in summary, across these six therapies, three approved and three unapproved, we have some therapies that are very broadly immune suppressives and then others that are very targeted and all seem to help NMOSD to various degrees.

Dr. GG DeFiebre: [11:32] And do they all have similar side effects or does that vary based on how they're administered or how they work?

Dr. Dean M. Wingerchuk: [11:40] Yeah, that's a great question. The side effects generally are more related to both how they're given and the mechanism of how they work. So, the medicines that are more broad immune suppressants, the issues there tend to be increased risk of infection. With drugs like eculizumab, the complement inhibitor that I mentioned, because it's so specific in what it's targeting, it has a specific side effect of putting people at risk for a particular type of infection with what are called encapsulated bacteria. And the real risk there is an infection with bacteria that can cause meningitis. So, the profile of side effects or risk is really specific to each medication and distinct from each other.

Dr. GG DeFiebre: [12:40] And then, are they all equally as effective at preventing relapses or do some work better than others?

Dr. Dean M. Wingerchuk: [12:48] Yeah, that's a very important question, but one that's difficult to answer based on the data that we have now. I think the randomized and controlled trials that were done and led to the FDA approving our three approved medications were very rigorous and showed that all three approved therapies are highly effective in preventing attacks. Basically, the ability to prevent another attack in someone who went on one of these drugs ranged from 75% to almost 95%. Comparing between the agents though is quite difficult. The best way to do that would be to conduct a trial that compared the drugs head-to-head, and we don't have that information. We do think it's likely based on the evidence we have that the approved therapies are more effective than the older, unapproved therapies. Again, we don't have head-to-head data, but looking at what we do have that's accumulated in the literature over time, it seems most likely that the approved therapies are more effective.

Dr. GG DeFiebre: [14:11] And then, when someone is considering what long-term treatment to use, are there any factors that they should consider? So does age matter, gender or the severity of previous attacks or the number of previous attacks?

Dr. Dean M. Wingerchuk: [14:29] It's not clear that any of those factors necessarily predict a better response with one drug compared to another. The most important factor is whether or not patients have the aquaporin-4 antibody because if they do, then they're a candidate for one of the approved therapies and it's very likely that they would have good protection from any of those. I think what often matters for people are things like the side effect and safety profile and the route of administration - intravenous versus self-injection, the frequency of injection and these are largely personal preferences that are driving these kinds of decisions. So overall, I think it's much more important that people be on the medication that works than a specific medication. But we do think that over time we're very likely going to be able to personalize this to be more specific. That is, we'll be able to use, for example, blood tests to help us understand what medication is best for an individual person.

Dr. GG DeFiebre: [15:45] And then you've mentioned the aquaporin-4 antibody. So, if someone is positive for that, are there specific recommendations for those who are positive versus not in terms of medications or is that something we don't yet know? Or if someone tests positive for the MOG antibody?

Dr. Dean M. Wingerchuk: [16:03] Yes. So, for patients who have NMOSD but do not have an antibody associated with it, we really don't know what the best treatment is. I would say that the standard still would be to use one of the unapproved therapies. So those older immune suppressive therapies, which do seem to have an effect at re ducing relapse risk. That group, antibody negative people, is a major area of interest now to try to understand that group better both for diagnosis and for treatment. Some people who have symptoms that look like NMOSD but have the MOG antibody probably need to be treated differently. We don't have any randomized controlled trials completed yet in that disorder although there are some now finally underway and we're still learning about what the best treatment is for that group of patients.

Dr. GG DeFiebre: [17:10] And then are these medications ever used together or are they always used separately? So, one person, are they ever on two medications or these medications used in combination with other kind of immune suppressant medications?

Dr. Dean M. Wingerchuk: [17:25] Yeah, that's a great question. So, the approved therapies generally are not used in combination but there were many people who entered some of the randomized controlled trials that were completed who were on a therapy, for example, one of the unapproved immune suppressive therapies and then they had breakthrough attacks. And when they went on the study, they continued their prior therapy and went on either a new therapy or placebo. So, we do have in those people some data on combination therapy and that's particularly true for eculizumab and satralizumab. It seemed that in the results of those smaller groups of patients though that there wasn't necessarily a clear advantage of being on combination therapy, that the therapy of either eculizumab or satralizumab alone seemed to be about the same as combination therapy. The other thing about combination therapy of course is risk. One would be concerned that if you're on two agents, that that might increase the risks of, in the long-term, in particular, of certain things like infections. So, our goal typically is to try to control the disease with a single therapy if possible.

Dr. GG DeFiebre: [18:58] And then, are there any particular considerations for pediatric patients or is it the same as adults?

Dr. Dean M. Wingerchuk: [19:05] Well, there are important considerations there because there are not any approved therapies right now for pediatric patients with NMOSD. There are studies that are ongoing or will begin to study the effects of some of these medications in children with NMOSD. But right now, typically a decision is made about using one of the unapproved therapies in those cases.

Dr. GG DeFiebre: [19:37] And then a question we get frequently because of sometimes issues with insurance, are there any kind of particular insurance considerations someone should think about when choosing a treatment option?

Dr. Dean M. Wingerchuk: [19:50] Well, the things that impact insurance decisions most frequently are an accurate diagnosis and establishing whether a person has the aquaporin-4 antibody or not. So, having that antibody, again, is one of the most important factors in determining whether somebody is a candidate for one of the FDA-approved therapies. So generally speaking, if somebody has that antibody, we try to get through their insurance, try to get approval for one of the FDA-approved drug therapies for them.

Dr. GG DeFiebre: [20:36] Okay. And then at the beginning you talked a bit about acute treatments versus long-term treatments. If someone has a relapse and they're on one of these long-term medications and they happen to have a relapse when they're given acute treatments, do these have an impact on the effectiveness of the long-term treatments or on how they're given or any sort of considerations there that someone should know about?

Dr. Dean M. Wingerchuk: [21:00] Yeah, that's a good question. So typically, we would, if somebody was on a preventive therapy but had a breakthrough attack, we would treat their acute attack the same as we would in any other instance, that is with steroids, maybe with plasma exchange. Having a breakthrough attack always raises the question of whether or not one should change therapy. But let's say that the treatment for whatever reason wasn't changed, the biggest factor probably that would impact a long-term treatment would be whether plasma exchange was used and whether the preventive drug was given recently, because if plasma exchange was given and could pull off a medication, pull it out of the system, then it might need to be repeated. But again, in many instances, if there's a breakthrough attack, we're considering the potential to change therapy, which we would do after the acute therapy was complete.

Dr. GG DeFiebre: [22:03] Okay. And then if someone has not had a relapse in, let's say, five years or more, is there a point where you recommend no medication because the risk of relapse is lower than potential risks with the medications or does this differ at all based on antibody status as well?

Dr. Dean M. Wingerchuk: [22:23] Yeah. Well, I can tell you my approach, which it really needs I think a lot more data to help us understand the best treatment, but my approach is the following. If someone is aquaporin-4 positive, I do not currently think it is safe and I do not recommend really ever stopping treatment because we have quite a bit of experience to show that discontinuation of treatment can result in recurrence of attacks. And we also have some published data on that now from Korea in particular showing that the risk of relapse after stopping therapy was quite high in that group. I do think though that in the future there will be ways that we can deescalate therapy, so use lower cumulative doses for, example, of therapy to try to reduce the risks of long-term therapy while keeping the disease under control. And what we're trying to achieve, of course, in future studies will be curative kinds of therapies, something that, for example, would allow us to eliminate the antibody. If we could do that convincingly, then yes, withdrawal of therapy ultimately would be one of the important outcomes there. Things are a bit different I think though for the patients who have, the people who have NMOSD without the aquaporin-4 antibody or without the MOG antibody because that's a much less certain group. I do think there that there is the potential to, after a long period, several years of remission, to withdraw therapy gradually. I would retest for the antibodies after the therapy was out of the system. And if those were negative, then just observe. So, we have done that successfully in some people. But I think when the antibody has been present, that's a different story. That portends what seems to be unfortunately a lifelong risk.

Dr. GG DeFiebre: [24:38] And if someone is newly diagnosed and received some acute treatments like steroids or plasma exchange, does that impact whether or not they might test positive for aquaporin-4 antibody?

Dr. Dean M. Wingerchuk: [24:51] It can. We generally recommend that, if possible, people are tested without those kinds of medications or interventions interfering. So, if somebody for example is getting plasma exchange because they had a bad attack and then they had their blood drawn in the middle of plasma exchange and it was negative, that would not be convincing to me that it was negative. I would want to retest that person several weeks after they had completed their plasma exchange therapy. And there are some people who test negative early on but on repeated testing with the best available essay in the future test positive. And another time we sometimes see an increase in antibody levels is around the time of a new attack. And so that's also a good time to test although of course nobody wants to have a new attack.

Dr. GG DeFiebre: [25:46] And then, is there an advantage at all to switching medications every few years? I know you mentioned that some of them work in different ways or is it something that, if it's working for someone, they should likely just stay on that medication?

Dr. Dean M. Wingerchuk: [25:59] Well, I think if something seems to be working, sticking with it is probably the right answer. It is an interesting question as to whether or not changing therapies to different mechanisms of action, for example, would be advantageous over time. To my knowledge that's never been studied. So, I don't think I can endorse that at this point.

Dr. GG DeFiebre: [26:24] Got it. And then, so if someone happens to have another attack, new inflammation is seen while they're on a treatment, does that mean that they should then consider switching treatments or it's the possibility to increase the dosage or how is that determination made?

Dr. Dean M. Wingerchuk: [26:42] Yeah, that's a great question. If a person is already on one of the approved therapies, there are standard doses for each of those. And so, in most instances, if a person is taking their therapy and they have a breakthrough attack, we would consider switching to a different therapy. It is a little bit different for the unapproved therapies, however, where often there is a lot of variability in the dosing and sometimes, we see people who have had a breakthrough attack and they probably were on an inadequate dose. So there one option may be to increase the dose as you suggest.

Dr. GG DeFiebre: [27:24] So what are the chances that someone will have an attack while on a long-term treatment?

Dr. Dean M. Wingerchuk: [27:29] Thankfully, the chances of that are getting smaller. So, with the approved therapies, what we've seen is that only between about 5 and 25% of people had even one attack during the randomized controlled trials. And interestingly, as those people were treated and continued to be followed on the trial, they had fewer and fewer attacks. So, in some instances it seems that getting the drug on board and allowing it time to work seems to be very effective. Now with the older, unapproved immunosuppressive therapies it does seem that the risk of attacks over time is higher. It's probably in the order of at least 30 and maybe as high as 60 to 70%. So, we do think that the approved therapies are better in that regard.

Dr. GG DeFiebre: [28:27] And then are there any supplementary, non-medication treatments that are used to prevent new attacks or do we mostly stick to medications?

Dr. Dean M. Wingerchuk: [28:35] Well, I wish I knew what else really could prevent attacks. There are some data dating back over the past decade to suggest that people who are low on vitamin D are at higher risk of having attacks. So, if we find that somebody is low on vitamin D, we boost their levels up into the so-called

normal range, if not a bit higher. We usually recommend supplementation for everyone and hope that that might also help. But we would do that in conjunction with a standard preventative therapy. Other than that, we're still on the lookout for things that we might be able to do lifestyle-wise that would really impact the disease in the long-term. I think another area where we could take action in some people would be smoking; discontinuation of smoking I think is very important in this condition because there is evidence to suggest that smokers have more disease activity.

Dr. GG DeFiebre: [29:41] And then are there any current trials that are going on or studies looking at long-term treatments in NMOSD?

Dr. Dean M. Wingerchuk: [29:48] There are and it's changing all the time and it depends on whether you're talking about the United States or other countries. As I mentioned earlier, there are studies underway or planned in the short term, in the near term, to study some of the currently approved therapies for adults in children to understand whether we can extend their use to children. The fact that we have approved therapies that work by distinct mechanisms has sparked a lot of interest in other medications that work similarly but might be more effective. And then of course there are always new immune therapies coming down the pike and I know of several of those where NMOSD is thought to be a particularly attractive disease to study because of the antibody and how well we understand the disease. And then of course, people are often very interested in things like stem cells and how that kind of approach might ultimately help even cure the disease. So, it's early days with respect to those kinds of therapies but ultimately of course that's the goal is to cure NMOSD.

Dr. GG DeFiebre: [31:10] Thank you. And then do you have any final thoughts or anything that we didn't cover that you think is important to mention about choosing a long-term treatment for NMOSD?

Dr. Dean M. Wingerchuk: [31:20] Well, I think we covered many of the elements quite well. We could of course go into much more detail on every one of the questions that you asked, but I think it's important to recognize how much effort and time and energy that people with an NMOSD have put into this research and into the trials that are now benefiting the community. I think it's quite remarkable the dedication that those people and their families and caregivers have shown and would like to thank them. It's really pushed the field forward. It's helped all of the adults and children and it's going to help people in the future.

Dr. GG DeFiebre: [32:02] Definitely. Thank you and thanks so much for taking the time to chat with me today. I really appreciate it.

Dr. Dean M. Wingerchuk: [32:08] It was a great pleasure. Thank you.