Editor's Note: This is a transcript of an online course released in October 2023. It has been lightly edited for clarity. To obtain credit for participation, CLICK HERE.

Module 1: Neuromyelitis optica spectrum disorder (NMOSD) pathogenesis and epidemiology

The first module is all about the pathogenesis and epidemiology of NMO or NMOSD. NMOSD is fundamentally a disease of immunity against the aquaporin 4 water channel. What is the aquaporin 4 water channel? It's the water channel in the central nervous system that facilitates water transport crossing astrocytes from the synapse to a blood vessel and back, and its role in water function has nothing to do with the disease. The disease is just an aberrant immune response against a naive target, which is the aquaporin 4 water channel. The channel is expressed in the astrocyte end-foot at the blood brain barrier, maintains energy balance and electrolyte flow. And within the central nervous system, there's only 1 water channel, which is the aquaporin 4 water channel. But it is also expressed throughout the body: in the lungs, stomach, kidney, other places, but in the disease, inflammation is strictly confined to the central nervous system.

We know that this disease is mediated by immune-mediated aquaporin 4 because patients with NMOSD all harbor an antibody against the aquaporin 4 water channel. It's called the aquaporin 4-IgG or the NMO-IgG. And somehow, this antibody does get across the blood-brain barrier where it can fix complement at the astrocyte end-foot and contribute to inflammation. There's probably a lot of aquaporin 4 immunity far upstream of that process. The aquaporin 4 antibody does play a role and is considered pathogenic in this disease.

Upstream here, within the blood, so we have T cells and B cells that are aquaporin 4 reactive. They're communicating and conspiring probably in a lymph node, or somewhere outside of the central nervous system, to attack the optic nerves or spinal cord. At that point, when B cells become activated, they differentiate into plasma blasts and start spewing out aquaporin 4 antibodies. The inflammatory process also recruits the innate immune system, that's eosinophils, granulocytes, complement, and then there's a breach across the blood-brain barrier which is here in gold. And once the blood-brain barrier is breached, then you have inflammation, aquaporin 4 binding to the astrocyte end-foot, fixation of complement, lots of swelling and demyelination and neuronal damage.

We know that there are certain components that are involved and are particularly good drug targets. Interleukin-6 is one of those that's involved. Interleukin-6 is produced by monocytes and by B cells, and contributes to the differentiation of B cells to produce the aquaporin 4 antibody. Without IL-6, you don't get class switching, you don't get aquaporin 4 antibody production.

On the complement side, we know that there's not only the formation of the membrane attack complex and primary injury to astrocytes, but we think that complement activation is also involved upstream in the disease process, maybe even upstream of where the T cells and B cells are communicating. But it's involved upstream and downstream and in IL-6 as well, all along the pathway of disease.

Trials for prevention and treatment of NMO are focused on these targets. Satralizumab and tocilizumab is off-label on the IL-6 receptor, so this disrupts communication between the T cells and B cells. We have inebilizumab and rituximab. These are B cell-depleting drugs. Without B cells, how does that interfere with disease pathogenesis? And then eculizumab which targets terminal complement, we have drawn here, right at the astrocyte end-foot, as sort of like a missile shield to protect against membrane attack complex, but eculizumab also probably acts upstream in prevention of NMO attacks as well.

The clinical course of NMO is very severe. These patients sustain severe damage to the optic nerves and spinal cord and that causes blindness and paralysis. We call those attacks acute relapses and, based on these trials where we have a placebo control, we know that about 50% of the patients will relapse within 1 year and 70% within 2 years. And every time these patients have an attack,

there's partial healing, but incomplete recovery leads to permanent disability.

It was thought to be a monophasic form of NMO which is much, much rarer, less than 10%, and those patients probably do not have the aquaporin 4 antibody type. It's much more common to have seronegative patients with optic neuritis and transverse myelitis that looks like NMO, but a lot of these patients end up being monophasic. We're really going to focus on the relapsing disease that's aquaporin 4-positive.

Those patients have attacks of the optic nerves, not just the nerves but also where the nerves meet before they enter the brain at the optic chiasm. A lot of posterior-based lesions and chiasm-based lesions and long lesions in the spinal cord are common in NMO. Within the spinal cord, transverse myelitis attacks are also long, so we call those longitudinally extensive, when they extend at least 3 vertebral segments. There's also clinical manifestations of these longitudinally-extensive lesions, including paralysis and sensory loss, bladder dysfunction and, in the healing phase, you get a lot of tonic spasms and neuropathic pain. These are very devastating, severe attacks.

One of the unique features of NMO is this thing called an area postrema syndrome. The area postrema is the lower part of the medulla, right before the brain stem hits the spinal cord, and it has a fenestrated blood-brain barrier there that seems to sample the blood for any triggers for vomiting. In NMO, inflammation in this area happens in about 10% to 12% of patients, and it triggers this 3-week episode of incredible nausea, vomiting, 8, 10, 12 vomits a day, and then a very uncomfortable hiccupping. And this lasts 2 to 3 to 4 weeks and then always goes away and it seems to be spontaneously resolving, with no permanent damage. Unlike the other attacks on the optic nerve and spinal cord, these people do heal completely and we expedite the healing with a course of steroids, if we're smart enough to know that this is an NMO attack.

Neuropathic pain is the scourge of the healing process. Between 75% and 80% of patients have it. It's horrible. It really deteriorates quality of life. And when I interview patients about whether they would prefer to walk again, see again, be able to control their bowel or bladder function or to get rid of the pain, most people choose pain. Pain is by far the most disabling feature of this disease.

The patient demographics are predominantly female, it's 10:1 in the aquaporin 4-IgG group. In the seronegative group, there seems to be a mix of MOG and other diseases, and the frequency of females is a little bit lower compared to males. But if we focus on IgG, aquaporin 4-IgG-positive, which is where the treatments were developed, it really is 10:1. The average age of onset is probably something like 39, and the current average age is somewhere in their 40s, and anybody over 60 who has a new transverse myelitis or optic neuritis, that's very, very typical of NMO.

The race distribution is also skewed. It seems to go away from Caucasians. In the United States, for example, more than half of the NMO patient population is comprised of non-Whites, mostly African Americans. If you consider that African Americans only make up 13% of the general population, they are more than 3- or 4-fold over-represented in the NMO patient population. In Europe, the Afro-Caribbean population is also overrepresented and, in Asia, where we see a lot of NMO relative to the sort of classic western MS, we know that NMO is also more common in that population.

Finally, we see a lot of overlapping autoimmunity with NMO. We see lupus, Sjogren's, psoriasis, myasthenia gravis. These are the common ones in more than 25% of patients. Overlapping autoimmunity is very common. So is family history of these same autoimmune diseases.

My summary is that NMO is a disabling, horrible neuroinflammatory disease that attacks the aquaporin 4 water channel and leaves behind lots of damage, causing neurological dysfunction, blindness, paralysis, and a lot of pain.

Module 2: NMOSD diagnosis

How do we make the diagnosis of NMO? We have an updated 2015 diagnostic criteria that was created by consensus. And consensus was that people who test positive for the aquaporin 4-IgG in the context of any of 6 core clinical characteristics. And those clinical characteristics are transverse myelitis, optic neuritis, area postrema attack or 3 other nontypical attacks that could be anywhere in the central nervous system. Any of those manifestations in the context of an aquaporin 4-positive test that we consider reliable, which would be by cell-based assay and exclusion of alternative diagnoses, that's enough to make a diagnosis of NMO. We know that these people who do harbor the antibody are going to relapse if they don't go on treatment, so we don't need to classify them as monophasic or not if they test positive for the aquaporin 4 antibody.

If they test negative for the aquaporin 4 antibody, there's a much higher bar, much higher threshold for meeting the diagnostic criteria. You have to have at least 2 core clinical attacks, so optic neuritis and transverse myelitis. They have to be disseminated in space. They can't be in the same compartment, can't have recurrent optic neuritis or recurrent transverse myelitis. You have to have a dissemination in space, but you don't have to have dissemination in time. I said we know of cases that are monophasic of optic neuritis and transverse myelitis and usually those people are aquaporin 4-negative.

We do have a lengthy list now of exclusion diagnoses that includes MOG and, of course, multiple sclerosis. And those have to be excluded to make the diagnosis of seronegative NMO.

Here are the 6 core clinical characteristics. I mentioned optic neuritis and transverse myelitis. We also talked about what an area postrema attack is. There are other acute brain stem syndromes that can involve eye movements and any number of problems with movements, motor weakness. We can have sensory changes as well, often an acute brainstem syndrome. We also know that the hypothalamus can be involved in NMO. There are these very strange attacks that involve both sides of the hypothalamus and it leads to these strange narcolepsy type of syndromes. They can have endocrinopathies even, and we don't tend to see these unless patients tend to relapse over and over again, but this is something that we've definitely seen with NMO. And then involvement in the brain. Some very strange attacks that have occurred, large lesions in the brain, usually abutting the ventricles, but these bottom 3, acute brainstem syndrome, hypothalamic attacks and cerebral syndromes, are pretty rare. Ninety percent of attacks are optic nerve, spinal cord or area postrema.

As I mentioned, the additional criteria for convincing us that an attack is due to NMO, especially in the seronegative group, is that we like to see by MRI that these lesions are long. That is the typical lesion length in NMO. With the optic nerve, for example, we see that especially the contrast-enhancing lesions are extending at least half of the length of the optic nerve or more. And in the spinal cord, we like to see that the lesion length, not the enhancement but the TQ swelling, is at least 3 contiguous spinal cord segments. Within the area postrema, these lesions can be hard to find. They can be as small as you want. They tend to not be enhancing. They're usually bright on flare. You might catch it on a sagittal section, but it's in the area postrema syndrome and it's associated with that clinical event that I mentioned. In acute brainstem syndromes, also rare, but you might find them especially near the roof of the fourth ventricle, maybe extending up from the area postrema. These are the MRI criteria that we typically see with NMO.

The differential diagnosis is, it's easy if you test positive for the aquaporin 4 antibody. It's almost always NMO. You really just have to rule out things like MS or MOG antibody disease, but in most of those cases where the aquaporin 4 is positive by cell-based assay, I would say the vast majority are going to be NMO.

It's only in those who are aquaporin 4-negative that we're looking for—really paying attention to—the differential diagnosis, looking for diseases like MOG antibody disease. About half of people who test negative for aquaporin 4, who otherwise meet

criteria, will test positive for MOG antibody disease and that's a whole other disease. Looks a lot like NMO, but responds to different treatments altogether.

MS can be more difficult to rule out. We're looking for oligoclonal bands in the spinal fluid and usually less than 50 cells, white blood cells per microliter and, even during an attack in MS, if you see more than 50 cells, that leans more towards NMO or MOG. And then the MRI is critical. We do see, about 13% of the time, we'll see a brain MRI that kind of looks like MS with periventricular lesions, but most of the time, in NMO, the brain is largely spared. And in MS, the brain is largely not spared. That's how we make the diagnosis. We use all the clues, CSF, labs, and MRI.

There are a lot of misdiagnoses associated with NMO. A lot of people who initially present with optic neuritis, especially to ophthalmologists, not trying to ding the ophthalmologists, but many of them will see a case and say, okay, this is typical of monophasic optic neuritis. You're going to be fine. But if they would test for aquaporin 4 and MOG, then they could accurately make a diagnosis and potentially prevent the relapse. That's why it's so important to test every patient who comes in with optic neuritis or transverse myelitis.

The most common misdiagnosis for NMO is MS, has always been MS. Back in 1999, more than 95% of NMO cases were just labeled as MS. Even after the aquaporin 4 antibody was discovered and widely used, even by 2007, the misdiagnosis rate was more than 30%. Again, mostly patients were called MS. But we know MS patients do not test positive for aquaporin 4. That is an exclusion for MS. We know that most optic neuritis cases in MS are unilateral. They're pretty mild and they get better on their own. With NMO, they can be bilateral, they can be severe and longitudinally extensive, and they can lose vision and not recover it well. Oligoclonal bands, much more common in MS. In NMO, there was a study that showed that up to 18% can have oligoclonal bands, but they tend to go away over time or they'll be monoclonal, so not 4 bands, but just 1 or 2, and that's more typical of NMO.

Lesion locations within the spinal cord are mostly central, whereas in MS the lesions tend to be more peripheral within the white matter. Cortical lesions in the brain are very rare in NMO. We've only seen a handful. But, with MS, as we know, very common. And within the spinal cord, lesions that are really long, extending 3 segments or more, those are much more likely NMO or even vascular neurosarcoid or something else, and not MS. With MS, we see really short, focal lesions in the spinal cord.

There are other diseases. Probably one of the most common overlaps now is with MOG antibody disease or MOGAD. MOGAD is also inflammatory. It's demyelinating. It looks just like NMO at onset. These people can have long lesions, severe lesions. It can be optic nerve and spinal cord. But they test negative for aquaporin 4. They test positive for MOG. By the time they come back to your clinic in 3 months, they can largely see again and they can walk again. Their recovery's much, much, much better than NMO. So that's 1 of the distinguishing features.

With GFAP encephalitis, you can also get GFAP myelitis and even GFAP optic neuritis, not as common. Mostly you see a lot of encephalitis, but it's worth testing. And spinal fluid is better to test than the blood.

If I could give you 1 point to take away from this session, it is that the aquaporin 4 antibody is our favorite tool to help make the diagnosis of NMO. It is 99% specific in the context of optic neuritis or transverse myelitis or even in area postrema attack. And the sensitivity is somewhere in the 80 percentile, so if you have an aquaporin 4-positive patient in that context, your workup is done.

Module 3: NMOSD treatment

This is where we jump into the treatment. Treatment we divide into 2 parts, we have the acute treatment, the management of acute disease. These are relapses. Hasn't changed really since the 1980s, unfortunately. What we use is high doses of corticosteroids, like methylprednisolone. We give a saturating dose of 1 gram IV daily for 5 days. We usually get a sense of whether they're responding or not within the second or third day. And for those people who do not briskly respond, we move towards plasma exchange to do 1 to 1½ volumes for 5 cycles, usually every other day, to try to remove 99-plus percent of the antibodies and other factors in their blood. And this occurs over a period of about 2 weeks, plus the initial steroid course. And then we follow that with a prednisone taper. All in all, this is a long treatment period, and some people respond quickly, especially if we treat early. We know that the earlier we treat, the better their outcomes.

Then we consider prevention therapy. We know everyone who tests positive for aquaporin 4 is at risk for relapse and we can prevent relapses.

On the preventive side on prevention of relapses in NMO, we have experience using off-label drugs. These are broad immunosuppressants, azathioprine and mycophenolate, that were widely used for similar diseases and that were used in NMO and put together in these case series. And we put together all the case series and compared failure rates and relapse rates using 2 of the most popular ones, azathioprine and mycophenolate mofetil.

Azathioprine was associated with about a 53% failure rate, meaning that 1 out of every 2 patients who were using this drug would have a failure and would relapse. The overall reduction in risk of relapse, though, was 72%, and this was better than anything we had at the time. With mycophenolate, though, we had an even lower reduction in the failure rate. This was probably because we could dose it better and we could follow lymphocyte counts as a marker of efficacy of the drug and, the reduction in the rate of relapse was 87.4%. Even better than azathioprine.

There are other therapies, monoclonals, biologicals that we've used off-label as well. These were validated only in observational studies except in the case of rituximab, where we have 1 phase 3 study, the RIN-1 study in Japan. Small number of patients, but proven to work. The way that rituximab works is it depletes B cells that express CD20. We know that, in observational studies, the failure rate of rituximab is somewhere around 20% or so, which is even better than mycophenolate and certainly better than azathioprine. And the other studies have confirmed that especially compared to azathioprine, rituximab appears to be superior.

Tocilizumab has studies in NMO and in MOG and in seronegative disease which shows a benefit as well. We recognize the mechanism of tocilizumab is to block IL-6 receptor and that blocks IL-6, IL-6 signaling between T cells and B cells. The TANGO trial showed that there's a lower risk of relapse when using tocilizumab, and most of those cases used IV tocilizumab at a dose of 8 mg/kg per month, but we also have some experience with subcutaneous tocilizumab, and that seems to be just as effective.

There were 3 trials that have launched with drugs that I mentioned before in the pathogenesis section. The first one that launched is eculizumab. Eculizumab blocks conversion, blocks cleavage of complement protein 5 to C5A and C5B. The drug is administered intravenously every 2 weeks. The infusion takes about 35 minutes and then there's usually a 1-hour observation period. Initially, it's every week, and then it's bumped up to a higher dose and that's given every 2 weeks. And you pretty much have to keep that 2-week schedule because if you delay that by even a few days, complement activity begins to rebound.

The study that was launched in NMO is called PREVENT. It enrolled only aquaporin 4-positive people. The thinking was that antibody was required for complement fixation, so only aquaporin 4 patients were enrolled, and that's different from other trials. Keep that in mind, in this study, 91% were women, as expected, as consistent with the demographics of the disease. And when this drug originally launched, the idea

was that this is such an expensive drug, and so inconvenient to be administered every 2 weeks, that is was really for people who failed everything else. The idea was this is for highly relapsing patients who had at least 2 relapses in the past year or 3 in the past 2 years, and who basically failed all other treatments, including rituximab.

The study enrolled over a period of 2 years and included a placebo arm. This is 2:1, 2 patients in the eculizumab arm, 1 in the placebo arm. Placebo patients were permitted to stay on some sort of background therapy, like mycophenolate or azathioprine, because it was thought that the true placebo arm would be a real risk to these patients. It would be almost unethical to let them relapse and suffer some permanent neurological injury.

At the end of the study, after 23 relapses occurred, everyone rolled over into an open-label phase. Also, if during the randomized, controlled period, if anybody relapsed, they were automatically rolled over into the open-label period where they got the drug from then on.

These are the results of the PREVENT trial. It showed that after 1 year, people in the placebo arm, 36% of them had already relapsed, and this is consistent with our experience with mycophenolate and azathioprine, for example, where there is a 30% to 50% failure rate, and we saw that in the placebo arm here as well. Now compare that with the eculizumab arm where only 3 patients relapsed, so 94% reduction in risk of relapse, 98% were relapse-free.

By 2 years, about half of patients relapsed. And by 3 years, there weren't that many placebo patients left. And over those 2- and 3-year periods, there was only 1 additional relapse, so 96% of patients remained in remission on eculizumab.

In the open-label extension period, patients knew that they were on the drug, and so many of them elected to stay on eculizumab as monotherapy. Remember, at the beginning of the study, they were permitted to be on background immunotherapy with mycophenolate or azathioprine, but when they rolled over into the open-label phase, many of them elected to discontinue that background drug. And when you look at patients who were on eculizumab monotherapy, 100% of them were relapse-free by 2 years and, at 4 years, only 1 or 2 patients had relapsed. And this is eculizumab monotherapy, no background treatment.

When you look at breakdown by demographics, there was no vulnerable population. It wasn't like Asians were more likely to relapse or women more likely to relapse. It was there were so few relapses that there was really no subgroup analysis that was meaningful in terms of who was vulnerable and who would respond. It looked like everyone was responsive.

The second trial that launched was inebilizumab. Inebilizumab is a B cell-depleting drug that targets CD19. You'll recall rituximab targets CD20 and has a slightly restricted repertoire, B cells compared to CD19. CD19 is expressed on pre-B cells coming out of the bone marrow before they start expressing CD20. CD19 is also expressed late in plasma blasts, short-lived plasma blasts, that are on their way to the bone marrow. They also express CD19 and they're producing the aquaporin 4 antibody, but they're not expressing CD20. They would escape from rituximab. Slightly larger cell population compared to rituximab. It is also administered IV, just like rituximab, and the same as rituximab, it's administered twice per year. With the induction period, though, there are 2 doses separated by 2 weeks, and thereafter it's every 6 months.

The trial that demonstrated inebilizumab efficacy was called N-MOmentum. This trial enrolled aquaporin 4 seronegative patients, but only about 17 of them out of 247—so only 230—were aquaporin 4-positive. Most cases were aquaporin 4-positive, but there are a few seronegative patients. They did not restrict patients to the highly active disease. They could've had 1 relapse in the past year or 2 in the past 2 years. Unlike the eculizumab trial, this trial was pure placebo, no background immunotherapy. In order to mitigate the risk of a relapse and permanent neurological damage, they limited the randomized, controlled period to only 28 weeks or about 6 months. Not 2½ years or anything like that, like eculizumab did; just 6 months. And after 6 months, even if you were in

the placebo arm, you got rolled over into the open-label phase and that's how they reduced the risk of relapse. They also randomized 3:1, 3 drug to 1 placebo to try to make it more ethically appealing to patients to participate.

They did complete enrollment, and similar to eculizumab, they looked at the time to adjudicated first attack and the results are here showing that, within 6 months, almost half of patients in the placebo arm relapsed. This is even more active than the eculizumab arm, but remember these patients were on pure placebo, no background immunotherapy. That's why there was even more disease activity in the placebo arm. But if you look at the treatment arm, there were only 13% who failed to prevent relapses. Now, this is the aquaporin 4 IgG population that's positive. The overall includes a few seronegatives and you can see the seronegatives, there were maybe 1 or2 who relapsed. And so the numbers are a little bit lower, but generally about the same. Those who were aquaporin 4-positive— and the few who were seronegative—equally responded to inebilizumab.

There was also an open-label extension period in this trial, and it demonstrated that those who responded well to the drug in the randomized period continued to respond well. There was an 83% attack-free period for over 4 years, and 92% who were attack-free after 1 year remained attack-free even over this entire open-label period. MRI findings and a lot of other secondary endpoints were performed in this trial, and they found that they had fewer new MRI lesions. That's consistent with the idea that if you don't have clinical relapses, you won't have MRI changes, and this study demonstrated the same. And there were fewer subclinical lesions, these so-called silent attacks that can occur in NMO, but there were a few and the clinical significance at this time is not known.

The third study that launched was with satralizumab. Satralizumab also blocks the interleukin-6 receptor. It's administered subcutaneously, and it is based on the parent compound of tocilizumab, but modified so that instead of an every-2-week injection, it's given every 4 weeks. It lasts longer than tocilizumab but does the same thing. It blocks that interleukin-6 receptor.

This study was called SAkuraSky. It also enrolled aquaporin 4 seronegatives. It also included a few teenagers because we had some safety data that we could use in teenagers. and it also enrolled patients who had just 1 attack in the past year or 2 in the past 2 years. This is similar to inebilizumab, but similar to eculizumab, the placebo arm was permitted to maintain on mycophenolate or azathioprine and this was randomized 1:1 for a period of 1.5 years, and they used the same primary endpoint, time to first attack.

And they showed a placebo group with 40% who relapsed in the first year in the placebo arm. This looks almost identical to the eculizumab placebo arm where patients were allowed to stay on mycophenolate or azathioprine. Same with satralizumab. We know that, with off-label drugs proven in these studies, the failure rate is somewhere between 30% and 50% and that's been confirmed over and over again, all 3 studies showed that.

Satralizumab, 91% were free from relapse in this trial. The aquaporin 4 patient population is different from the total population. After 2 years, a lot of the patients who were seronegative had many more relapses compared to the aquaporin 4 group. You see 91 vs 77. We're not exactly sure why that is. We don't think it's an effect of MOG antibody disease because only 1 patient tested positive for MOG. We're not sure exactly what that is. It may be a whole different disease population. It may be that aquaporin 4 seronegative disease has a really distinct immunopathogenesis that may not be as dependent on IL-6. But if you look at the aquaporin 4-positive population, there was a very distinct benefit.

The SAkuraSky trial, which allowed background therapy, was different from the SAkuraStar study. That was done as pure placebo arm, and this was only performed in the United States where they enrolled also aquaporin 4-positive and negatives and they still had to have 1 relapse in the past year, but patients in the placebo arm were not allowed to be on background therapy, and it was limited to

only 1 year. This was sort of a hybrid of inebilizumab and SAkuraSky trials. The same primary endpoint and they showed a benefit that was very similar to the SAkuraSky study. You'd expect in the patients who were on monotherapy, they had a few more relapses than if they were on combination therapy and that was especially true in the seronegative patient population. But again, overall in the aquaporin 4-positive population and this has been done—this has been looked at by combining the data from SAkuraStar and SAkuraSky—the overall risk and reduction of relapse is about 79%.

In open-label phase, people who respond to satralizumab tend to remain responsive. This is true of all 3 drugs. If you don't relapse within the first year, if you don't fail that drug mechanism, you're probably going to respond in the long term. Even at long term, more than 91%, 90% of patients did not have any severe attacks and even when you look at very minor attacks, most patients were responsive.

The takeaway here is that all 3 drugs were proven to be effective. This is eculizumab, inebilizumab and satralizumab, using 3 different mechanisms of action, all of which are involved in the disease pathogenesis of NMO, and all of which have profound benefits over any background immunotherapy that we were using off-label, between 70% and 90% or even 94% reduction in risk of relapse compared to background therapy alone. Remarkably effective drugs, and it turns out most of these drugs are very safe as well

Module 4: Expert opinion: selecting maintenance therapy

Among all of these different options, how do you select your favorite treatment? Well, the way that it works in many clinics is that patients are involved in the decision. When they're involved in the decision-making process, they're more compliant because they've made an investment in their own treatment. What I like to do is a shared decision-making model where I present all of the data, including efficacy, safety. We talk about route of administration, subcutaneous, intravenous. We talk about how often these drugs are administered, monthly, every 2 weeks or every 6 months. We also talk about safety issues, including risk of encapsulated organism infection with eculizumab. We talk about risks of increased cholesterol and platelet and blood clotting issues with satralizumab which we know is involved because IL-6 is important in those functions in the liver. And with inebilizumab, we talk about long-term immunity and hypogammoglobulinemia. All those safety considerations, all the efficacy data that I just showed you, along with all the logistics, and I put it all in front of the patient and I say, "What are your priorities?" And then they'll say, "Well, I really am concerned about the safety issue," or "I'm concerned about the cost." or "I hate IV drugs." or "I just want the most effective option." And then, based on those priorities, we narrow down their treatment choices.

We try to get them approved by insurance for the drug as quickly as possible because we know time is spinal cord. We want to avoid any risk of relapse in that time period between their acute presentation and onset of treatment. In the efficacy discussion, patients often ask, "Well which one is best, which one is most effective?" Of course, none of these trials were done head-to-head, so we can't say for sure. What we can show them is that a lot of the placebo arms were very even and so if you consider that as sort of a way to compare trials where we can compare the efficacy of each drug, a lot of patients will feel like eculizumab is really the heavy hitting drug, but a lot of them are nervous about the every-2-week infusion and the risk of neisseria meningitis.

Between satralizumab and inebilizumab, a lot of people are comfortable with inebilizumab because it works a lot like rituximab, and rituximab is widely used in NMO, on all the Facebook groups and patient websites. People are very comfortable and familiar with that mechanism. And satralizumab has the benefit that you don't need an infusion, so you can travel. You don't need to live near an infusion center. And among the 3 drugs, it is the least expensive, so favored by insurance companies, especially government insurance. All 3 drug options are very, very effective and safe. It's really just about priorities that the patient will express to you.

Monitoring efficacy, we do by, number 1, clinically. If patients don't relapse, that's proven success. Now, ideally, we would have a biomarker of efficacy even before a patient relapses. You'd like to know that the drug is effective. With B cell drugs, we often measure B cell counts and we think that if patients remain depleted of B cells, that that's a good sign that there won't be a relapse. With eculizumab and blocking complement, there are no really good complement measures. There's a CH50 test which will be completely inhibited. but that's not a very reliable measure of just C5A activity. And with satralizumab, we don't measure IL-6 levels or IL-6 receptor levels or anything like that. There are no really good blood tests for monitoring efficacy. What we really want to see is that patients don't relapse anymore. It's not necessary to perform routine MRIs like we do in MS, and lesions are very rare. We just wait for patients to report any problems. And if they report like a new symptom or you're finding new exam findings, then you'll want to get the MRI and see if the drug has failed.

We don't tolerate a single drug failure before switching to a new drug. If a patient was on drug A and then they had a relapse, we usually just switch right away. We don't wait for a second attack to say, yes, the drug is truly a failure for the patient. We just switch mechanisms altogether. And we don't usually switch from rituximab to inebilizumab, for example, because B cell depletion probably wasn't working for that patient if they failed with zero B cells.

Duration of therapy is lifelong. The disease is lifelong, so duration of treatment is lifelong. They don't have to be on the same treatment lifelong, but they have to be on some treatment. And so I tell patients that, from the beginning, that they're going to be on something for the rest of their lives, and it's not going to necessarily be immune suppressive their whole lives as we work on new and better therapies to be more antigen-specific.

If I could add 1 takeaway point for this section, it's that shared decision-making models of selecting a drug treatment has by far the best benefit for keeping patients compliant. Patients who choose their drug are much more likely to stay on it and much more likely to not have problems with that drug in the future. And if they do have problems, they're going to call you and then you can sit down and have a discussion about the next best therapy.