Navigating Treatment Options

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Intro: [00:00:00] 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.

[00:00:22] ABCs of NMOSD podcast series is hosted by SRNA, the Siegel Rare Neuroimmune Association and 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 Horizon Therapeutics.

GG deFiebre: [00:00:51] Hello, and welcome to the ABCs of NMOSD episode called "Navigating Treatment Options." My name is GG deFiebre, and I'm from the Siegel Rare Neuroimmune Association. The 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.

[00:01:34] For today's podcast, we were joined by Dr. Hesham Abboud and Dr. Chelsey Judge.

[00:01:39] Dr. Abboud is the director of the Director, Multiple Sclerosis and Neuroimmunology Program at University Hospitals and a staff neurologist at the Parkinson's and Movement Disorders Center. He is an Assistant Professor of Neurology at Case Western Reserve University School of Medicine.

[00:01:54] His special interests include multiple sclerosis, neuromyelitis optica, autoimmune encephalitis, autoimmune movement disorders, spinal movement disorders, spasticity management, and neuromodulation. Dr. Abboud earned his medical degree from Alexandria University in Egypt, where he also completed an internship and a residency in Neurology and Psychiatry.

[00:02:15] He obtained his Masters and Doctorate degrees in Neurology from Alexandria University before joining the Cleveland Clinic, where he completed a residency in adult neurology, a clinical fellowship in movement disorders and neuromodulation, and a clinical fellowship in multiple sclerosis and neuroimmunology. Dr. Abboud received special training in neuromyelitis optica and autoimmune neurology at Johns Hopkins University.

[00:02:37] Dr. Chelsey Judge studied Immunology at Case Western Reserve University, completing her PhD in 2016. She further studied immune mechanisms involved in HIV as a Research Fellow at the Ragon Institute of MGH, MIT, and Harvard.

[00:02:53] When her brother, Connor, became temporarily blinded and paralyzed by NMOSD, Chelsey co-founded the Connor B. Judge Foundation with her mother, Pam, aiming to raise awareness and research funds for NMOSD.

[00:03:04] She was eager to apply her research background professionally in neurological autoimmune diseases and joined Sanofi Genzyme as a Medical Science Liaison in 2017. Chelsey is passionate about her work as a Scientific Advisor with Connor B. Judge Foundation, where she provides rationale for where research funds are distributed.

[00:03:21] The Connor B. Judge Foundation has contributed to research funds for nerve repair, as well as a Mellen Center led project to understand outcomes in COVID-19 in NMOSD patients, the Foundation has helped launch the annual Ohio Rare Disease Day. Bringing together, patients, advocates, clinicians, researchers, and policy makers in the shared mission to improve the lives of rare disease patients and families.

[00:03:43] She helps run the foundation, social media platforms and is the host of Demystifying NMO podcast, a collaboration between the Connor B. Judge Foundation and the Sumaira Foundation for NMO. Her hope is that patients are empowered with education to make well-informed shared decisions with their clinical care team.

Chelsey Judge, PhD: [00:04:00] Hi, Dr. Abboud I'm so happy to be on the pod, ABCs of NMOSD with you, and we're going to talk all things today regarding NMOSD treatments.

Dr. Hesham Abboud: [00:04:11] Thank you. And thank you for having me.

Chelsey Judge, PhD: [00:04:13] So, I think first, maybe we could talk about different types of NMOSD treatments with regard to what to do when a patient's experiencing an acute relapse versus the treatments that are now, and some of them FDA-approved, to prevent relapse. So, what options or what considerations do you have when you discuss treatment options for your patients during acute relapse?

Dr. Hesham Abboud: [00:04:40] Yeah. So, obviously treatment for acute relapse is different from prevention of relapses. When it comes to acute relapses, there are two main interventions that we usually utilize in NMOSD attacks. One is high dose corticosteroids, typically given intravenously. We typically give one gram of intravenous methylprednisolone daily for three to five days to reduce the inflammation and shorten the duration where the symptoms are prevailing.

[00:05:13] In NMOSD, especially with aquaporin-4, we have learned that corticosteroids might not be sufficient for some of the patients, especially if the attack is severe. And we have learned that adding plasma exchange or immunoabsorption techniques to steroids usually improve the outcome better. Plasma exchange is the more typically used intervention, where the patient is connected to a plasma exchange machine. The plasma is taken out and then albumin or a replacement plasma is given back.

[00:05:51] The whole idea is that when we take the patient's plasma, we're removing the harmful antibody, including possibly anti-aquaporin-4 antibody. We're removing it from the circulation so it will stop attacking the spinal cord or the optic nerves or the brain. Immunoabsorption is less frequently used but equally effective technique in which, it's very similar but instead of removing all the proteins from the plasma, there's a medium that is added in order to selectively remove just the antibodies from the plasma and then return the rest to the patient.

[00:06:26] Most institutions would use either high dose corticosteroids, with or without plasma exchange, usually sequentially. So, you would try high dose corticosteroids first. And then if by the end of the treatment course, you're not seeing much improvement or the patient's just staying the same, or if the patient is actually worse despite corticosteroids, this is when we typically add about five sessions of plasma exchange.

Chelsey Judge, PhD: [00:06:51] Okay. So, I think that's a really good point. Is that typically, if you are experiencing acute relapse, you're going to use the high dose steroids. If you're not seeing a favorable response, then you're going to use some sort of combination, probably most likely PLEX. Do we have any available data on these types of treatments to manage acute relapses?

Dr. Hesham Abboud: [00:07:12] Yes. So, not very high-quality ones. Steroids have been kind of more historically used for treatment of all immune-mediated inflammation in general. Plasma exchange, we have more evidence-based data available. It started off with one famous randomized controlled trial that was done at the Mayo Clinic back in 1999.

[00:07:36] And this was a randomized trial of plasma exchange for patients who failed to respond to steroids alone. And it wasn't just NMO. It was any inflammatory demyelinating attacks that are severe, whether it's MS, optic neuritis, neuromyelitis optica picture. And this trial was positive, and it did show that adding plasma exchange to corticosteroids does improve the outcome as opposed to corticosteroids alone.

[00:08:02] And this was kind of high-quality evidence that supported the use of plasma exchange. Most other studies after that were mainly retrospective, looking at real life patients who were basically treated with plasma exchange and then compare them to patients who were treated only with corticosteroids, apart from maybe small pilot prospective studies, here and there.

[00:08:24] But I think most of the evidence comes from a large number of real-life patients that we looked retrospectively to compare the outcomes. I think one of the biggest was from the German group. And that came, I believe, in 2015 or 16, where they looked at over 800 patients in the entire country of Germany.

[00:08:46] And they compared patients who are treated with steroids alone, compared to those who are treated with some sort of apheresis, whether plasma exchange or immunoabsorption and the results were very clear that patients who were treated with plasma exchange did better, meaning they were more likely to go back to their baseline neurological status, compared to patients who are treated with corticosteroids alone.

[00:09:10] So, although this was not a randomized trial, not a prospective trial, but some of this retrospective data were strong enough, I guess, to change the practice across the world. So, now we all have a lower threshold to use plasma exchange when treating acute relapses of NMO. And, in real life, we're seeing that this is an effective approach.

Chelsey Judge, PhD: [00:09:33] Thank you for that. Just, so, I think you know my brother, Connor, he has NMO. That's why I'm here and I'm so passionate about it. And he, his first presenting relapse was very severe blindness, paralysis, classic NMOSD manifestations.

[00:09:50] And he was treated, just like you said, with high dose steroids and then, a few days later, PLEX was added on, and I think he got about five days of that. And, fortunately, we are so completely grateful he saw tremendous benefit. While, of course, he still has neurological deficit, he regained his ability to see and he can walk.

[00:10:12] That obviously took time. I would say weeks to months. The first, really moment of help was when, a couple of days after a few of his PLEX treatments, he could wiggle a toe and we were like, 'yay.'

[00:10:24] So, I bring this up, this personal anecdote, because I wanted to talk to what about the timing? When should patients expect to see benefit and how should we manage our expectations?

Dr. Hesham Abboud: [00:10:36] So, it's an excellent question. I think part of that question is what about the timing of introducing plasma exchange? Does it matter if we treat early versus late? And the answer to this is most likely it is better to start the treatment early. We already have some studies.

[00:10:52] Again, not very big studies, but some well-designed studies that showed that, if you treat with plasma exchange earlier, then you're more likely to get a better outcome. And that's why we're seeing some movement now towards starting plasma exchange and corticosteroids on the same day, really. Like when you start the treatment for acute relapse, you just start them together.

[00:11:13] So, the earlier that you start plasma exchange, the better the outcome. We see it clinically and also supported by some studies. The other part of your question is, 'How soon do we usually see improvement after starting plasma exchange?' And this is obviously individualized, so there's some individual variation to this.

[00:11:32] It depends on the age of the patient, how healthy the patient is otherwise, comorbidities, the severity, of course, and the type of the attack. Was it visual? Was it spinal cord? Was it brainstem, or so forth? But, practically speaking, in most patients, we typically see some improvements, some clinical improvement after the third session of plasma exchange.

[00:11:54] So, once we get to that kind of a benchmark, we usually see at least that we're going in the right direction. Like you said, there's some movement. There's some regaining of the vision. You know, if the patient has a brainstem attack and they're throwing up, we start seeing some reduction of that.

[00:12:09] So, of course, as I mentioned, not a solid rule for everybody, but practically speaking, it's the third session after which we start seeing some improvement. Going back to full recovery, which could be back to normal, or at least the maximum recovery that is expected in any patient, this, as you said, can take really weeks to months, with individual variations.

Chelsey Judge, PhD: [00:12:31] Yeah. Thank you. And, as an immunologist, I kind of visualize this NMO attack as the immune system is kind of creating a fire, so to speak. And so, we need to put the fire out as quickly as possible, so that, obviously, we can stop any further damage and then allow for any potential repair to happen, whether it's with the steroids or PLEX.

Dr. Hesham Abboud: [00:12:53] Exactly.

Chelsey Judge, PhD: [00:12:54] And also, I can imagine, right, where these are providing benefit, obviously. What about on the other side? What are potential side effects for steroids and PLEX or potential immune absorption that patients might need to be aware of?

Dr. Hesham Abboud: [00:13:09] So, again, that's an excellent question. High dose steroids, when they are given in the manner that we give, usually for acute attacks, intravenously, very high dose, and then, you know, not really, more like a pulse treatment, typically the side effects are actually mild compared to someone who's taking a much smaller those of corticosteroids, but long term.

[00:13:31] So, most of the famous corticosteroid side effects that happen because of long-term treatment, we usually don't see them during the three to five days of high dose steroid therapy. The typical side effects that can happen with high dose intravenous or pulse steroid therapy, mainly things like people can get a little bit irritable, a little bit agitated, moody possibly.

[00:13:54] Sometimes we see some insomnia. Increased urination is possible. Rarely, we might see some negative effects on the stomach, especially if the patient was not given a stomach protector. They can get ulcers or, rarely, bleeding from the stomach. And, of course, steroids always, almost always elevate the blood pressure a little bit and elevate blood sugar a little bit, as well.

[00:14:15] But, yeah, since these are usually given in a hospital setting, it is common that we kind of keep a closer look at blood sugars. We check it more frequently. We give treatments, if needed, we control diet a little bit, and we also do the same with the blood pressure.

Chelsey Judge, PhD: [00:14:31] That makes sense.

Dr. Hesham Abboud: [00:14:32] As for plasma exchange, the main side effect's a drop in blood pressure can happen sometimes, while the patient is being, getting the plasma exchange, and this is not uncommon. They can get dizzy a little bit. Sometimes they can have allergic reaction to the albumin or the plasma that is the replacement plasma that we're giving them back. So, this can result in itching, skin rash, again, drop in blood pressure, or difficulty.

[00:14:57] And then, because we do give some blood thinners during this procedure, sometimes bleeding can be a side effect of this procedure and this can be really anywhere in the body, but we see it more in patients who are prone to bleeding disorders at baseline basically. And usually, those patients are not good candidates for plasma exchange anyway.

Chelsey Judge, PhD: [00:15:16] So, those patients might have even been able to receive it, is what you're saying, or they'd be carefully monitored?

Dr. Hesham Abboud: [00:15:20] Yes, if there's clinically significant active bleeding or a bleeding disorder, sometimes we move away from plasma exchange.

Chelsey Judge, PhD: [00:15:27] I can definitely attest to the moodiness from the high dose steroids. Connor got very angry, but, you know, he was widely paralyzed and on high dose steroids, so, that's appropriate.

[00:15:37] I'm moving on to the economics of it, the insurance part. So, obviously, if you are going through a severe acute NMO attack, you're gonna accept whatever necessary medicine is being recommended to you, provided to you. And, like you said, most likely if you're an NMO patient experiencing a relapse, you're in the hospital, which will rack up costs. I remember we were very fortunate. Connor was under my father's insurance and so, everything was covered, but I saw some of those preliminary claims costs.

[00:16:08] And, again, while we are very grateful and, you know, help that we recovered, quite, quite, quite expensive. Could you speak to the best of your ability on the ability of insurance to cover these costs and what do patients do if they're not insured?

Dr. Hesham Abboud: [00:16:26] Yeah, I'm not sure I'm qualified enough to talk about that. I'll tell you kinda my take on it.

[00:16:30] If the patient is admitted and it's an inpatient hospitalization, then my understanding is that the insurance is just billed for the overall admission, not, kind of, not on every single intervention. So, that makes it a little bit easier. And we haven't had really any major issues with that in patients who are admitted.

[00:16:48] But if you try to do plasma exchange as an outpatient, there are costs involved with that, obviously, that could be too high, and the same for even intravenous corticosteroids because, you know, if you do it on an outpatient basis, even if the medication is covered, there are still expenses related to the infusion itself.

[00:17:08] So, being in an infusion center and, you know, having an infusion nurse and all these things, insurance coverage might not be full for these services. So, patients can end up with some co-payments that can be high, depending on whether you did it in a physician's office versus in a hospital setting versus in a standalone outpatient fusion center.

[00:17:28] So, sometimes, one way around that when it comes to corticosteroids, we can treat acute relapses with oral corticosteroids at a dose that is equivalent to the intravenous dose. So, although it's a 1,000 milligram or a full gram of methylprednisolone, there is an equivalent dose of oral prednisone that you can give the patient to take at home.

[00:17:52] It sounds tremendous, and patients get a little bit anxious when they hear because they really have to take 25 tablets of prednisone 50. That's, 1,250 milligrams of prednisone per day, which is the equivalent dose to the one gram of methylprednisolone. And they have to do this at home for three to five days.

[00:18:11] So, it sounds excessive, but it is really equally safe and equally effective to the intravenous methylprednisolone. And we have done this sometimes when the patient could not go to the hospital or if it was given on an outpatient basis, but the patient cannot afford the expenses related to intravenous infusion.

[00:18:32] And we've been successful with that. But keep in mind that steroids alone is usually not a sufficient treatment for a full-blown or a severe attack of NMOSD. So, it would only work in mild attacks. We've done this also during the COVID-19 pandemic, during the midst of the pandemic, when we did not want our immunosuppressed NMO patients to go out. So, we've reverted to treatment at home with oral mega dose corticosteroids for mild relapses.

Chelsey Judge, PhD: [00:19:01] Thank you. I think that was a lot of great information. So, thank you. That was really helpful and especially the nuanced options when it comes to IV versus oral steroids. I have seen the twenty-five pills a day process and yeah, it looks like a lot, probably tastes awful, but you gotta do what you gotta do. So, thank you for that. And for anybody who's listening, who wants a deeper dive into navigating the insurance abyss, Demystifying NMO has a podcast episode on that.

[00:19:29] So, we've covered how to manage acute relapses with NMO. What about preventing them preventing further attack or maintenance therapies? I know now we have what, three FDA-approved treatments? Yay. I know you've been a part of some of those clinical trials, at least one, I think. And I know there's other different types of immunosuppressants that can be used off label. Could you talk about all of that and what it means?

Dr. Hesham Abboud: [00:19:54] Alright. So, you know, it was a very exciting year, back in 2020, for NMOSD because all three medications that received the approval, they really came kind of back-to-back in mid-2020 to early 2021. The three medications received FDA-approval only for aquaporin-4 antibody positive NMOSD.

[00:20:15] So, although this is the majority of NMOSD patients, but that's not all NMOSD patients. At the present time, we can only use them for patients who are seropositive for the aquaporin-4 antibody. These

three medications include eculizumab, which was the first one to get approved. And this is a complement inhibitor that is given intravenously every two weeks as a maintenance dose, showed great efficacy in the clinical trials in prevention of relapses in aquaporin-4 positive patients.

[00:20:45] It was only tested in aquaporin-4 antibody positive NMOSD patients and was kind of tested as an add-on therapy to existing immunosuppressants, like mycophenolate or azathioprine, but also a subset of patients were not on anything. And it worked. It was effective in both subgroups, whether you are on existing immunosuppressive therapy or not on anything else. It did work for both subgroups in prevention of relapses.

[00:21:13] The second one was inebilizumab, which is an anti-CD19 monoclonal antibody. So, it basically depletes B-cells, which is a subtype of immune cells in the body that is kind of the main cell type implicated in the pathogenesis of NMOSD with aquaporin-4.

[00:21:31] It also depletes plasmablasts, which can be younger generation of B-cells that directly produces the antibody, which kind of is a broader spectrum than the typical B-cell therapies that we've used in the past, which we will touch on as we speak.

[00:21:47] So, inebilizumab also showed efficacy as a monotherapy. So, the trial was against placebo, not as an add-on, and was tested in both patients with aquaporin-4 antibody and without. And it did show in the treatment of the disease, but mainly in those patients who were aquaporin-4 antibody positive, not as much in the seronegative patients, but their number was very small.

[00:22:13] And it is given intravenously. Again, the maintenance dose is every six months, not every two weeks for this one. And many clinicians are familiar with B-cell therapy, so they feel comfortable with that, with this one. It's similar to what we've done in the past.

[00:22:28] The third medication was satralizumab, which is an interleukin-6 inhibitor. It also showed effectiveness both as a monotherapy and as an add-on to existing immunosuppressive therapies, like mycophenolate or azathioprine, simply because actually this medication had two clinical trials, one as a monotherapy and one as an add-on therapy. And we're positive it reached primary outcome and showed effectiveness in prevention of relapses. Both patients with aquaporin-4 antibody and without were included in the study. But, again, most of the benefit was seen in the aquaporin-4 antibody positive patients and that's what led to its approval only in aquaporin-4 positive patients.

[00:23:12] This one is given as a self-injection, subcutaneous injection, not intravenously, and the maintenance dose is once a month. So, it has a little bit, kind of more convenient dosing for some of the patients. So, these were the three medications approved by the FDA. I guess, before we talk about the off-label medications, do you have any questions about the three FDA-approved medications?

Chelsey Judge, PhD: [00:23:34] Yes. So, maybe this would be a good opportunity to talk about a couple of questions. So, my first one would be safety, so, any of the known side effects or things that patients need to be aware of?

[00:23:47] And then also you talked about how some of these clinical trials were studied as add-on therapies. And I thought, okay, so, maybe then do patients have interest, desire, or need to combine some of these approved treatments? Or what your clinical considerations would be on that?

Dr. Hesham Abboud: [00:24:02] So, for the first question, yes, of course, every medication has side effects and risks involved with its use. When it comes to the first one, eculizumab, the main side effects include the

things like infusion reactions, which, you know, meaning you get a little itchy or a little dizzy when the infusion is going in. Those infusion reactions actually are very mild and not very severe usually for this particular infusion, compared to other NMO infusions.

[00:24:31] It can increase the risk of common infections. Upper respiratory tract infections, urinary tract infections, and things like that have been reported with this medication. But the main big risk with its use is infection by encapsulated bacteria because our defense mechanism against those particular types of bacteria with a capsule around them, it does need the complement system, which is inhibited by eculizumab.

[00:24:58] So, the biggest risk is for meningococcal meningitis. So, it's a type of infection of the coverings of the brain, meningitis. And especially if it is caused by this meningococci, which is a type of bacteria that can cause this. So, because of this, vaccination against meningitis type A and B is actually mandatory before treatment with this medication. Patients can get the first dose of the vaccine before a treatment, but then they can get the rest of the vaccine doses after starting treatment, if needed.

[00:25:30] Other encapsulated bacteria include pneumococci that can cause pneumonia, or meningitis, also aspergillosis, which is a fungus infection, and a gonorrhea, a sexually transmitted disease. So, these are all of particular concern. The rates are not very high, but they can happen and it's always a concern with this medication. And it is to be noted that meningitis can occur, even if the patient was vaccinated before treatment.

[00:25:56] As for inebilizumab, that's a B-cell inhibitor or B-cell therapy. So, we know that some of the common side effects include increased risk of infections. That includes common infections, but also sometimes serious infections. So, with Inebilizumab, serious infectious can happen, especially if hypogammaglobulinemia occurs.

[00:26:16] Hypogammaglobulinemia is when prolonged B-cell therapy leads to reduction of not just the bad antibodies, but also all antibodies, including protective antibodies. And this can increase the risk of infection even further, including serious infections. So, that's the main risk.

[00:26:32] Some B-cell therapies have been, not inebilizumab in particular, but other B-cell therapies have been implicated in an increased risk of complicated COVID-19 infection. So, that's one of the things to consider while, you know, with the COVID-19 pandemic. So, this is one of the possibilities as well. Infusion reactions can happen within inebilizumab, although in the clinical trials, they seem to be much less, compared to other B-cell therapies and usually are generally mild in severity.

[00:27:01] Another thing to consider is that B-cell therapies can decrease the effectiveness of vaccines in general, including COVID-19 vaccine. So, that's one consideration also to think about. Although not tested with inebilizumab in particular, but with other B-cell therapies, we have seen a reduction in hormonal response or antibody response to vaccines, including COVID-19 vaccine.

[00:27:23] As for satralizumab, some side effects that have happened, include upper respiratory tract infections, urinary tract infections, and some injection site reactions. So, if it's a self-injection, sometimes the area where you inject might get red or swollen a little bit, but nothing major there.

[00:27:41] One of the risks that can happen is a liver injury. The rates for that were actually very small during the clinical trials, but it's a potential risk involved with this treatment. And it's why regular checking of liver enzymes is something that we usually do when the patient is on satralizumab.

[00:27:57] And then there have been very rare cases where patients actually did show some reduction of their immune cell counts while taking this medication or reduction in antibody levels, like hypogammaglobulinemia.

These are very rare with this medication, but not impossible. So, these are kind of the main safety and risk signals with the three new medications for NMOSD.

Chelsey Judge, PhD: [00:28:19] I was just going to summarize. As you said, to start with, right? There's risks with anything. And so, with all of the FDA-approved NMO treatments to prevent relapse, right, you have obviously the potential risk for some of these side effects, but at the same time, if left undertreated or not treated, you have a very high risk potentially of another NMO relapse or disease activity.

Dr. Hesham Abboud: [00:28:42] Exactly. I mean, the risks involved with all three are actually extremely rare. The side effects are, side effects is different from risks. Side effects are some inconvenient, you know, things that might happen. They are not dangerous. And you know, some infusion reactions here and there, that's not a big deal, but the dangerous things like, you know, meningitis or liver damage, these are extremely, extremely rare.

[00:29:03] While, like you said, NMOSD, if left untreated, it is almost guaranteed that there will be significant disability accumulation for patients, especially with aquaporin-4 antibody. We know that the risk of recurrence and having recurrent attacks is extremely high, so we cannot leave it untreated. So, really definitely the benefits of these medications way outweigh the risks of the reach.

Chelsey Judge, PhD: [00:29:27] And you brought up that there, these are the FDA-approved treatments, but I know there are others that have been used prior to FDA-approval of these treatments and that they still might be used. And we use the term off-label. Could you explain what off-label means? And then, as a clinician, are you still using these other off-label treatments, compared to the new FDA-approved ones?

Dr. Hesham Abboud: [00:29:50] So, you know, off label means that they did not receive FDA-approval for this particular indication. And that mainly means that they did not meet the criteria or the requirements to get the FDA-approval or the company did not seek FDA-approval for that indication, even in the presence of evidence.

[00:30:09] The evidence behind the use of off-label medications and NMO in general is there's some evidence, but it is not, none of them really has a huge phase three randomized clinical blinded clinical trial at the size similar to what brought the three FDA-approved medications that we have.

[00:30:26] The off-label medications typically or commonly used in NMOSD include rituximab. So, that's kind of the original or the prototypical B-cell therapy that we've used for years for NMOSD. It is still being used, of course, for double seronegative NMOSD patients, meaning patients who do not have the aquaporin-4 or the MOG antibodies.

[00:30:48] So, they do not have anything FDA-approved these patients and they still constitute a good percentage of NMOSD patients. So, of course, we still use that in this subgroup.

[00:30:58] Also, patients who are aquaporin-4 antibody positive who were already on rituximab prior to the approval of the three new medications, if the patient is stable and, you know, having no side effects and no relapses while on rituximab, at least some clinicians would see no reason to switch those patients and kind of rock the boat. So, some of these patients are on rituximab.

[00:31:21] The other off label medications include oral medications like mycophenolate and azathioprine. These have also been used for years for prevention of relapses and NMOSD patients. They are not as popular as B-cell therapies, but, again, if someone is on one of these medications, been doing great, no side effects, no risks, and no relapses, usually there is no strong reason to discontinue that.

[00:31:44] There are some reports that these oral medications can be linked to skin cancer or development of lymphoma, if the patient has been on them for a prolonged period of time. So, that's sometimes a consideration too. To consider switching just to, you know, for safety reasons, if the patient has been on them for a prolonged period of time.

[00:32:03] And to answer your question about using the FDA-approved medications in conjunction with other medications, like some of these off-label medications, again, there is really, we know that these medications work by themselves. So, if there is no reason to combine them with something else, it would be safer to kind of simplify the medical plan for the patient. Just keep them on one immunomodulating therapy instead of two or three.

[00:32:28] But we know from the satralizumab clinical trials that, because they had two trials, one as an add-on and one as a monotherapy, we know that the trial that had the add-on design, that the rates of relapse prevention numerically were higher than in the monotherapy trial. So, there is at least some scientific evidence indirectly, I guess, that shows that adding some of these medications together may be more effective than monotherapy. I guess this is something that we do not do clinically or in kind of real-life setting, unless the patient has extremely severe disease or have already failed one monotherapy or two monotherapies.

Chelsey Judge, PhD: [00:33:14] Thank you. And I'm just slightly curious, kind of going back to insurance considerations, is there a difference in potential insurance coverage of the FDA-approved treatments versus the off-label ones? Or are they generally approved at the same rate?

Dr. Hesham Abboud: [00:33:31] Yeah, that's kind of a new thing, so we're learning and it's really a case by case. So, insurances have different rules when it comes to using these medications. So, some insurance does, might actually cover only FDA-approved medications and probably would be more economic for the patient to prescribe an FDA-approved medication, as opposed to an actually much cheaper, off-label medication. But, because of insurance coverage, it will, for the patient, will be actually makes more sense to prescribe the FDA-approved medication.

[00:34:01] But some insurances, they do require, kind of have more of a hierarchy or you need to try this before you go to that, including some insurers that we've seen that would kind of require treatment with, let's say, rituximab first before trying one of the new FDA-approved medications.

[00:34:20] In general, we try to always get the patient what is best for them and what they, what I'm more comfortable with, regardless of insurance denials. We try to just appeal and, you know, kind of negotiate with insurance and, in many places, we've been successful in getting the patients what they really want to be on and what we as a team, patient and doctor, think is the best for the patient. And usually insurances, you know, they listen when we put, you know, strong evidence and we negotiate with them reasonably. They usually listen. Yeah.

Chelsey Judge, PhD: [00:34:51] You emphasized the shared approach to deciding on a treatment, right? You and the clinical care team, along with the patient and the patient's preferences. I was curious a little bit about how does deciding on a treatment look like within your clinical practice? Like you said, I'm sure it sounds like it's shared decision-making. What do you think are the biggest things that drive selecting a preventative treatment?

[00:35:17] Would it be the efficacy from the clinical trials? What are the safety considerations? How it's administered? What do you think? If you had to like rank them, what do you think would be the top factors?

Dr. Hesham Abboud: [00:35:27] Yeah, those are different from one provider to another and also from one patient to another. Some patients are, you know, the kind of risk takers. So, they will say I'm not worried about a one in a million risk, but I don't want to suffer from ongoing, inconvenient side effects. So, they would care more about the inconvenient side effects, as opposed to the rate of risks. And, you know, that's understandable.

[00:35:53] While others, they don't mind a little bit of infusion reactions here and there, or having to, you know, self-inject, or whatever. As long as they would avoid a big risk. And that's also understandable. So, really that's the same for the doctors too.

[00:36:08] So, it's really very individualized here. I think my own experience is we give the patient the diagnosis, we give them an overview of all the available treatments, and then we give them reading material on the available treatment options. That includes, you know, the efficacy data and the side effect profile, and then we involve a pharmacist usually in the discussion, as well.

[00:36:32] It's a little bit, for NMO, it's, it's a little bit different, compared to other neuroimmunological conditions, mainly because all the FDA-approved medications came in the midst of a pandemic, which obviously made most discussion really kind of focused on safety.

[00:36:52] Safety kind of took the upper hand just because of the timing of the release of these medications. So, in my experience, safety really determines the choice of the medication by most of the newly diagnosed patients that we're seeing. And we, as clinicians, we also look at comorbidities. You know, we look, what other medical conditions does this patient have?

[00:37:13] Does having one of these put them at a high risk for one of the medications? Should we avoid certain medications because of this comorbidity? Should we choose one medication because of the comorbidity that this medication might work for? So, these comorbidities or other medical conditions also play a major role in the decision making when it comes to medication selection.

Chelsey Judge, PhD: [00:37:34] So, I think this was a lot of really great information. The first couple of things, I can obviously only speak for, you know, helping my brother watching him and his experience. And his was seven years ago, outside of a pandemic. So, he made a decision not based on, you know, avoiding a deadly virus. But his big thing was, of course, since he had a severe relapse that he just didn't want that to happen again, ideally.

[00:37:59] So, he was, I don't want to say he didn't care about the side effects. He obviously did. But he was like, 'Just hit me with whatever you consider the most effective treatment potentially. That's what I want.' As opposed to, I've seen other patients, like you said, who have different levels of risk comfort or risk aversion.

[00:38:20] And I'm glad that you brought up the pandemic because my next question is I'm sure that there's other considerations that people need to make for their treatment options as they come around, like a global pandemic, like wanting to make sure they have a good vaccine response.

[00:38:36] And then you also brought up comorbidities and bringing in pharmacists. When you consult or bring in the pharmacist, is that to check how potential NMO treatments might interact with other treatments that patients are on or what would their insight be?

Dr. Hesham Abboud: [00:38:51] The clinical pharmacist is part of the neuroimmunology clinic in some academic institutions. And we think of them as an extension of the clinicians. They have more time to talk

about medications with the patients and kind of go in more detail about, you know, the potential side effects and the risks involved with their treatment.

[00:39:13] I'm not aware of any significant interactions that can happen with the newer NMO medications. And it is already reassuring that, at least some of them, were tested as add-on therapy to existing treatments. And we know that we can combine them with other medications without major concerns. But I think the role of the clinical pharmacist usually is more in patient education and help them make that decision.

Chelsey Judge, PhD: [00:39:38] I think that's wonderful. Yeah, because these can be really overwhelming, and you need someone who has expertise to go over it with them. I did that with my brother, just using my immunology experience, but everyone needs someone who they trust to spend more time. 'Cause this is very confusing, if you have no science or medical background and it can be scary, especially when you throw in a pandemic. So, I think that that's wonderful.

[00:39:59] NMO, obviously, affects mostly women. And you know, in the stage of their life where they might be considering having children, becoming pregnant. So, what would be treatment considerations or what, what would that conversation look like with a woman who's considering family planning?

Dr. Hesham Abboud: [00:40:18] It's a good and difficult question. None of the FDA-approved medications or really of the off-label medications were tested in NMO patients who are pregnant. So, kind of the umbrella statement here is none of these medications really are safe during pregnancy.

[00:40:35] When you think about it from the practical standpoint, there are some medications that have a long-lasting effect. For example, B-cell therapies. If you give one dose of a B-cell inhibitor, like inebilizumab or rituximab, you do expect that there will be a long or lingering effect on the B-cell counts in that patient. And, although most of these medications are typically dosed every six months, the impact on the B-cells can linger for longer than six months in some patients.

[00:41:11] We really do it every six months because this is the label and this is kind of on average, this is what will keep most patients protected. But some patients can actually go probably longer than six months because the effect on B-cell therapy is, you know, I've seen it go for over a year, or year and a half, sometimes from a single dose.

[00:41:29] So, because of this, one thing that can be considered is to give the patient one dose of B-cell therapy and then ask them if they want to try, although the FDA recommendation is not to try until it's been six months from the last dose, but most likely the medication itself will be out of the system sooner than that.

[00:41:51] And the lingering effect will be there, but the lingering effect does not have any effect on the B-cells, will be there, but that should not be typically not, shouldn't be teratogenic to the patient by any means, I'm sorry, to the fetus by any means.

[00:42:05] So, one strategy that can be done from the practical standpoint is to get this one dose of a B-cell therapy, maybe try to get pregnant a month later, and then hope that the course of pregnancy, the patient will be protected fully or partially by that one dose that they received before pregnancy, because it can have a lingering effect.

[00:42:26] Pregnancy seems to be protective against MS relapses. That's not very well characterized in NMO. There is some kind of data that suggests that maybe pregnancy is not protective against NMO attacks, but we know that the postpartum period is really the highest risk for relapses for both MS and NMOSD.

[00:42:46] So, one of the things that we always recommend is, once the pregnancy is over and the patient gave birth, we usually recommend that we restart treatment right away, even if this will interfere with breastfeeding because that period, the postpartum period is where most of the relapses will occur.

[00:43:02] We have done, in MS, sometimes intravenous immunoglobulins during pregnancy, they are relatively safe, and some studies have shown that it can put MS at bay during pregnancy. I'm not aware of a similar data in NMOSD and I've never done it personally in NMOSD patients.

Chelsey Judge, PhD: [00:43:22] So, this is a lot of information, right? Like I am, you know, the NMO world, neuroimmunology, I mean, it's a booming field, right? We're kind of combining the frontier of medicine, immunology, and neurology together in a very rare patient demographic that makes up NMOSD.

[00:43:40] So, what do you recommend to patients who experienced NMO who might be initially seeing a neurologist, like a general neurologist who might not be near some of the major academic centers or, you know, big cities, who doesn't have much experience with NMO or neuroimmunology?

Dr. Hesham Abboud: [00:43:58] So, one thing that a lot of academic centers have been doing and they think it's a successful model is kind of co-treatment. So, you know, if a patient has a rare disease like this, they may request a referral to a nearby academic center or neuroimmunology center that is kind of known in the field and they can get like one or two consults, even a one-time consult, kind of to go over options or maybe once a year visitation with that academic expert.

[00:44:30] And then they can still continue to see a local neurologist on more regular basis for symptomatic treatment and for emergencies. And communication can be, of course, facilitated between the local neurologist and the NMO expert in an academic center.

[00:44:46] And, of course, the better solution for that is to give more NMO education to community neurologists through professional organizations, of course, and through pharmaceutical companies that are involved in the medications for NMO and also the patient-based organizations, Connor Judge, and Guthy-Jackson, and so forth.

Chelsey Judge, PhD: [00:45:07] Dr. Abboud, thank you so much. You're a wealth of information. I do just quickly want to acknowledge we did not discuss symptomatic treatment. We really just focused on acute relapse management, as well as preventative or maintenance treatment. Because that's what we think can potentially modify or at least reduce the severity of the disease versus treating the some of the symptoms that can come in NMOSD patients.

[00:45:31] I think we need a whole other podcast episode for that, with you for that. But just thank you so much and I hope that this really, like you said, empowers patients so that they and clinicians too, who might not treat and NMO, so that they can better understand it.

[00:45:45] So, just thank you so much for your time with us and also just your clinical insight's very helpful. Thank you.

Dr. Hesham Abboud: [00:45:53] Thank you very much for having me.