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Treatment Advances in Generalized Myasthenia Gravis: Clinical and Laboratory Criteria for Diagnosis and Optimal Treatment Selection

Announcer:
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CHAPTER 1

Dr. Bril:
This is CME on ReachMD, and I'm Dr. Vera Bril. Here with me today is Dr. Jonathan Strober, and we are going to present 2 cases, 1 each.

So the first case is one of mine. This is John, 40 years of age, married with 2 children, aged 7 and 12. He teaches American History at a local community college. John has a 10-year history of intermittent double vision and has been under treatment by a local neurologist. He has been diagnosed tentatively with ocular MG by that neurologist and given pyridostigmine 60 mg 3 times daily. His double vision was generally well controlled on this medication until 5 years ago, when he developed drooping of his eyelids, chewing difficulties, and weakness in both upper and lower extremities. The pyridostigmine was titrated upward to 90 mg 3 times a day, but his symptoms did not improve. He has been referred to me for more in-depth evaluation and treatment as necessary.

So this is the first case, and Dr. Strober, you will present your case now.

Dr. Strober:
Of course, thank you. So I'm going to talk about Alicia, who is 15 years of age, sophomore in high school, and she actually has a 12-year history of juvenile idiopathic arthritis as well as submandibular calculus that presented to me with ptosis. The symptoms began following an upper respiratory tract infection, and she also complained of some lower extremity weakness, worsening stamina throughout the day, and some difficulty swallowing, which was initially thought to be due to her previous diagnosis of the submandibular calculus and dry mouth. She did not have any diplopia, and she did not have any problems with breathing at the time. She was first seen by a different neurologist who thought she had functional ptosis because she had breakaway weakness on her exam. And so she came to see me at the request of her rheumatologist for a second opinion and possible further interventions if warranted.

Dr. Bril:
So at this point, we're going to discuss the cases a little bit. So Dr. Strober, what do you think about John's presentation?

Dr. Strober:
Well, I think ocular is the most common way a lot of these patients present, and double vision being a big way that ocular myasthenia will present, although a lot of times we also will see the ptosis or eyelid drooping at the same time. I think it's really interesting that it was 5 years before he had more generalized symptoms, as we often see generalization of symptoms a little bit earlier, but it is definitely

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something that can happen in a lot of patients.

Dr. Bril:
Yes. And sometimes in those who present with ocular, treatment may prevent the development of generalized disease, but the treatment has to be directed at the immune system. He was getting a symptomatic treatment, which worked for him, and that is why, I suppose, nothing more definitive was given him in treatment. But at this point, clearly, he needs more investigation, I think, or more intervention of different types.

For your patient, it's kind of unusual that the weakness was breakaway and led to a diagnosis of a functional ptosis. I find that kind of interesting, because she didn't have a background history of anxiety or depression, if I have read the history. She did have juvenile idiopathic arthritis, so she had one autoimmune disorder, so that might make her more prone to another autoimmune disorder, although she doesn't have double vision. And so she had presentation of limb weakness, but she also had swallowing difficulties. So I think there was some confusion in her initial diagnosis because of some items that were a little bit misleading to begin with. I should note that she did present with ptosis as well early on, so you would think that that might have triggered the suspicion of myasthenia gravis.

Dr. Strober:
I agree. I think that a lot of our adolescent patients often get diagnosed with functional neurologic disorders, because in myasthenia, as we know, you're strong in the beginning, and then as you keep using the muscles, you get weaker and weaker, and so that could be perceived as breakaway weakness.

Dr. Bril:
And I think too, that with limb weakness, it's usually more proximal than distal weakness. It hasn't really been described well in these cases, but basically, the weakness can be diffuse in very severe myasthenia. But ocular, bulbar, and limb weakness are classical features of generalized myasthenia gravis. And as you say, those presenting with ocular generally go on to more diffuse involvement earlier than 5 years, unless they're treated definitively with immunosuppressants.

So I think that is interesting in the cases. And for those of us who don't deal with the pediatric version, such as myself, it is interesting to understand how they're often misdiagnosed as having a functional disorder, because that must be distressing to the patients, I would think, and their families as another element of myasthenia gravis in the pediatric population.

Might I ask, just out of interest, what's the youngest MG patient you've had?

Dr. Strober:
The patient who presented the youngest was actually an 11-month-old who actually had antibodies. It does happen. I mean, there is a 2- to 5-year age group that ocular myasthenia alone is pretty common. And often those patients get referred to ophthalmologists and diagnosed with strabismus. So we're used to dealing with a lot of misdiagnoses in the pediatric age group, where I think in adults, a lot of patients get sent automatically to neurologists first.

Dr. Bril:
Yes. But some from ophthalmologists are neuro-ophthalmologists. And also a fair number are diagnosed as having a functional disorder as well, because they complain of weakness, and yet, when they are seen in the physician's office, they're strong, they're not tired, and the physicians may not be attuned to the diagnosis of myasthenia gravis. And then if they don't find anything on examination, they may feel that the patient is functional. And one of our main differentials can be fibromyalgia or chronic fatigue syndrome from myasthenia gravis. These present challenging problems.

Dr. Strober:
The other thing I think that was a little unique in my patient is that, as you mentioned, weakness is often proximal, which she did have more proximal weakness in her legs and she didn't have any weakness in her arms, which I think also kind of makes it a little bit more difficult to kind of think of a diagnosis of myasthenia, which we think of more as a generalized kind of condition.

Dr. Bril:
I agree.

So these initial case presentations have given us a lot to think about. Stay tuned for the next chapter, Chapter 2, when we'll go deeper into diagnostic and management processes for myasthenia gravis. Thanks for listening.

CHAPTER 2

Dr. Strober:
This is CME on ReachMD, and I'm Dr. Jonathan Strober. Here with me today is Dr. Vera Bril.

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So we have begun to discuss our approaches to our cases in myasthenia gravis diagnosis, and we're going to continue now with the discussion by assessing additional aspects that go into managing these patients.

Dr. Bril, will you continue telling us about John?

Dr. Bril:
Yes, I'd be happy to. So for John, pyridostigmine at 90 mg 3 times a day proved to be ineffective in controlling the spread of his symptoms. He had an acetylcholine receptor antibody test with an elevation at 29.7 and the normal range less than 0.5. Because he was young, he had a thymectomy performed, and the pathology showed thymic hyperplasia. If he had had a thymoma on imaging, then he would have had thymectomy for sure. But thymectomy is generally performed in those under 50, and in some centers under 60.

His symptoms got better after the surgery for about 8 months but then worsened again. At this point, he was started on prednisone 30 mg on alternate days and had a great improvement in his state, but he didn't return to normal. His ocular and bulbar symptoms resolved fully, but he had ongoing weakness in his arms and legs, so he was started also on intravenous immunoglobulin 1 g/kg every 4 weeks. But after 3 months of this therapy, he had not really responded very greatly. He felt about 60% of normal. His PASS question, however, was a yes, and his MGII was 4.

So the PASS question is a holistic question that asks if the patient had to stay in their current state for the next few weeks or months, is that acceptable or not? And it's a yes or no dichotomous response. So even though he was only 60% of normal, his PASS was yes, meaning he had adjusted to his disease somewhat.

And the MGII, the Myasthenia Gravis Impairment Index, is 4 points only. The total maximum score is 84 points, so his disability is not very high, despite the complaint of weakness in all extremities. And usually an MGII of 10 or less is associated with PASS yes, whereas the percent of normal question is usually above 73% with PASS yes, but here he had adjusted.

In the office, his physical examination was normal. And at this point, plans were to monitor the patient.

So this is the update on patient number one, so now I'll turn it back to Dr. Strober to talk about Alicia.

Dr. Strober:
Yes, so we also performed a series of tests on Alicia. And she had a normal brain MRI scan. We sent all the antibodies to look for all the ones that we know of in myasthenia and they were all negative, the acetylcholine receptor, MuSK, and LRP4. And she was starting on pyridostigmine 60 mg 3 times a day. And she did have some symptom relief from that for a little while. She had an EMG and nerve conduction study with repetitive nerve stimulation, which was unremarkable. And an MRI of her thymus was done and was normal. A month later, after starting the pyridostigmine, she actually developed really severe lower extremity weakness, where she couldn't walk and she had to be carried around the house. And she was having trouble taking a deep breath, so I asked them to bring her into the emergency department. In the emergency department, she had bilateral ptosis, as well as some weakness, more in the lower extremities than the upper extremities, more proximal than distal, and some trouble swallowing. So some bulbar weakness as well. We performed the ice pack test, and she actually had improvement of her ptosis, so that helped us confirm we really were dealing with a diagnosis of myasthenia. She was showing some signs of respiratory depression with her negative inspiratory force being -38. Her saturations were good. At the time, her respiratory rate was also normal. So people were not overly concerned about her, but we admitted her and started her an IVIG 2 g/kg.

Dr. Bril:
I just wanted to make some more points about John, my patient. He expressed satisfaction with his current status, although he only felt 60% of normal. And this is a sign that, in many adult patients, they come to terms with their state of weakness and are happy with it—not really happy, but accept it and are a little nervous about upsetting things. Since the IVIG was not effective, it should be discontinued. Sometimes patients get left on a therapy they're started on without a good reason, but just as it wouldn't work after 6 months, if it didn't work after 3. So I think it's important to evaluate a therapy in an MG patient and adjust it as you need to.

The Myasthenia Gravis Impairment Index, MGII, showed that there was little impairment. And this scale asks how you're doing in the last 2 weeks, and it also has levels of impairment. So for arm weakness or fatigue, how long you can use your limbs, et cetera, or legs. And the fact that there's only 4, when each level can go up to 3, shows that it's fairly low.

So at this point, you would consider monitoring the patient before you throw in another therapy. But if the PASS becomes no and there's more impairment, I think that's when you might consider other therapies. Perhaps 4 out of 84 isn't very high at all. You might consider increasing his steroids. I don't know.

What do you think, Dr. Strober?

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Dr. Strober:
I agree with you. I think, one, it is very interesting that when we get to be adults, we're willing to put up with a lot more. Adolescents, there's so much going on. It's not just work and home, there's school, there's friends, there's a lot of stuff, and they don't want anything holding them back. So a lot of times they really will push to try and get rid of every little bit of complaints that they have. And I do think that there is a trade-off, right? Because all these treatments that we use have their potential risks and side effects. And so it really is trying to manage the risks versus the benefits of each of these things.

Dr. Bril:
So I totally agree with you. And with adults, if you do surveys, which a lot have been done in the last few years, a lot of the patients in a survey will say they're dissatisfied with the fact of their state, although perhaps when they come into your office, they're not willing to upset an apple cart and change therapy. So it's challenging sometimes to really get into how a patient's feeling and what they're willing to do next.

Dr. Strober:
And I think, that's why we do listen, hear what the parents have to say. And it is sometimes interesting that the parents will have a different perception of what the child is reporting. Sometimes there is underreporting from the child for fear of what that would mean if they reported bad things. And sometimes they actually augment the problems that they're having, and the parents feel like they're doing fine. They're just not pushing themselves enough, or they're just not doing this enough, sometimes, are what we hear from some of the parents. So trying to put all the stories together could be a little difficult, but it really is what's best for the patient.

I do think it's interesting that we both started our patients on pyridostigmine, but as you mentioned, really, immunosuppression is important. And we both started with IVIG for our patients. So I think that's a pretty common thing that we see in a lot of our centers around the country. IVIG is often used.

Dr. Bril:
I think what's also interesting is your point about antibody testing, because when it is positive, it helps with the diagnosis. When it's negative, you can do the electrodiagnosis with repetitive nerve stimulation and single-fiber EMG. But the fact is, neither of those tests is totally specific for neuromuscular junction disorders. And when you don't have the antibodies, you always have in the back of your mind, have you got the right diagnosis? Could it be a myopathy? Could it be something else? And especially if they don't respond to therapy. If they respond to therapy, it's easier. But if they don't respond to therapy, then you have to up the treatment so much, which you would do in an antibody-positive patient without hesitation. But when you get into an antibody-negative patient, just how far do you push it? It's a very interesting conundrum, I think.

Dr. Strober:
I think that's why the ice pack test, which I don't know if a lot of people actually do, it really can be helpful, because again, once it was positive in our patient, I didn't expect that a patient would be reading about an ice pack test if they were trying to make us think they had some condition, to know that their ptosis should get better after having ice on their face. So it really does help kind of make the diagnosis in someone where you really are worried, especially if they're not doing well, and the diagnosis of functional neurologic disorder has already been raised by other people.

But I also agree with you that, again, tailoring your treatments based on the patient and how they're responding, and not continuing treatments that are not seemingly effective, is super important. So constantly evaluating what's going on every time they come in. And following them even if they're doing well, just to make sure that you're not missing something or you need to step in sooner and then you have a bigger problem, is super important.

Great. So in this chapter, we continued to develop and discuss approaches to our respective case presentations in myasthenia gravis. Please stay tuned for Chapter 3, where we will dive deeper into the management of our patients, while also addressing how we select the best treatment options to optimize patient outcomes.

Thank you for listening.

CHAPTER 3

Dr. Bril:
This is CME on ReachMD, and I'm Dr. Vera Bril. Here with me today is Dr. Jonathan Strober.

So we're going to talk about how to select a therapeutic approach for a patient diagnosed with myasthenia gravis. This is not a simple exercise, and we will discuss some of the issues we must keep in mind in this chapter.

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So I'm going to continue first with my case, John, who you recall, started with ocular symptoms and, after 5 years, developed generalized symptoms, not responding to pyridostigmine alone. And then IV prednisone and IVIG was started, but the IVIG really did nothing to improve his status, that he still had weakness in upper and lower limbs. The ocular and bulbar symptoms he had resolved with prednisone. John estimates that he is 60% of normal. And the PASS is yes, which we talked about, and the MGII is 4 out of 84 possible points on this impairment scale that incorporates fatigue. However, when you examine him in the office, his clinical examination is normal, which is not at all an unexpected finding. So at this point, because it's limb weakness and no ocular or bulbar, and he's been on steroids, could he have steroid myopathy? Could it be something else?

So we did repetitive nerve stimulation studies that were normal. There was a 3% decrement. It has to be 10% in our lab to be abnormal. Single-fiber electromyography was abnormal; 17% of the pairs were abnormal in the frontalis muscle. Up to 10% are allowed to be abnormal. And the jitter was 47.4 microseconds, which should be about 35 microseconds. And the blocking was 9%, and there should be no blocking. Blocking refers to when you are measuring from 2 muscle fibers connected to the same action potential, and there's a little variability between those fibers, which is the jitter. But if the variability becomes greater because failure of neuromuscular transmission, then the second fiber fails to fire sometimes, and it's called blocking. So that is associated with the weakness.

So John is still on the 30 mg on alternate days of prednisone, pyridostigmine 60 mg TID, and the IVIG, as we said, 1 g/kg every 4 weeks. So at this point, what would I do? What would we do? I would stop the IVIG, consider other therapies, such as FcRn inhibitors, or just monitor him, because his PASS is yes. The patient throws you a curveball. When they say, yes, they're satisfied with how they're doing, do you really want to start intervening with something else that's going to give them, possibly, side effects? So there's always that balance between therapeutic benefit and the cost of the therapy and side effects.

So Dr. Strober will continue with Alicia.

Dr. Strober:
Sure. So unfortunately, Alicia got worse after her IVIG. Her NIFs dropped from the -38 to -30, so showing more respiratory distress. So we thought she was going into crisis. And the treatment for crisis, if not IVIG, is plasma exchange, which we did, and we started her on a low dose of steroids that we started to increase from 10 mg up to 60 mg. We had considered doing rituximab. After the PLEX was done, she got 5 rounds of PLEX, and actually she started feeling better with each round of the PLEX. So when we were done, after 5 rounds, we gave her the rituximab 750 mg/m^2, which was followed by a second dose of IVIG a week later, and then another dose of rituximab to finish off the loading of it, 2 weeks later. She actually was able to start walking again, which was great, about a month after she finished, when she got her last dose of rituximab.

We decided to start dropping her steroids a little bit. She had only gotten up to 20 mg at this point, so we decided she was on a low dose, and we would try to wean her off of it. And we dropped it down to 10 mg. But in a couple of days, she significantly went into respiratory distress, and her NIFs dropped to -13. So we went back up on the steroids, but she continued to do worse, so we repeated her plasma exchange. I'm happy to say that she's actually much better now, able to not be on any respiratory support and starting to regain her strength that she had before she went back into crisis.

So the plan is now to continue her rituximab every 3 months and continue some IVIG as well every month. But you know we don't know if she will continue to be difficult to treat. So we do have some thoughts of whether or not we want to do an FcRn inhibitor or a C5 inhibitor. She has had low C4s, according to her rheumatologist, so complement inhibitors may be beneficial for her as well, since complement plays a role in her condition. However, they both, of course, have their risks and complications.

Dr. Bril:
I think this is a really interesting case you're presenting. And rituximab actually doesn't work that quickly, right? It works at about the 3-month level, I think. I mean, you have to wait for the effect, and probably that's why she worsened again as the steroids were dropped, because there was not enough time, and some of her antibodies were removed by PLEX. But, you know, just she was challenging and needed more therapy.

Dr. Strober:
Yeah, I mean, this is not typical of a lot of our patients. I'm happy to say that a lot of our younger patients don't necessarily go into crisis, but it happens every once in a while. And I agree, it just depends on how fast they're making antibodies. And most likely, she was making antibodies faster than we could keep up. And the rituximab hadn't really done its job. Or the IVIG that she had gotten as well had prevented her from making more antibodies. But I do think it showed that she does respond well to having her antibody levels, whatever antibodies they are in her system, lowered, which is why an FcRn inhibitor is something that we really are considering for her, should she need more support.

Dr. Bril:

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Yeah, I would say in our population, if it's a young woman, we won't use mycophenolate because of the teratogenic risks. Azathioprine, we've been very fortunate with. It's worked well. And we did a review of our women who'd had children, babies, and found that it was quite a safe drug. Cyclophosphamide, I haven't used in years. I know they use it a lot in India and in some areas of the world where the newer therapies are far too expensive. IVIG, they can't get. PLEX, they may or may not get, so that a lot of them use cyclophosphamide. It's a great drug for myasthenia if you can get over the fact that it can cause cancers, can make you lose your bladder, can suppress your bone marrow, make you lose your hair. There's so many risks for cyclophosphamide that, really, we don't use it at all anymore. Although the last time I used it was in a very refractory patient, whom actually, I guess, I started seeing when she was 16 and really hard to control. My most challenging patient yet.

So what do you think about John?

Dr. Strober:
Yeah, so, I mean, I agree with you. I think it's interesting that he's only 60% in normal but yet he's satisfied where he is. But I agree, when you're that weak, you really want to see if you're making the right diagnosis and if there's something else going on. So back to what we talked about earlier with making sure you have the right diagnosis kind of thing and pushing a little bit further. We have trouble with single fiber in a lot of our patients, especially the younger kids, just because they have a hard time sitting still for a test like a single fiber. Even adolescents, some of them are able to get through it, and some of them have a little bit more of a needle phobia or pain issue, making it really hard to do that testing. But we do use it if we really need to try and get more information that we're treating the right thing.

I think, again, the idea that we both kind of utilize similar treatments, like the prednisone and the pyridostigmine and IVIG. And I agree. I think it's nice that we have these newer drugs now that we didn't have even a while ago, and we were using more azathioprine and mycophenolate and even cyclophosphamide, which our rheumatologists aren't as scared of as our neurologists seem to be, for some reason. And I've used it many years ago for lots of autoimmune disorders, but we just don't use it as much as we used to use it, and for all the reasons that you stated.

I mean, I think that the biggest problem we have right now in the pediatric population is that all the drugs are approved for 16 and over, which is what the adult trials are, even though there are trials in the pediatric age group that are going on, and I think are going to show that the drugs, the newer drugs, are working just as well in the adolescent age group and the younger kids, as they are in adults. So hopefully we'll be able to get them approved more and more, because the insurance companies like to kind of stick to the approval guide, even though in pediatrics, we are used to using drugs that have never been tested in kids or approved in kids. So for us, it's not an issue, and it gets to be a little frustrating. But I do like the more focused treatments that we're developing now, rather than the older ones, which are bigger guns and really hitting more of the immune system, which definitely cause increased risk of complications.

Dr. Bril:
And I've heard from some of my colleagues with Fc receptor inhibitors, you might think that if they failed IVIG, they wouldn't respond to Fc receptor inhibitors, but some of the patients do. So you can't just assume that there would be lack of response. And we usually go to complement inhibitors after Fc receptor inhibitors, because of the requirement for vaccination against Neisseria meningitidis, meningitis. So because of that, we like to go through Fc receptor inhibitors first, and then if those fail, go on.

So in this chapter, we discussed many of the traditional therapeutic approaches for managing myasthenia gravis. We also discussed some critical patient factors in that choice and introduced a novel treatment approach, namely inhibition of the neonatal Fc receptor, or FcRn. Stay tuned for Chapter 4, where we will continue our myasthenia gravis treatment journey by providing our thoughts on selecting the most appropriate treatment for each individual patient at their stage of living with myasthenia gravis. Thank you for listening.

CHAPTER 4

Dr. Strober:
In this chapter, let's look a bit deeper at some of the patient factors that help with selecting the most appropriate treatments for our patients living with myasthenia gravis, regardless of where they are on their journey.

So, Dr. Bril, do you want to talk a little bit about how you decide what medications you think are best to use for these patients?

Dr. Bril:
Yeah, it's a very challenging question. But it's important to assess their antibody profiles to select therapy. So if they have acetylcholine receptor antibodies or MuSK antibodies, they are eligible patients for the new FcRn inhibitor therapies. Acetylcholine receptor patients can also be treated with complement inhibitors, but MuSK patients cannot, because MuSK is an IG4 disease, and IG4 does not go via complement, does not damage the neuromuscular junction via complement. So complement inhibitors cannot be used for MuSK

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patients or should not be used. Therefore, antibody assessment is really important in selecting the therapies.

Currently, all the evidence is in anti-acetylcholine receptor and anti-MuSK patients, so you can't use any of the Fc receptor inhibitors or complement inhibitors for seronegative patients. There are companies doing studies on double seronegative or triple seronegative, if you can consider LRP4 patients, using FcRn inhibitors, but they're not out yet. And the regulatory authorities, the FDA and Health Canada, have not approved – or the EME in Europe – have not approved use in seronegatives.

You have to look at disease severity and treatment history. And you can see from my patient, he was PASS yes, even though he was only 60% of normal, and his exam was normal and his impairment index was very low. So really, you have to think about disease severity in the patient's eyes as to whether you're going to intervene. You have to look at the prior response to immunosuppressive therapies and the current symptom burden to guide personalized therapy choices. John was only on a fairly low dose of steroids; 30 on alternate days is not a high dose to see if it's going to benefit him. And it did benefit his ocular and bulbar symptoms, so you begin to wonder whether he was a little undertreated with even that classical therapy.

And then we stratify patients for biological therapies, as I've mentioned. If they're acetylcholine receptor positive, we'll start with FcRn inhibitors in our unit, and then we'll go to complement inhibitors if the first fails. I predict that IVIG will be used less and less as we have access to FcRn inhibitors. IVIG is good to use if you are thinking of impending crisis, if you think of bridging therapy, if you want to start azathioprine and it takes 12 months to take effect. Or preoperative preparation, if they're going to have thymectomy, you don't want to start immune suppressants beforehand. So there are definite places where you'll use IVIG that I think will be replaced by using FcRn inhibitors and maybe complement inhibitors.

So this is when I consider using FcRn inhibitors and the preoperative preparation for thymectomy in those with acetylcholine receptor antibodies. If you have MuSK-positive patients, there is really no role for thymectomy. But bridging therapy, or less than optimally controlled patients on immunosuppressants and those who need a rapid response to therapy, because these agents usually work in most patients within the first 2 weeks of starting the therapy.

Dr. Strober:
I agree. I think that it's important on how fast you need to get the symptoms under control. So it's important to know how fast these medications work. Some of the older ones definitely take a little bit more time to work. Steroids can really take a couple of weeks to kick in. I think, for us, besides the not having the luxury of the FcRn and complement inhibitor approvals, so we're kind of stuck there for right now. We also look at how often these patients are going to need to get treatments, right? So when I sit down with my patients and families, and we talk about taking an oral medication daily or weekly, or getting an infusion, be it monthly, or rituximab, which you get 2 doses 2 weeks apart, and then a lot of us have been doing every-3-month infusions to start for the first year, versus IVIG, which is every month, or the newer medications, which are every other week, although I think the newer complement inhibitor is going to be once a month, if I'm not mistaken. So I think that that also plays a role for a lot of our patients and families and how often they need to get the treatment done, so it adds a little extra level of complexity into trying to figure out.

I think that's why a lot of my patients do like rituximab, because it's less of a requirement, and I'll often give a little bit of IVIG with it. But my patients do love IVIG too, since it is only once a month, although it's a longer infusion than, say, the other newer medications, which, even though it's every other week, can often be given at home and given quicker, smaller infusions. So we do consider lifestyle as well, but it also, again, it depends on how fast you need to get them treated and get them on therapy.

And we know that some of our patients will go into remission spontaneously within the first year or so, and so we don't necessarily push for thymectomy early on. I think in your patient, he actually had been having symptoms for a long time, so thymectomy is definitely a good option when they've been having symptoms for a long time. Although we do struggle a lot with our ocular-only patients as to whether or not they should get a thymectomy, if it would benefit them at all. That's been the debate going on as well. But agreed, if you're on steroids and then you want to do a thymectomy, that could affect wound healing and infection and other complications. So trying to put all the pieces together and figure it out could be pretty complex.

Dr. Bril:
Our surgeon really prefers the patients not to have been on steroids, because he says it interferes with the surgical plans as well. The steroids produce changes in the tissue, so that we try as much as possible not to have patients on steroids before surgery. And that's where we need agents such as IVIG, if the pyridostigmine is insufficient and they have severe enough disease. And this is where I see Fc receptor inhibitors being used.

The regimen that you choose depends a little bit on the drug. For efgartigimod, the first one, they're weekly infusions for 4 weeks, and then an observation period for 4 weeks. Then 4 weeks on, 4 weeks off, and they're intravenous infusions, each taking about an hour. And so it's therapy on demand. Although they have now done a study where they dose regularly every 2 weeks instead of on demand,

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and they find that the IgG levels remain suppressed sufficiently. They don't bounce up; the patients don't get worse. And I will say that patients that I've started on 4 weeks on, 4 weeks off, somehow they feel really worse in the 4 weeks off, and they want to reduce that observation interval so that there has to be some flexibility.

Rozanolixizumab is a subcutaneous administrated drug given once a week for 6 weeks, and then the patients are observed again and treatment on demand. But they too, started with every-other-week treatments in open label, and they work. So the dosing is going to be more flexible than the phase 3 studies, I think, when you get out into private practice or into clinical practice.

So there are several Fc receptor inhibitors in development. Nipocalimab had a successful phase 3 study and is under priority review by the FDA. We may see approval granted sometime this year. The dosing interval is a little less frequent. So far, most of us think the Fc receptor inhibitors have comparable efficacy or response rates, so it's comparable side effect profiles so that the choices may be on frequency of administration more than anything else.

Dr. Strober:
Actually, nipocalimab is also in clinical trials for adolescents, and the data was actually presented at the end of last year. The first data in adolescent FcRn inhibitors that has been released and showing that it works pretty similar to what we see in adults. So that's very exciting, and hopefully we will have that as a tool to use. But a lot of our patients do look forward to the day that they turn 16 or older and become adult, able to get those newer drugs.

Dr. Bril:
And our patients are coming in now, they see the TV ads, and they come in asking for this new therapy. They don't want to take prednisone. They don't want to take something else. They want the new therapy. And one of our challenges is going to be convincing the patient that, no, you can't just have the new therapy as standalone therapy. In our particular province, they won't fund us for rituximab for generalized MG unless it's MuSK MG. Very shortsighted. We can continue that patient on IVIG, but we can't put them on rituximab when rituximab might suppress them for 9 to 12 months. It's a very great struggle to get reimbursement.

With the Fc receptor inhibitors, I think what is so exciting is that they are so rapidly acting and have relatively minor side effects, although there is an increased infection risk, particularly of upper respiratory tract and urinary tract infections. So you might monitor them for immune suppression, but actually, they don't really get that. We don't do the IgG levels. The question is if they had a preexisting immune deficiency, then you might have to be concerned. The other thing is some of them cause headaches; some of them cause diarrhea. So there are different side effects that may come with them, but they start within 2 weeks.

And it's very interesting in open-label therapies, when you do on-demand treatment, that some people need treatment every 3 to 4 weeks, some people 4 to 12 weeks, and some people don't need a treatment for more than 12 weeks. It's really strange. But that is the observation, that you can't predict what cycles a patient will need and how often they'll need a cycle every year.

The mean, I think, in the open labels, is 4.5 or 5 cycles per year or 4. But that's not all the patients. As I say, some are more frequent, intermediate, and then those long-affecting ones.

So we monitored John, and he worsened somewhat. So we decided to try an Fc receptor inhibitor, and he responded to the 4 weekly, 4 on, 4 off, 4 on. He felt 85% of normal. Finally, we got him above 60. His PASS was still yes, and his MGII was 1. So he really did well.

Dr. Strober:
That's awesome to hear. I'm so glad our patients are doing better and that we have the ability to treat them.

We tend to follow our kids, especially the ones that kind of present during adolescence. We develop a strong bond, and a lot of them don't want to leave us, and we don't want to give them up to the adult side. But we know that if they're still continuing to have the need for treatment as they cross over into the adult world, that they are going to need somebody to follow them for a long time and have considerations that we may not necessarily think about in the pediatric population. So we do need to transition a lot of them over to our adult colleagues, or, I should say, colleagues who take care of adults, which is a good thing when we can do that just because it means that the patient is doing well and is old enough and able to move on and have conversations about pregnancy and other issues that develop for them as they get older.

So in this chapter, we discussed how patient factors can influence treatment choice. We also discussed the place of FcR antagonists within myasthenia gravis treatment structure. And while Chapter 4 concludes our current program, we encourage you to visit or revisit Chapters 1 through 3, in which you'll find valuable information you can bring into your medical practice today. Thank you for listening.

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