ABCs of NMOSD: Understanding Clinical Trial Results for NMOSD

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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 "Understanding Clinical Trial Results for NMOSD Therapies". ABCs of NMOSD is a ten-part education podcast series to share knowledge about neuromyelitis optica spectrum disorder. My name is GG deFiebre from the Siegel Rare Neuroimmune Association and I will be moderating this podcast.

[00:01:25] ABCs of NMOSD is made possible through a patient education grant from Viela Bio. Viela Bio is dedicated to the development and commercialization of novel life-changing medicines for patients with a wide range of autoimmune and severe inflammatory diseases. The company's approach, which targets the underlying molecular pathogenesis of the disease is aimed at enabling the development of more precise therapies, identifying patients more likely to respond to treatment, and pursuing multiple indications for each product candidate. For additional information about Viela, please visit vielabio.com.

[00:02:01] For today's podcast we are pleased to be joined by Dr. Levy and Dr. Sotirchos.

[00:02:06] Dr. Michael Levy is an Associate Professor of Neurology at Massachusetts General Hospital and Research Director of the Division of Neuroimmunology and Neuroinfectious Disease. He completed the MD PhD program at Baylor College of Medicine with a focus on neuroscience. In 2009, Dr. Levy was appointed to the faculty as Assistant Professor at Johns Hopkins, where he started the Neuromyelitis Optica Clinic and Research Laboratory. In 2019, he moved to the Massachusetts General Hospital and Harvard Medical School to develop the Research Program in Neuroimmunology. Clinically, Dr. Levy specializes in taking care of patients with rare neuroimmunological diseases, including neuromyelitis optica, transverse myelitis, MOG antibody disease, acute disseminated encephalomyelitis, and optic neuritis. In addition to neuroimmunology clinics, Dr. Levy has a special interest in patients with superficial siderosis of the central nervous system. Dr. Levy is the principal investigator on several clinical studies and drug trials for all of these conditions. In the laboratory, research focuses on the development of animal models of neuromyelitis optica and transverse myelitis with the goal of tolerization as a sustainable long-term treatment.

[00:03:20] Dr. Sotirchos is a neurologist and Director of the Johns Hopkins Neuromyelitis Optica Center. He earned his medical degree from the National and Kapodistrian University of Athens and completed his neurology residency training at the Johns Hopkins Hospital. He subsequently pursued fellowship training in neuroimmunology at the Johns Hopkins Hospital as a National Multiple Sclerosis Society Sylvia Lawry Fellow. His research focuses on the application of imaging techniques, including retinal optical coherence tomography and brain magnetic resonance imaging to study multiple sclerosis, neuromyelitis optica, and other neuroimmunological conditions. His work especially focuses on visual pathway involvement in these conditions and aims to characterize mechanisms of neurodegeneration and to identify novel biomarkers for predicting and monitoring the disease course and therapeutic response.

[00:04:13] Welcome, and thank you both so much for joining us today.

Dr. Michael Levy: [00:04:16] Thank you. Thank you for having us.

GG deFiebre: [00:04:19] Thank you.

[00:04:20] To start, we're going to talk a bit about what goes into a clinical trial, what are the aspects of the clinical trial, and what it means for individuals with NMOSD. I'm going to turn it over to Dr. Levy first. Who conducts clinical trials for drugs? Is it pharmaceutical companies, medical institutions, educational institutions?

Dr. Michael Levy: [00:04:39] All of the above. Anybody can conduct a clinical trial. Typically, it depends on whether the drug still has patent life and if companies can still make money off of the drug, then the companies will conduct the studies because they have some return on investment to make. There are lots of older drugs that can be repurposed. Generally, those don't have any more patent protection, patent life. Those studies are done either by government funding or, or academic institutions or big philanthropic organizations.

GG deFiebre: [00:05:15] Great. Thank you. And then, what are the requirements a drug must meet before it moves into the clinical trial phase with humans? Dr. Sotirchos?

Dr. Elias Sotirchos: [00:05:28] That depends to some extent, kind of to what Mike already said us to, if it's a completely new drug or a drug that's already been around and has some safety experience. If it's a completely new drug, typically, a drug will be initially developed in the lab and will be tested in animals. In order for a clinical trial to begin, in order to move into kind of phase one trials in humans, the drug that should receive an investigational new drug approval from the FDA. The way that that works is whoever is sponsoring this new drug - so typically if it's a completely new drug that will typically be a pharmaceutical company - that the drug sponsor would have to apply to the FDA for approval, showing the safety data based on animal testing and preclinical development, in order to justify that this drug has the potential to be efficacious in the condition under study, and that there is sufficient safety data in order to start in human testing.

GG deFiebre: [00:06:27] Great. Thank you. And to go on that, Dr. Levy, what are the different phases that clinical trials go through and what does each one entail? I would say starting from this preclinical phase as well.

Dr. Michael Levy: [00:06:40] The preclinical phase is usually in the laboratory where the drug is being studied, maybe in mouse models or rat models or other models that, as Dr. Sotirchos was saying, can give you some confidence that this drug is going to do what you think it's going to do. And then you bring that preclinical data to the FDA to launch a phase one study, where you propose, either in healthy controls or in your disease population, to expose people to that drug and see if there are any safety concerns that come up. It's usually a small study and it's not a lot of exposure. The idea is that you just want to get a safety signal, and if it proves safe in that context you move on to phase two, which is usually in the disease population and includes a dose strategy. So you want to know how much of a medication, so you might have several different arms with different doses. And you also want to try to get a sense of which outcome measure you want to use in a big study. So outcome measures could be a relapse risk, or it could be a disability level, or whatever your outcome is, you want to try to test that out in your phase two study. So that by the time you launch your phase three study you have everything perfect. You know what dose you want to use, you know what outcome you want, you know that the safety is going to be okay. The phase three study is really where you demonstrate efficacy, and you bring that data to the FDA and the FDA will say, 'yes, it's effective in the context you propose, it's safe enough' and then they approve it or not.

[00:08:16] Then there's a phase four, usually sponsored by the pharmaceutical company to continue to collect more information about the drug in the real-world setting. Because in the real world, it may not be as controlled as in a clinical trial. And you want to know if there are any new safety signals or efficacy concerns that come up later.

GG deFiebre: [00:08:35] And are there any differences in the population that is in each of the phases? Dr. Levy?

Dr. Michael Levy: [00:08:41] Usually phase one is healthy people, but it could sometimes be the patient population. So for example, I've proposed some phase one studies for drugs that have not been used in the US, and I've proposed to use them in our patient populations. You can do that. Usually pharmaceutical companies will want healthy controls just to see if there's some safety signals that may come up. And then in phase two and phase three and phase four, it's all usually almost always, in the exact patient population that they want. In fact for NMO, it's parsed even more because there're NMO patients who are positive for the NMO antibody and then you have those who are negative. The trials that we'll discuss today included either one or both, seronegative and seropositive, but ultimately the FDA concluded that for all three drugs, the drugs are only efficacious for seropositive, aquaporin 4 seropositive.

[00:09:34] The patient population is one thing, but even finer, granular detail about which patient population within NMO, that the FDA can make a ruling on that as well.

GG deFiebre: [00:09:45] Okay, thank you. And then after a drug has gone through these phases of the trials, what requirements must a drug meet to eventually get FDA approval to be a medication available to the public? Dr. Sotirchos?

Dr. Elias Sotirchos: [00:10:01] As Dr. Levy discussed a bit going through the phases, the sponsor would have to demonstrate to the FDA that the drug meets efficacy criteria for the indication that is proposed. In the case of NMO, for example, the primary outcome in the phase three trials was a reduction in the hazard of a relapse, so reduction in the risk of relapse in patients with NMO and demonstrating also that the safety profile is acceptable.

[00:10:31] And again, it's not like the sponsor goes after the phase three trial to the FDA. The FDA is typically involved in this process early on, because as I mentioned, the FDA needs to grant approval for a drug to initially move into phase one testing by granting the investigational new drug on the status for that drug. So the FDA is involved kind of in all stages and can help guide, the process of the clinical trial in order to ensure that things are done appropriately and meeting their criteria for approval. But generally again, it's proving that the drug works and proving that it has an acceptable safety profile.

GG deFiebre: [00:11:12] Okay, great. Thank you. And then what is the typical timeline for a clinical trial, starting from this preclinical phase? And then, how long does each phase kind of take to complete? Dr. Levy?

Dr. Michael Levy: [00:11:23] It's too long. That's the problem. So the preclinical phase could take a year, year or two or three or four, depending on how much is known about the drug. And then the phase one study is probably the fastest, because it's just a few number of patients and all you're looking for is safety. Phase two can sometimes take two, three, four years, because it's basically a full trial, you just have many different parameters that you're testing out. And then a phase three study, all the ones in NMO took four or five years even before they got FDA approval. Patients have to wait a long, long time before an FDA drug is approved.

GG deFiebre: [00:12:04] Right. And then, can you explain a little bit about the difference between, different types of studies? So for example, someone might hear the term placebo controlled or blinded or double blinded. Dr. Sotirchos?

Dr. Elias Sotirchos: [00:12:19] So starting first of all with the comparator arm. So whenever we're testing a drug, we have to prove that it is better than some sort of comparison in general. And because otherwise we won't know necessarily... So, if we do just a pre/post comparison and see if somebody got better, for example, or had a decrease in their relapse rate after starting a drug, we don't necessarily know if that would have happened anyway or if the drug actually did that. So the way that trials generally work, especially once we get to the phase three stage where we're trying to prove efficacy of the drug, the way that the trials work is that patients who are prospective participants in the trial are randomized, which means that they are randomly allocated to receive either the drug that we want to prove as efficacious or some sort of comparator treatment.

[00:13:14] Now, in the context of a disease for which there is no approved drug available such as NMO when all these trials started, the comparator arm received a placebo. So that is, they received, for example, if the drug was an infusion, they would also receive an infusion with the same schedule as the patients who were treated with active drug, but it would be only saline, which is essentially just water. So no drugs. And the reason for that is in order to avoid any other factors influencing the groups. Ensuring that really the only difference between the two groups that are being studied - the people who received active drug or the placebo in this case - are pretty much similar in other characteristics and have a similar risk of the outcome being studied.

[00:14:02] Now, if there is already a drug available, generally, new drugs are often compared to the standard of care that is already used or a condition, because it would potentially be unethical to expose the patient to a risk of being on a placebo when there's a drug already approved for that indication or treatment. So that's the one aspect, the comparator.

[00:14:26] In terms of blinding, typically, phase three trials will be double-blinded, which means that neither the treating physician nor the trial participant will actually know if they are receiving the active drug or the placebo in the case of the NMO trials that we are discussing. And the reason for this is to avoid bias creeping into the study. Because, for example, on the side of the physician, on the one hand, we really want to feel that the things that we are doing are benefiting the patient. If I am the treating neurologist and a patient I know is receiving active drug or placebo, that might influence my perception of if the patient is responding to the therapy or not. Not knowing that, not having that information, removes that from the equation. The same is true on the side of the patient, allowing the participant in the trial to know what

they're allocated to, and either know that they're allocated to a placebo or an active drug can influence their perception of their symptoms and of how they are perceiving the effects of therapy. So either positively or negatively. So the participant could, knowing that they are treated with active drug, potentially experience side effects, for example, that may actually not be related to the drug just because they have that knowledge and they may be attributing things that are not related to the drug to that.

[00:15:52] Alternatively, a patient could have subjective improvement just by knowing that they are under treatment with an active drug rather than placebo. So this kind of avoid these biases in the study.

GG deFiebre: [00:16:04] Great. I think that was a really good overview about the different terms that might be used and how to help folks understand the study results. We also talk about perspective versus retrospective studies and, Dr. Levy, if you could talk to us a little bit about what these terms mean, and then what are the benefits of each or the negatives of each as well?

Dr. Michael Levy: [00:16:29] Retrospective studies are those where you look backwards. You look back at all the charts from your patients and when you answer the question based on the data that's already there. The problem with retrospective studies is that sometimes you see data the way you want to see it, and it doesn't actually work that way in real life if you were to do a study that's prospective. So in a prospective study, you start collecting data after you ask the question and then the answer you get depends on that data that you're going to start collecting.

[00:17:05] And they're different. Because if you look back at data, you might say, 'well, I'm not going to include this chart because of XYZ', or 'I'm not going to include that piece of data because I know something else'. And it really biases the way that you collect data. Whereas if you start prospectively and you say, 'okay, I'm going to ask this question and then I'm going to start collecting the data' it's harder, it's harder to be biased because you can't even see the data yet. And then at the end of that study you can answer that question. So prospective studies are considered to be more reliable and rigorous than retrospective studies. The problem is, of course, if you want to conduct a retrospective study, that's easy. You could with just a little, a few hours and some help, you can go through a bunch of charts and answer the question quickly. Whereas a prospective study, you're going to have to start collecting new data. That's going to take some time. There are pros and cons to both. It just depends on what the question is, what data you're going to have to collect in each case. And again, if it's something like a treatment study, prospective studies are always much, much better, much more reliable than looking back in time and saying, 'well, yeah, I think this drug works because these three patients did well on it.' It's much better if you start a new study and you say, okay, let's see how well they do under these conditions.

GG deFiebre: [00:18:28] Great. Thank you. These three new drugs that just came out were all done with prospective studies, but prior to these studies, were there any retrospective studies conducted on NMOSD treatments? And if so, what were the findings of these studies? Dr. Sotirchos?

Dr. Elias Sotirchos: [00:18:43] Prior to these drugs being approved, there were a lot of treatments that have been used off label for a treatment of NMO, including things such as rituximab, mycophenolate, azathioprine, and other immunosuppressive medications. Despite the fact that these drugs have not been subjected to testing of their efficacy in large phase three randomized controlled trials, we did have some evidence for their efficacy based on a combination of retrospective and prospective studies. However, not as I said, large phase three randomized controlled clinical trials. And these studies in general have shown that all of these medications that we have been using off label for decades now, actually, for the treatment of NMO did appear to be efficacious for the treatment of NMO. That's where we derive a lot of that evidence. However, again, despite the fact that these treatments were available, given the lack of they're in a randomized controlled clinical trial, the FDA had recommended, had mandated that these new drugs be subjected to placebo-controlled trials for that reason. Because again, it's really difficult, as Dr. Levy already said, to make conclusions from these retrospective and prospective studies. Medical literature is full of examples where physicians think that something works based on experience with a limited number of patients. And then once that intervention goes through a randomized controlled trial, we find out that it actually did not work, but that a lot of the biases that we were discussing previously, crept into people's perception of the effects of the treatment. This is something that has actually come a lot into the news recently in the setting of COVID-19, where there are multiple drugs that are being, and multiple interventions promoted in the news and news outlets and social media, which however have not been subjected to clinical trials. And this shows how difficult the process can be sometimes. And really the gold standard is prospective randomized controlled trials in order to assess a drug's efficacy.

GG deFiebre: [00:21:00] Great. Thank you. As we've talked about, and I would like to go into a little bit more detail about these three new drugs and trials that have been recently approved. Dr. Levy, if you don't mind talking about them and how they might compare to each other or to the drugs that have been previously used and what we know about each of them at this point.

Dr. Michael Levy: [00:21:21] I'll just start with broad brush strokes. There were three trials, one with compliment drug called Solaris, that's the brand name, the generic is called eculizumab. It would normally block the compliment system, which is necessary to fight off a few infections. But it's a system that's important in causing damage in NMO. And this drug is given every two weeks, IV infusion, and the results suggest that if you use this drug and you're compliant with it every two weeks, then the risk of a relapse dropped 94% compared to the placebo patients who are also getting some sort of therapy like CellCept or one of the off label drugs that Dr. Sotirchos mentioned, but not rituximab. So compared to those treatments, using eculizumab reduced your risk of relapse by 94%. There were some side effects that we'll talk about including headaches and upper respiratory infections, but for the most part, it was tolerable. And this drug had been approved for other diseases in the past and now it's being made available for NMO. Only aquaporin-4 seropositives were tested. And as far as I know, there may be two aquaporin-4 seronegative patients who were treated, not in the trial, but in my hands. And maybe Dr. Sotirchos has some experience as well with seronegative. But for the most part, we don't have experience in seronegative.

[00:22:54] The second drug is inebilizumab and the brand name there is called Uplizna. And that drug targets B cells like rituximab, but even broader. And the other major difference between this drug Uplizna and rituximab is that the new drug removes B cells not through a compliment system, which would normally cause serum sickness for all of you who are on rituximab, you know that, especially after your first infusion, you get this serum sick feeling that comes from killing B cells in your bloodstream. This new drug, Uplizna, doesn't have that infusion reaction. It basically just removes the B cells using other immune cells rather than destroying them in the bloodstream. So that's the difference, and in the trial, the reduction in risk of relapse was 77% among aquaporin-4 seropositives. Now they included seronegatives in this trial, but not enough. And the FDA felt like there was not enough information. I think there were 17 patients maybe, something like that. I can't remember, but there doesn't seem to be a big difference amongst seropositives and seronegatives in responding to the drug, but the FDA felt like there wasn't enough information there. The side effect profile was fairly benign as well. And, like I said, there were no infusion reactions. There was some joint pain and some headaches and things like that were pretty minor.

[00:24:27] The third drug is satralizumab and the brand name is Enspryng. That drug is a, it's not an infusion like the other two drugs. It's an injection, and it's given once a month. It goes right under the skin and I think the plan, the idea in the future is to get this into the patient's hands so they can do it at home. This blocks the interleukin six receptor, which is a way that immune cells communicate with each other and is used in many other indications, including rheumatoid arthritis. But this one is a once a month drug, whereas all the other indications use a either weekly or every other week treatment. And then this study among the aquaporin-4 seropositive patients, there were two trials. One was 79% reduction in relapse risk, one was 74% reduction in relapse risk, depending on whether patients were on background treatments like CellCept. Side effect profile was very benign, not even injection reactions in one of the trials. So again, just some joint pain, headache, the typical things you see with biological therapies.

[00:25:39] By and large, all three of these drugs were fairly safe, and they were all very effective. And the FDA approved satralizumab as well for aquaporin-4 for seropositive only. They had enough seronegatives, but they did not show benefit. I think that they're planning a separate study in seronegatives and MOG, but for right now, we don't use them in seronegatives. Eculizumab we also don't use in seronegatives. Inebilizumab, like rituximab, we used rituximab in the seronegatives, but again, the FDA did not feel like there was enough data there.

[00:26:13] So that's the broad brush strokes. And I think we can drill down into each trial if those questions come up.

GG deFiebre: [00:26:20] Sure. That's great. Thank you for that overview. Dr. Sotirchos, are we able to compare these three treatments to the prior drugs that have been used in NMOSD, or are we not able to do that at this point?

Dr. Elias Sotirchos: [00:26:33] I think that's one of the questions that most people would want to hear, which of these drugs works best is an obvious question. How do they compare to the prior off-label therapies that we use? However, that's incredibly difficult to say with the current data that we have. And the reason for that is that... so Dr. Levy was

mentioning the percent reduction in risk in each of these trials, but it's important to bear in mind that each trial generally cannot be necessarily compared to one another. Since, as I mentioned previously, the way that it works is prospective participants in each of these trials were randomly allocated to placebo or to the drug separately. So the populations that were enrolled in each of these studies are somewhat different. And what I mean by that is that, potentially there were different patient characteristics, different risks of having an attack. Unless you really do a head to head trial where you take participants, you flip a coin, essentially, and randomly allocate them to one or the other drug and then compare the outcomes, it's really difficult to compare the efficacy results across trials. I would say that, based on the results that we have, all of them appear to work very well. And this is not a problem that is unique to interpreting the trials in NMO. This comes up a lot. And even in common conditions, such as multiple sclerosis, where there are many drug DMTs approved, but we have disease modifying therapies, but we have a lack of head to head trials in order to better inform selection. And what happens then in clinical practice is that we have to take into account individual risk factors for severity of disease. How people have done previously in terms of how aggressive their disease may be. Their risk factors for side effects from each medication. So, for example, some of these medications are associated with an increased risk of meningococcal. So Soliris is associated with an increased case of meningococcal infection, or Uplizna is contraindicated in people who have chronic hepatitis B infection. So there are multiple patient-specific factors that we have to take into account and tailor the therapy in clinical practice. Other things that have to be taken into account is patient preference. As was mentioned, all of these drugs have different routes of administration, different frequencies of administration. Eculizumab is an infusion every two weeks. Satralizumab is an every four weeks self-injection at home. Inebilizumab is given every six months as an infusion at an infusion center. And people may have different preferences potentially for what they find to be more acceptable in terms of logistics and in terms of self-administering medication, potentially, and things like that. Again, I think it's difficult to compare both across these studies and to compare it to the off-label therapies that have been used previously. And I do think that in clinical practice what will end up happening is that as these medications now have become available, we just have to tailor them to each patient individually. And this is kind of where, to some extent the art of medicine comes into play because we have a lack of a lot of evidence. And then an additional thing, an important thing to bear in mind is that there are phase four studies that happen after drugs become approved. And even though, again, these are not randomized controlled trials, the emergence of real-world treatment data can help to further inform therapeutic decision making.

[00:30:13] As we learn more, as these drugs are offered to more patients in the real world, we will also learn more about the side effect profiles. Because safety in a few years in a clinical trial, in which a couple hundred people have been exposed is not necessarily what will happen in the real world. And we know that as drugs come into the real world and they're used more broadly, we may become aware of different safety signals that were not observed in the clinical trials. So this is going to be somewhat of a moving target in the future.

GG deFiebre: [00:30:45] Great. Yes. And I think it's a great point about the fact that these drugs have different ways that they're administered and thinking about patient choice in that. I think that's an important point that you brought up. So thank you. We've gotten several questions about, those with NMOSD might be seronegative, so they don't test positive for the aquaporin-4 antibody or they might have tested positive for the MOG antibody. Dr. Levy, can you talk a little bit about the trials and whether or not they included folks without the aquaporin-4 or with MOG, and what this might mean in terms of getting the treatments approved or using the treatments for these patients?

Dr. Michael Levy: [00:31:23] The first thing to understand is that the MOG antibody test is only available in the US in 2017, October 2017. By the time that these trials launched in 2014, in 2015, the antibody test wasn't even available. We didn't consider MOG in the inclusion criteria. Now, it's reasonable to ask 'well, can we look back at all the data and then see who tests positive for MOG now based on serum that was collected back then, and then be able to figure all that out?' Well, the answer is not for the FDA, but for ourselves, yes. We've asked the two companies that enrolled aquaporin-4 seronegative patients to go back and say, 'okay, well, how did the MOG patients do?' And I've seen some of the data from inebilizumab, and I don't remember if it's in public yet, so I'm not going to talk about it, but there weren't that many patients in the inebilizumab trial. For the satralizumab trial, that data has not yet been released to us. So I don't even know for the satralizumab trial how many MOG patients there were. But the better way to do this is to look forward, to do those prospective studies. As I mentioned, it's always better to look forward, collect the data anew based on MOG, sero status. And then there's also the double seronegative. What about patients who don't test positive for either antibody? How are they going to do? And for satralizumab I think that they enrolled enough patients that they could really try to figure that out. For inebilizumab I think the FDA ruled that they don't have enough data to rule that out. And for eculizumab, by the

mechanism of action, they just said, 'we don't know if anything else would work. ' They didn't even try. And for MOG antibodies, maybe there is compliment involvement. Maybe there isn't. I think that data is still kind of mixed and we don't know. They haven't even tried it. But I think all of these are fair questions. And what we really need to do is be able to create these studies in each individual patient population in a prospective manner to answer the question really correctly. But for now, as I said, all three of the drugs have only been approved for aquporin-4 seropositive patients.

GG deFiebre: [00:33:44] Okay, thank you. And does that mean that if someone is seronegative, is this based on the insurance company or is it something that they can even try to get approved? Or how does that work kind of in practice?

Dr. Michael Levy: [00:33:56] In practice, there may be some sense in trying one of these drugs. But the insurance companies don't necessarily have to approve it. So in my experience trying these new medications, insurance companies do everything they can to avoid paying for it. But it's, since it's FDA approved, sometimes they just can't get out of it. And one of the things that they try to insist on is this, is aquaporin-4 sero status, and whenever they come back with some sort of block in why they don't want to pay, you have to really explain to them what is going on. So, for example, I'll use the inebilizumab as an example, where they didn't have enough cases of seronegative to convince the FDA that it's helpful. But in my experience with rituximab, we treat a lot of patients who are aquaporin-4 and MOG seronegative. The double seronegative, treat them with rituximab and a lot of times it helps. That might make sense, and it might make sense either to use inebilizumab or rituximab in that context.

[00:34:54] So for every case, as Dr. Sotirchos was saying, there may be an individual reason why you may want to use one of these new drugs or not, and then you just have to appeal to the insurance companies to cover it.

GG deFiebre: [00:35:06] Okay. Great. Anything to add to that? Dr. Sotirchos?

Dr. Elias Sotirchos: [00:35:09] No, I agree with Dr. Levy that we need more information, and hopefully prospective randomized controlled trials will be done in MOG, so we'll have answers regarding these questions in a few years. But in the meantime, we have to act in the absence of evidence, and I agree completely with Dr. Levy's approach, which is similar to what I do as well.

GG deFiebre: [00:35:32] Okay. Great. Thank you. We did get a question that someone has been on Rituxan and stable for more than six years. They are NMOSD positive, but also have lupus. They know that Rituxan is used for other autoimmune diseases. Are any of these new medications that have come out for NMO also known to help with other autoimmune diseases? Dr. Sotirchos?

Dr. Elias Sotirchos: [00:35:53] That's a great question. These drugs, some of them have been studied in other conditions. So eculizumab, which is soliris, specifically has I believe three other FDA approved indications. But these are for rare conditions, including myasthenia gravis, which is an autoimmune neurological condition. And then for two other conditions called atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria. Those are the other FDA indications for that medication. Inebilizumab, the only FDA approved indication is neuromyelitis optica. However, my understanding is that there are ongoing studies, including in rheumatologic conditions of that drug. And that makes sense because as Dr. Levy mentioned it targets B cells like rituximab, but in a little bit of a different way and potentially more broadly as well. Based on its mechanism of action, we do anticipate that that medication would potentially be beneficial for rheumatologic conditions. Satralizumab is also only FDA approved for NMO. However, it is very similar to another medication called tocilizumab, or Actemra, that has been studied in a number of rheumatologic conditions, including rheumatoid arthritis, giant cell arteritis and others. And, based on the shared mechanism of action, we would expect that satralizumab can potentially also be beneficial for those. However, again, the data is rather limited for these other medications in rheumatologic diseases. However, we can infer based on their mechanism of action, potential benefits. We need more evidence.

GG deFiebre: [00:37:39] Okay, thank you. Dr. Levy, I know you mentioned when talking about the three trials that were done, that some of them people were taking the new medications in addition to the medications that they had been on previously. Moving forward, are these new drugs going to be given in addition to other drugs or on their own?

Dr. Michael Levy: [00:37:58] That's a good question. In the eculizumab trial, the comparator was, to background therapy patients were allowed to be on azathioprine or prednisone or mycophenolate, but in that trial, there were enough patients that we could tell and being on background therapy did not help. So if you were on just eculizumab then, in this study at

least, nobody relapsed who were just on eculizumab. If you're on background therapy plus eculizumab, there were more of those, but there were three relapses in that group. So we don't think that with that drug, that you need to be on any background therapy. In the inebilizumab trial, there was no control group that had a background therapy. It was a pure placebo. It allowed us to see exactly what the benefit of inebilizumab was. So that 77% relapse risk reduction that I mentioned is considered a true placebo, the statistic. With the satralizumab, there were two trials. One was with background therapy and one was without background therapy. And in one study with background therapy, the aquaporin-4 seropositive patients seemed to do better than the monotherapy group. Not a lot better, but mildly better. I think the numbers were 79% versus 74%. So you get a little bump in efficacy if you're on CellCept or something else. The whole calculation of risks changes though because you have to consider the risk with the background therapy, like adverse events with mycophenolate or, or prednisone or whatever else you're on. So the risk/benefit calculation changes depending on whether you're on a background therapy. But right now, my thinking is with satralizumab, that's really the only treatment where there's a demonstrated benefit to adding something else on. Even though it's only a little bit of benefit.

GG deFiebre: [00:39:56] Okay, thank you. Just as a follow-up. Why did the placebo group in some of these trials exclude people on rituximab?

Dr. Michael Levy: [00:40:05] Oh, so that's a good question. So with eculizumab, the reason that rituximab patients were excluded is because with rituximab you need a functioning compliment system in order for rituximab to work. And eculizumab blocks that system so you can't use them at the same time. With inebilizumab, of course there was no background therapy, but much of the mechanisms are the same between rituximab and inebilizumab. So you wouldn't want to mix them. And then with satralizumab, I'm not really sure why rituximab was not included in that, in the allowed therapies. I'll look into that and get back to you.

GG deFiebre: [00:40:43] Thank you. We did get a question from someone who's on rituximab, which he said raises cholesterol that they have now been placed on a statin for. Are there any studies done with these medications to know the risk of heart disease as a potential side effect, and should neurologists, knowing the possible risk of developing and/or increasing cholesterol levels, be sending folks to their primary care or cardiology physician to follow this? Dr. Sotirchos?

Dr. Elias Sotirchos: [00:41:12] Based on the studies Dr. Levy discussed a bit the side effects that were, that were found in the studies. I think that overall it's important to bear in mind that as drugs are approved and come into the real world, we learn more about their side effect profiles because the number of patients who receive a medication increases. And the companies are mandated by the FDA to perform these phase four studies, collecting data on patients who are receiving the treatments in order to better understand the safety profile. At present, there is no recommendation for a specific monitoring of lipid profile or cardiovascular risk. Notably, the drug that is similar to satralizumab, called tocilizumab, has been associated with an increase in cholesterol. So that's one where it would be potentially reasonable to look at that. However, generally our recommendation is to simply do kind of age appropriate screening for cholesterol. And also rituximab generally is not associated with an increased cardiovascular risk or increased cholesterol. There are some small studies that have potentially shown that, but it's a rather mild association that will show it even in small uncontrolled studies. Generally, we do not perceive based on their mechanism of action that these drugs will it be associated with an increased cardiovascular risk. And notably given that, to some extent, cardiovascular disease is associated with inflammation, there are some studies that have looked at things like the way that the blood vessels respond and their elasticity and things like that. And some data that may even suggest that some of these anti-inflammatory treatments can potentially even be beneficial. But we really need more evidence, real world, in order to understand better how these drugs affect things like cardiovascular risk.

GG deFiebre: [00:43:00] Great. And as a follow-up to that: I know we talked a little bit about phase four trials. Dr. Sotirchos, can you talk a little bit more about what goes into a phase four trial? And then also if someone's not enrolled in a trial, but getting the medication from their physician, are potential side effects or other adverse events monitored and how is this reported to the public, if at all?

Dr. Elias Sotirchos, MD: [00:43:23] Drug adverse events related to medications are reported, actually. So physicians can actually report these directly to the FDA and through the company portals as well. This is all monitored and mandated by the FDA. Any patient receiving these medications, their physician should be reporting side effects that are potentially attributable to the drug.

GG deFiebre: [00:43:46] Okay, great. Thank you. And then, if someone's interested in participating in a clinical trial, how can they go about doing this? Dr. Levy?

Dr. Michael Levy: [00:43:56] The best way is to go on clinicaltrials.gov and put in your information to see what trials you are eligible for. You could also just contact me, I can tell you what you might be eligible for or contact any of the foundations like, like SRNA or Guthy Jackson, and they can tell you as well.

GG deFiebre: [00:44:16] Okay. Great. Thank you. And then we just got a question from someone who is newly diagnosed. What determines which treatment the patient gets? And for patients who are not on any of these three treatments, what would determine that choice? Dr. Sotirchos?

Dr. Elias Sotirchos: [00:44:31] That's a great question. And it's also a very difficult question, I have to say. Because I think that, as I mentioned previously, we don't really know, in the absence of head to head trials comparing these treatments, necessarily which one works better or which patients they work better for. So I think that in a newly diagnosed patient, the initial decision would have to be made, again, taking into account patient-specific preference, risk factors for adverse effects. And I think that any of these three medications would be a valid choice for a newly diagnosed patient with NMOSD.

[00:45:10] We have an extensive clinical experience with a lot of the off-label therapies. Despite the fact that there are three FDA-approved therapies for NMO, we do have very extensive experience with drugs like rituximab and mycophenolate, and that makes neurologists and neuroimmunologists very comfortable with their past experience using them. To some extent, actually may remain valid options. And also as we mentioned previously, satralizumab may be considered as an add on therapy. Patients could potentially be on two medications, one off label, immunotherapy, plus something such as satralizumab.

[00:45:49] In terms of people who are already on therapy, my personal approach is if people are doing well, are not having relapses, I'm not recommending to my patients to switch to a new medication provided, again, that they're not experiencing relapses, they're not experiencing side effects. Because it is difficult to predict how they may respond to a different medication. Let's say that I have a patient who has been on rituximab for several years, has not had an attack, is not experiencing any side effects, I am generally not inclined to rock the boat. If it ain't broke, don't fix it. That's kind of my personal approach to people already on therapy. People who are having breakthrough disease activity, I think that on a specific medication that they're already on, I think that it would be an indication to consider switching to a new disease-modifying therapy. And then multiple factors come into play, including what therapies has somebody been on in the past and failed treatment. And maybe switching to something that works differently might be more beneficial in somebody who has failed the medication in the past. And also, again, taking into account individual preference and risk factors, as I've repeatedly mentioned.

GG deFiebre: [00:47:08] Thank you. Dr. Levy, do you have anything to add to that?

Dr. Michael Levy: [00:47:11] No, I completely agree with what Dr. Sotirchos said. For, for every case, I think there's so many things to consider from patient preference and side effect profiles and everything else. Really, what I like to do is to present patients with like a menu of different options, including the new drugs and the old drugs, and go through with them and just present the data. And first, just get a sense from them where their priorities are. Efficacy, safety, logistics, lifestyle, and money, so many things to consider.

[00:47:43] There's really no one answer for anybody. And I'm always surprised what patients prioritize and sometimes I think, well, the most important thing for you would be X or Y or Z, and they have exactly the opposite set of priorities, and really, it's their priorities that matter. I think it's just an individualized decision in every case.

GG deFiebre: [00:48:02] Great. Thank you. As we're getting to the end of our time, I just wanted to open it up and see if there was anything else that you wanted to talk about that we haven't talked about that you think is important for this topic, Dr. Sotirchos?

Dr. Elias Sotirchos, MD: [00:48:13] First of all, I just wanted to say that how exciting the fact that within the span of a year, three medications have been approved and have completed phase three clinical trials for such a rare condition. I think it's very, very encouraging. And despite the fact that, again, the drug development process can be slow, patients can become frustrated by how much time the process can take. It's important to bear in mind that this ensures that the drugs are

adequately studied before they become approved for use and ensures that there's a reasonable safety profile and that efficacy has been adequately studied.

[00:48:52] I just wanted to say that this should be considered an incredible breakthrough in the treatment of NMO, especially given how rare a condition it is. And it's very encouraging for other rare neuroimmunological diseases such as MOG IgG Associated Disease, which has, again, only recently really been more understood. And we're still learning more about the disease's pathogenesis, the prognosis. And I think that this is definitely encouraging for what the future holds for developing treatments for rare neuroimmunological conditions.

GG deFiebre: [00:49:25] Great. Thank you. And Dr. Levy, do you have anything to add?

Dr. Michael Levy: [00:49:29] No. I just appreciate the opportunity to present to everybody.

GG deFiebre: [00:49:34] Great. Well, thank you both so much. We really appreciate it. This was super helpful for understanding all these exciting new treatments that have come out for NMO. So thank you so much.

Dr. Elias Sotirchos: [00:49:44] Thank you.

Dr. Michael Levy: [00:49:45] Thank you again.