What are the long-term treatments for NMOSD and MOGAD?

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[00:00:05] **Dr. Benjamin Greenberg:** Okay. So, with that in mind, we're going to switch gears, and our next topic, what are the long-term treatments for neuromyelitis optica spectrum disorder and MOGAD. For this topic, we have Anastasia Vishnevetsky. I got it, right? Yes. From Massachusetts General Hospital where she is finishing her fellowship and made a horrific decision to join the faculty at MGH despite counseling from those of us who know better. So, I'll invite Anastasia up to the stage to talk to us about what's going to happen in both of these conditions.

[00:00:45] **Dr. Anastasia Vishnevetsky:** Hi, everyone, and thank you to SRNA for having me here, as well as to my fabulous mentor, Dr. Michael Levy. I'm going to talk about the very small topic of what are the long-term treatments for both NMOSD and MOGAD. So just to kind of take a step back, there are the acute treatments that putting out the fire for relapses with NMOSD or MOGAD. And then there's the preventative treatments, preventing the fire, preventing the relapses from occurring. And I'm really going to focus this talk on the preventative treatments. And there, I'm going to kind of break it up into two sections.

[00:01:30] So, at first, I'm going to talk about the FDA-approved therapies for NMOSD. And I'm going to add in Rituximab there just because there's also been a more recent clinical trial of Rituximab for aquaporin-4 positive NMOSD. After that, I'm going to talk about the off-label therapies for MOGAD, there's not an FDA-approved drug for MOGAD quite yet. And also, off-label therapies for NMOSD including both seronegative NMOSD, as well as the seropositive ones. And there's a lot of overlap between the off-label therapies for MOGAD and for seronegative NMOSD, as you can see with the red. Overlap medications all highlighted. Before I do that, I want to take a step back and just kind of say a few words about how we think about approaching the long-term management of NMOSD and MOGAD.

[00:02:30] So for NMO attacks, typically, we really fear any and all relapses, because recovery can be very limited and the attacks can be very, very severe. And with minimal exceptions, almost every patient who has syndrome consistent with neuromyelitis optica to and aquaporin-4 antibodies will be started on a long-term preventative immunotherapy. In almost no cases, are we going to recommend that that therapy be discontinued as of yet. There are some cases where people have done that or needed to do that, and we'll learn more about those cases as time goes on. But as of now, long-term therapy is really what we do for all

of these patients. In some cases of seronegative patients where maybe they had two relapses, so they fit the criteria, but then they've had long-term stability.

[00:03:25] There can be a discussion about whether discontinuation or changes in the management could be appropriate. For MOGAD though, the situation is a little bit different. So, a substantial proportion of patients with MOGAD might have just a single relapse. They might have a single attack and then not have another one regardless of what we do. And so, we really have to balance the downsides of the immunotherapy that we give with the upsides of preventing a potential attack. So, in some -- there are some exceptions where we might still treat somebody after their very first attack of MOGAD. So, one is if they have really significant residual disability or risk of disability with the next relapse.

[00:04:10] So, if they lost vision in one eye, the difference between losing vision in one eye and then losing vision in the second one is really, really significant. If someone has really high MOG titers that might play into the decision-making or evaluation of what the risk is. And then personal preference plays a major role in all of our clinic visits as well. If someone says I'm -- I want to start on a therapy, because I just can't -- it's so anxiety-provoking to think about a possibility of a future relapse. We take that into account as well.

[00:04:43] But even if patients do start on a therapy, there can be a conversation in a couple of years about stopping that therapy. With all of these conditions, there's no single right answer and there's a lot of different therapeutic options that exist. So, some patients have really strong preference about whether they want IV or subcutaneous therapy. The side effect profile differs between these and it's often really difficult to balance, how do you think about a really serious side effect that happens extremely rarely, and how does that compare to a more common side effect that happens, but that is less severe. And then onset of action, some of these drugs take action very quickly and others take longer.

[00:05:30] And again, patient preference plays a huge role in all of these decisions. So, there's no single right answer. So, I'll start with talking now about the long-term treatments for NMOSD and particularly the FDA-approved therapies for NMOSD. So, in 2019, there were three major clinical trials for dedicated drugs for neuromyelitis optica, and I really like this figure and also the name of this paper from mechanisms to trials, because these three drugs really approached different mechanisms that we learned in the lab about how neuromyelitis optica functions. So Eculizumab is one of the drugs that was approved, and it acts on the complement pathway. Inebilizumab attacks B cells as does Rituximab.

[00:06:27] And then Satralizumab attacks both B cells but is on IL-6 receptor blocker. And so, the science really led to huge breakthroughs in NMOSD therapeutics. So, comparing these four different drugs and remembering that these are the three that are FDA-approved. At the top, that's the name of the pivotal trials that were conducted and the different mechanisms that I discussed. So, complement inhibition IL-6 receptor blocking, and then blocking B cells in two different ways. And there are some really impressive risk reductions in relapses for all four of these therapies. For Eculizumab, and I use the generic name for the some of you might know this drug as Soliris as well. The treatment arm had a 96.4% of them were relapse-free at 144 weeks, compared to 45.4% of patients who were on the placebo.

[00:07:34] So, this is a really, really dramatic breakthrough, a dramatic drug effect. For Satralizumab, there are actually two trials that I'll take you through one is SAkuraSky. This one which allowed background therapy. In the aquaporin-4 seropositive population also really impressive efficacy and a little bit less effective in the overall population that included both the seronegative and the seropositive patients. This is the additional trial of Satralizumab that didn't allow any background therapy, any other oral medications while taking it. And it also showed significant reduction in relapses, but a little bit lower rate. And finally, this is the Inebilizumab

trial that again showed really dramatic reduction in relapses. So, 87.6% of patients did not experience a relapse compared to 56.6% over that same time period.

[00:08:38] This has been a huge success story and something that was alluded to yesterday about how getting the diagnosis of neuromyelitis optica today is a really different experience than what it was several years ago. Efficacy is not the only thing that is worth considering when you think about these drugs, and I'll say that there's really a mix of these that we use in practice. Eculizumab had really impressive efficacy data, but it's very expensive and does require an infusion every, at first step, every week for four weeks and then every two weeks after that, which can really affect people's lifestyles and ability to travel to live their lives freely. It also -- there is an associate risk of severe meningococcal infections.

[00:09:31] Everyone has to be vaccinated against that, and that's something that we continue to monitor for as well. Satralizumab on the other hand is medication that's very convenient. It can be self-administered subcutaneously. So, you cannot even have to go into an infusion center and take this medication. Overall, well tolerated, and safe medication although like all the others also has its own side effects. It does seem to be a little bit slower in terms of its efficacy onset. So that's something to consider as well. And Inebilizumab, medium time of onset, it is a more significant immunosuppressive drug. So, vaccine efficacy something that we all think about in the context of the COVID pandemic can be reduced, and all of these medications can increase infection risk somewhat.

[00:10:24] It's also a relatively convenient option in that you go into an infusion center once every six months or so to stay on these therapies very similar to Rituximab which some of you might be familiar with. So, Rituximab an old mainstay. It is a similar, medium, and onset, and it is given as an IV infusion, sometimes, rarely can even be given at home. Typically, it's every six months, but different dose regimens are available. You can monitor blood counts and give it either less frequently or more frequently. So, there's four really great options for neuromyelitis optica to and particularly aquaporin-4 positive. So, these three Eculizumab, Satralizumab, Inebilizumab are not approved for the patients who don't have an aquaporin-4 antibody. So, I want to now transition into talking about the long-term treatments for MOGAD, and the off-label therapies for neuromyelitis optica.

[00:11:27] So, this kind of these additional two sections, and I'll talk about them concurrently. So, to finish off the conversation about Rituximab, it's a really great therapy for neuromyelitis optica, it's a really great therapy for multiple sclerosis. But in MOGAD, it's been a little bit less effective. There's some conflicting data, but at least a third of patients might relapse through Rituximab even when it's kind of fully taken effect. And some series, Chen et al also showed 61% of patients relapsing on Rituximab over a longer period of time. Very different from some of those relapse-free rates of 80% to 90% that we saw earlier.

[00:12:13] And, one option that I've seen quite a bit is, if there are some cases where it's not 100% clear. Is this a MOGAD cases, is this an MS case. Maybe we're still trying to figure that out. And so sometimes Rituximab can be used in that context, kind of, try to cover a little bit of both bases. It's also, I would say, probably the most commonly used medication for seronegative neuromyelitis optica, and many patients also use it for the aquaporin-4 positive cases. It can be quick to get approval. a lot more doctors are familiar with its use, it's been around for longer. So, it's often kind of the first drug that people reach for. Going back a little bit in time to an oral medication that's been around for a long time is Azathioprine.

[00:13:01] It is a very general immunomodulator, immunosuppressant. It doesn't have a neuromyelitis optica or MOGAD's specific mechanism. It generally blocks DNA and RNA and protein synthesis and decreases over-activation of the immune system that way. But there's a few downsides to it. One is that it can take a

very long time to take effect. And so, during that time, you have to make a decision about whether to also continue treating with steroids. It also requires monitoring and can cause low blood counts or infection similar to many of the other medications that we talked about. And its efficacy is quite a bit lower, both for MOGAD and for neuromyelitis optica.

[00:13:47] So, in that same series, 59% of patients relapsed over time on Azathioprine which is again a pretty significant proportion. Other studies have found lower relapse rates, but there hasn't been any prospective randomized trial to really explore this. And there was one randomized trial in neuromyelitis optica comparing tocilizumab which I'll talk about a little bit later to Azathioprine and relapse rates were higher in Azathioprine group. So, 67.8% of patients were relapse-free in this Azathioprine group. And this I should say is -- it was a trial that was done in both aquaporin-4 positive patients and negative. So, another drug that's very similar or used kind of often talked about in the same breath as azathioprine, is mycophenolate mofetil, some of you might know the drug as CellCept.

[00:14:46] And this also inhibits DNA synthesis has a very general mechanism of action, not anything in particularly honed to neuromyelitis optica or MOGAD, and it similarly takes several months to take effect. So again, you have to make a decision about, until the patient really has the CellCept or the mycophenolate mofetil on board, do you continue with steroid therapy? Also is dosed orally, so it's just a pill that people take, it's widely available and very commonly prescribed worldwide. And there was one prospective cohort study that showed really quite significant efficacy for CellCept, so it showed just 7.4% of patients relapsing on that compared to 44% on placebo in the same group.

[00:15:40] But other series and reviews have shown my much higher relapse rates. So, the jury's still out a little bit on that data. It's often, what we reach for patients who want a convenient daily medication to take instead of IV infusions or subcutaneous injections, which just goes to show how much patient preference plays a role, because I think an oral medication is one of the hardest things to remember to take every single day. For neuromyelitis optica, there are a lot of older studies before the advent of the new drugs that I talked about in the first part of this talk that show that it reduces relapse rate. I would say, we're not really starting many patients on this medication today although there are patients who have been on this for a long time and not experienced relapses who choose to stay on it. So, this brings me to Tocilizumab. This is a drug that's an IL6 receptor blocker. Just like Satralizumab which was in those larger neuromyelitis optica trials.

[00:16:42] It's unlike Satralizumab which is given subcutaneously, Tocilizumab is given IV typically once monthly, not always and there is actually a subcutaneous formulation as well that's been studied. Also has side effects of low sometimes low blood counts, infections, diverticular perforation is a rare side effect that's been described. But overall, it's a well-tolerated drug. And there was one case series of 10 patients who had had pretty active refractory MOGAD, who showed no relapses while they were being treated with Tocilizumab. There is an ongoing randomized control trial of Satralizumab that you'll hear more about over the course of the day that really uses kind of the same -- so the same principle. But for the moment, we have Tocilizumab available, and you can use that off-label.

[00:17:36] For neuromyelitis optica can also be used off label for seronegative cases. There are some seropositive patients who might still stay on that medication as well. And the clinical trial, I mentioned earlier, that showed not particularly impressive relapse free rates for the Azathioprine group 67.8%, showed a 91.5% relapse-free rate in the Tocilizumab group. So, a little bit more evidence for that use. So, this brings me to IVIG. And so intravenous immunoglobulin therapy, as well as subcutaneous immunoglobulin therapy. So, this is likely the most efficacious MOGAD therapy that we have available today that outside of a randomized trial. And in a large series, 20% of patients on IVIG relapse compared to the much higher rates that we already talked about in Azathioprine, Rituximab, and cells after mycophenolate mofetil.

[00:18:44] And the reduction in the relapses is seen whether you're starting the IVIG upfront in newly diagnosed patients, or if you're starting IVIG in patients who have already had relapses on other medications. So that's relatively impressive as well. There are some variations in how you can dose the medication, and how frequently you administer it. And so, it does seem like higher frequency and higher doses are more effective although the convenience and the side effects are a downside if you give higher doses and more frequently. The availability and the cost and the convenience are all a significant concern. You start off with five days of therapy typically with IVIG, and then you have to retreat monthly, and depending on weight and dosage that might be a re-treatment that spans several days. It can be given at home, but that's not always easy to arrange.

[00:19:42] And subcutaneous IVIG is another option-- or subcutaneous immunoglobulin is an option as well for self-administration at home. But for a lot of patients, the high liquid volume can make it really hard essentially after they are administrative subcutaneous, they might feel a large, kind of, rough area. Someone yesterday described that they felt like they had a tire around their abdomen after administering the subcutaneous medication. So, for some patients that can work, but there are some downsides as well. There are quite a few other treatments that I haven't mentioned just in the interest of time and because we're using them a little bit less often. So Mitoxantrone was used in the past, Methotrexate, Cyclophosphamide. And there's a lot of other therapies that are being studied and will probably be discussed in the next sessions on clinical trials in MOGAD and NMOSD. So, with that, I'll take any questions if there are any. Thank you so much.

[00:20:58] **Audience Member 1:** Hi. Are there any studies on combining medications or therapies like CellCept and IVIG?

[00:21:05] **Dr. Anastasia Vishnevetsky:** Great question. So, I don't know of any combining CellCept and IVIG specifically for MOGAD. Some of the studies in neuromyelitis optica did combine therapies. So, for example that first clinical trial of Satralizumab allowed background immunotherapy, not with any immunotherapy, so Rituximab was not allowed, but for example, Azathioprine or mycophenolate mofetil were. So, from that, you could potentially extrapolate to, based on mechanism, that that would give you a little bit of an idea about combining mycophenolate mofetil, and let's say, Tocilizumab as well. There's more case reports of people talking about combining those, but there's really not a lot of kind of really high-quality data on combination approaches.

[00:21:59] **Audience Member 2:** Hi. Julia Leffler from the MOG project. I just want to make a comment about the subcutaneous IG. While if people may have problems with, it being under the skin, there are ways to go around that for anybody's interested. You can ask for more needles, and so that's spread over a larger portion of your body. So, for instance, they normally give you four. So, you might have four large places that it's under the skin. You can ask for as many as you want and spread it out. So, like on your thigh or in your stomach. So, you don't have that large tire.

[00:22:38] **Dr. Anastasia Vishnevetsky:** Great. And I also should credit Julie with giving me that quote on the large tire. So, thank you.

[00:22:52] **Audience Member 3:** Hello, I have some questions from the online audience. Yeah, one is, which of these drugs are approved in Europe? If any?

[00:23:03] **Dr. Anastasia Vishnevetsky:** That is a great question. I -- actually, I'm not sure. I don't know if someone else in the audience. I can phone a friend if someone knows, what's approved in Europe?

[00:23:18] **Audience Member 3:** That's where in Europe is a question indeed. I think this comes from the UK. The question comes from the UK. So yeah.

[00:23:28] **Dr. Benjamin Greenberg:** Yeah. So, for in Europe, it's country by country-specific, and health system by health system specific. And so, my understanding is, in the UK, you can get access to these drugs via the national health system, but you have to have advocacy from one of the centers that's certified to prescribe it. And so, my understanding is they're all available. And actually, Michael Yeaman is here, I don't know if you have better information than I do. But in the UK, it's through that system. My understanding is they are all approved. So, from the EMA, which is the European version of the FDA, they've all passed and are approved, but accesses based on the health system you're in. Michael, is that fair? Yeah.

[00:24:27] **Michael Yeaman:** I just was going to add to Ben's point that every country has its own methods for review and approval of different drugs. I think many of the three drugs that are approved in the United States are approved in many countries worldwide, but maybe Cheryl or Shervin might want to comment on those particular drugs.

[00:24:47] **Audience Member 4:** So, I just want to clarify that. I work for a company called Horizon, and the product we market is Inebilizumab, also known as Uplizna. We were recently, this year, approved in Germany and France looking for multiple approvals in the EU next year, as well as Latin America. Unfortunately, I can't speak to the other products that are FDA-approved.

[00:25:25] **Audience Member 5:** Shervin from Genentech. So just confirming what Michael mentioned, yes, it is approved in UK, and I believe 77 other countries as we speak.

[00:25:39] **Dr. Benjamin Greenberg:** Any other questions?

[00:25:42] **Audience Member 6:** So, I know that we've discussed that patients with aquaporin-4 positive NMOSD are going to expect to be on treatment indefinitely. How long would you counsel a patient to expect to be on treatment with relapsing MOGAD disease?

[00:25:57] **Dr. Anastasia Vishnevetsky:** So, I think it depends a lot on the individual patient and their relapses. I think at -- if someone's had a second relapse, we would at least do a two-year treatment trial, and then kind of reassess at that point, if the patients had absolutely no signs of any relapse, maybe they've made a really good recovery. The other thing we could look at that point is their MOG titer. That's not something that's kind of particularly guideline-based, but something that seems to be associated with relapse risk, so we could take all of those together with how well the patient's tolerating it and start thinking about whether after two years or so, it makes sense to discontinue. But I think that as many different experts in treating MOG that you'll ask; you'll get a slightly different approach or a different strategy. But I think that's -- I wouldn't necessarily have, unless someone's had a lot of relapses, say, okay, you're going to be on an indefinite therapy, I would kind of reassess that after several years and look at some of those other factors.

[00:27:11] **Audience Member 7:** If you're NMO-positive and you've been on Rituxan and your relapse-free, and you've got these other options, would there be a point where you would say you've been on Rituxan long enough, and maybe it's time to try one of these other three?

[00:27:27] **Dr. Anastasia Vishnevetsky:** I would say, we usually use the opposite approach of, if something about the medications not working, if you're experiencing a relapse, or you're having significant side effects then to transition or consider transitioning. I think if you're transitioning -- if you're on a medication that's really working for you, but it's very inconvenient to take, that might be another reason to transition. We typically, I would say, with you say, if something is working well, stick with it. There's some suggestion that may be very long-term use with Rituximab could lead to increased infection, but there are a lot of patients who have

been on this therapy for a very, very long time and done well. So, I probably wouldn't rush to switch to any of the new therapies if there's not a particular reason.

[00:28:23] **Dr. Benjamin Greenberg:** Great. Thank you. Appreciate it.