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Released: 04/25/2024
Valid until: 04/25/2025
Time needed to complete: 60 minutes

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On the Clinic Floor: Addressing the Most Critical Questions of Frontline Clinicians in Multiple Sclerosis Management

Announcer:
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[CHAPTER 1]

Dr. Shin:
Hello and welcome to “On the Clinic Floor: Addressing the Most Critical Questions of Frontline Clinicians in Multiple Sclerosis Management.” I'm Bob Shin, and I'm really excited that you could join us for what I think is going to be a really fun and interesting discussion. We're fortunate that in the MS space, things have been evolving and improving constantly over the past several decades, and our understanding of this disease has increased tremendously. But as we've learned more about MS, it has, in turn, led to additional questions about how we can better manage multiple sclerosis.

So today, what we're going to try to do is tackle these challenges we all face when managing MS. What's a little bit different about this program is that we invited video submissions from four practicing clinicians from the community to voice their most pressing questions in this space. So these are individuals who treat multiple sclerosis but do not necessarily specialize in MS management, so they're going to help us really get to the bottom of what people need to know in day-to-day practice.

I want to give a quick special thank you to these providers, doctors Kyle Smoot, Carolyn Geenen, Sangjin Oh, and Robert Sterling, for providing us with the questions that we're going to be tackling today. And by we, what I mean is our incredible panel. So I'm Bob Shin in Washington, DC. I'm a Professor of Neurology at MedStar Georgetown University Hospital, and I'm joined today by Dr. Jiwon Oh, who's Medical Director of the Barlow MS Program. She's an Associate Professor at the University of Toronto. And joining us also is Dr. Enrique Alvarez, Associate Professor and Vice Chair of Clinical Research at the University of Colorado. So welcome Jiwon and Enrique, we're excited to have you here.

Dr. Oh:
Thank you very much. It's nice to be here.

Dr. Alvarez:
Thanks. Happy to be here.

[CHAPTER 2]

Dr. Shin:
Alright, so our first questions.

Dr. Geenen:
In which patient subgroups are you testing for NMO spectrum disorder antibodies? Do you do it routinely?

Dr. Smoot:
Do you check for MOGAD in all your patients, even though the features are consistent with multiple sclerosis?

Dr. Shin:
So these questions are really diving into a relatively recent challenge, which is the recognition that there are conditions that can mimic multiple sclerosis but have different pathophysiology and potentially different treatment options. So Jiwon, I'm going to throw it to you first.

Dr. Oh:
Sure. So you know, I think the short answer to the question of whether I routinely check for MOG antibody or NMO-IgG in all patients is no. I think it's, you know, important to remember that even though we have access to all of these advanced imaging measures and lab tests, we are first and foremost clinicians, and we need to remember that clinical judgment is really important. And so in a typical individual presenting with symptoms that are very typical of MS there's nothing out of the ordinary on their clinical exam that jumps out as a red flag. And on the MRI, if I see features that look very characteristic of what I typically see in people with MS, this is not somebody that I would just send you know, a panel of screening tests.

However, if somebody does have any clinical features that are a little bit atypical raise red flags or even pink flags and on any of my clinical exam or MRI, if I identify any features that I think are atypical for MS or concerning these are absolutely people that I would do additional tests to ensure that I'm ruling out any other diseases that could be responsible.

And so, you know, just to give you a few examples of what I mean by clinical red flags, you know, in somebody who's presenting with, say, bilateral optic neuritis or severe optic neuritis that has had poor visual recovery, people who have altered level of consciousness or encephalopathy, people who have profound fatigue or headache, or who have a complete transverse myelitis on the MRI, if I saw atypical features of MS, including meningeal enhancement, evidence of infarct, symmetric, confluent lesions, bleeding, just to name a few, again, this would prompt me to do many other paraclinical tests, which include not just the antibodies that we talked about, but a systemic autoimmune screen, as well as MRIs, of additional parts of the nervous system, as well as CSF studies.

Dr. Shin:
Enrique, do you agree? Do you practice the same way?

Dr. Alvarez:
Totally agree. I think it kind of reminds me a little bit of the questions back in the day when people would have a panel of like checking B12 and syphilis testing and things like this, automatically for anybody that would come in. And I think if, you know, if everything's pointing that this is MS, you know, I think you're good. If you start getting some of these – I like that Jiwon did the pink flags – more borderline type things. And I think that that's where, you know, you start doing more stuff, and that might be the MOG and the NMO, or other testing as might be needed.

Dr. Shin:
I don't know if you guys agree with this, but the one area I am challenged by is a presentation of optic neuritis maybe even if it's unilateral but severe and it's their first presentation, I struggle because I want to make sure that I'm not missing MOG or NMO even at that beginning. So that's one scenario where I've been – it's harder for me to say that it's atypical or not typical, and so I've been checking that pretty consistently.

Dr. Alvarez:
Yeah, I agree. I think that that's a perfect place. One of my favorite you know – I think this one, you know, that question, if that's allowed in this program you know, for residents is always, you know, what's the most common diagnosis with bilateral optic neuritis? And you know, I think a lot of the residents will always go to sort of NMO or MOG but the answer really is MS. You know, an uncommon presentation of a common disease is much more common than a common presentation of an uncommon disease. and so I think it's you know, but at the beginning for some of these things, I think you know, that's where you take a little bit more liberty in getting more testing. you know, when patients don't have a lot of lesions that really support one diagnosis or the other, you know, the patient that comes in with just a few lesions you know, I think that that's where you have to be a little bit more careful.

Dr. Oh:
I was going to say exactly what you said. I think it can be challenging. And you know, I think there's generally a typical way that most people with MS present with optic neuritis, but then there's always the bell curve of severity, right? And so, of course, we are going to

get severe optic neuritis in MS, but then it could be many of these other diseases.

And I also find the same thing actually, with this, you know, clinical red flag of having a complete myelitis. Because you know, we typically say most people with MS will present with a partial myelitis, but I have, you know, not uncommonly, also seen people with what looks like a transverse myelitis as their first presentation. So I think, you know, bottom line is, it's always good to err on the side of caution and to be careful when there's anything that kind of in the back of your mind raises suspicion.

And then just wanted to add one more thing, Bob, I actually have had a false positive NMO-IgG back when I first started practicing. And that, you know, really taught me that this is why it's important to use clinical judgment and not necessarily go on a fishing expedition for every patient, but if there are any features that raise any sort of suspicion, even a pink one, that's when we should do additional testing.

[CHAPTER 3]

Dr. Shin:
Maybe along the same lines, but digging in a little bit more, is a question about oligoclonal bands.

Dr. Geenen:
In which patients are you now doing lumbar punctures for oligoclonal bands? If you have a patient that's presenting with classic relapsing remitting MS, do you ever do that test anymore?

Dr. Sterling:
Is a lumbar puncture with CSF analysis really necessary, especially for that first presentation when you think somebody may have demyelinating disease or multiple sclerosis specifically?

Dr. Shin:
Alright, Enrique, how about over at University of Colorado?

Dr. Alvarez:
Yeah, I mean, I think this is always a little bit of a moving target, right? And I keep offering to do spinal tap in patients. And surprisingly, I don't get a lot of takers, you know, for, I think, some of the patients that have very classic MS. So I would say, if we have some of those pink or red flags, you know, then I would encourage to get a spinal fluid. I think it does add some additional information. It helps a little bit on the prognosis side. So, I mean, even the patient that you brought up before with the optic neuritis, where you're not quite sure, you know, maybe they do have two lesions to kind of squeak in the diagnosis of MS. You know, there's a little bit of a prognostic ability that comes in with having the spinal fluid data to it.

Here we can see that, you know, the study that pushed getting oligoclonal bands back into the diagnostic criteria. They were there, then they disappeared, and then they got brought back in for the 2017 McDonald criteria. I imagine they'll stay there with the new version this year. but this study was a big one that helped support that. And we can see that it adds on the specificity side of things. So if you're looking for inflammation, that does help maybe rule out some of those patients that are having little white spots, that maybe are due to headache or other nonspecific spots that we might see in them. And it'll be interesting to see a little bit how much potentially things like central vein sign, PRL cells, you know, so paramagnetic rims are slowly evolving lesions, that they will maybe make us use, you know, spinal taps less and less in some of the patients. But I think for the right group of patients, it does add some very helpful data for us on the diagnosis and the prognosis.

Dr. Shin:
How about you, Jiwon?

Dr. Oh:
I find the likelihood of doing CSF studies in the context of MS diagnosis is very regional and center dependent. Normally, I find if there is a big kind of neuroimmunology component of a clinic they tend to do a lot of spinal taps, just because it's very useful and also clinically useful fluid that is useful for many scientific reasons as well. And so at our center, we have a huge patient population, and in the vast majority of patients, we don't do spinal taps. But it's in people with these atypical clinical syndromes or MRI findings that it's a very useful tool to either ascertain the diagnosis of MS or to look at other differential diagnoses.

But recently, we have brought on a number of neuroimmunologists, and interestingly enough, I found that the number of spinal taps that we are doing routinely for diagnosis has increased a bit. So this kind of proves my theory of the frequency of spinal taps. But there's no denying clearly how useful it can be diagnostically and prognostically, as Enrique already said.

Dr. Shin:
Speaking of biomarkers, this is a question about retinal nerve fiber layer testing, or OCT.

Dr. Sterling:
Have you found that assessing the retinal nerve fiber layer really helps with the acute or even subacute evaluation for a possible demyelination diagnosis, specifically multiple sclerosis?

Dr. Shin:
So Dr. Sterling was asking a question about optical coherence tomography. so this is a tool that's found in most ophthalmology offices, which allows you, in a non-invasive way, to get an assessment of the thickness of the retinal nerve fiber layer, which in some sense, is really part of the central nervous system. It gives you an assessment of the health of the neurons in the back of the eye. to answer his question, I actually pulled up one of the earliest studies looking at OCT in people with multiple sclerosis. This goes back to 1999 so now almost 25 years ago, there was a study which looked at people with MS who had had optic neuritis to see whether OCT could be a useful tool. And this was a small number of patients, but they showed that, as one might have expected, the eye that had had the optic neuritis, had thinning of the retinal nerve fiber layer compared to the opposite eye, you know, the eye that had not been affected by optic neuritis.

But what I think was actually very interesting about this study is they noticed that the unaffected eye in the multiple sclerosis patient, so the eye that had not had optic neuritis, had a thinner retinal nerve fiber layer than the nerve fiber layer in people without MS. And I think what's very interesting in terms of the past 20 some, 25 years, is this was really the first hint that neurodegeneration occurs early on in the course of disease, and maybe independent of clinical relapse activity. So in other words, separate from the clinical optic neuritis, there was evidence of retinal nerve fiber layer thinning in the, quote unquote, unaffected eye in these individuals with MS. So I think this message has sort of in a way, been verified by everything we've learned about MS since that time.

Having said all that, I actually don't tend to use OCT in clinical practice for individual patients. And one of the challenges is that, although I think this is a great tool that has been refined in terms of looking at populations, so for example, patients with more aggressive versus less aggressive disease, or even an endpoint in some clinical trials if you look at evidence of clinical benefit of different types of therapies. I still find it challenging to know what to do with a specific number for an individual patient in my office, and so I don't know how you guys feel about it, but I think this is a tool that's taught us a lot about disease state, but I'm not sure how to use it in my practice to follow an individual patient. Maybe I'll ask Jiwon to comment first.

Dr. Oh:
Yeah, I tend to think of it like brain atrophy in MS, and obviously in groups of patients, we know that there's an accelerated rate of atrophy. But again, in that individual patient, and knowing the measurement variability, and not knowing what threshold I should be using, and knowing that the threshold changes with comorbidities and medications and age, that is a challenge. So I know we're not talking about brain atrophy, and everything is not all about MRI for me, but I think there are a lot of principles that are similar in that it's really useful scientifically and in clinical trial settings, but in an individual patient, not that useful from a clinical standpoint.

Dr. Alvarez:
I will maybe take a different stance a little bit, and not that I use it a lot. But every couple of times a year, I think sometimes it can be helpful to go back to the non-specific symptom patient, you know, sometimes when they start to have, you know, vision and you're trying to kind of figure out, you know, maybe was a, you know, migraine aura-ish, and the little white spots, or, you know, non-specific, little white spots you know, if they're having repeated events, I think if you see a normal OCT, it's reassuring. And then following up patients, sometimes I like to use it for the patient that comes in a lot of times with episodes, you know, three, four times a year, where they're having eye pain with eye movement. And, you know, classically, we're told that this is, you know, a patient that has to be having active inflammation, because that's the only way you would have eye pain with the eye movement. And if the OCTs are fairly stable, then it provides a little bit more reassurance that that patient on a highly efficacious therapy, you know, is probably well covered, and you can kind of work on maybe trying to manage some of the pain, and don't need to keep doing, you know, high-dose steroids for those events.

So I think it provides a little bit of that. It'll be interesting a little bit, because I was not involved with the new diagnostic criteria that'll come out later this year. But I think everybody's kind of expecting that optic nerve will become that fifth part of the brain, if not sixth part, you know, with other areas maybe getting added in, but at least you know, the role of OCT and the diagnostic criteria may come into play and the OCT may become a little bit part of those criteria. So, more to come I guess maybe later on.

[CHAPTER 4]

Dr. Shin:
Alright. Here's a question not so much about assessment and diagnosis, but really more about treatment.

Dr. Geenen:
Can you describe the typical demographic of a patient in whom you would consider high efficacy therapy at the time of diagnosis?

Dr. Shin:
There isn't really a lot of agreement in our field, so I think people can come from different perspectives. Maybe Enrique, you could start?

Dr. Alvarez:
Yeah. I mean sometimes when I get asked this question, I think my nonchalant answer a little bit, and so it's always an MS patient with a heartbeat. I come from a center where we tend to really believe in using high efficacy therapies early, and so we might push the envelope, and would probably overtreat some. and so I have a low threshold for starting high efficacy therapy earlier.

I think data like this is data that maybe pushes us towards kind of our experience with this. Additionally, we have a lot of things that helps us try to predict how aggressive somebody's MS is going to be. And the reality in clinical practice, to go back to the discussion about populations versus individuals, we realize that those prognostic factors are really crappy when applied to the individual. And so we have a lot of people that end up failing and having to kind of escalate their therapies.

And so this was a study where they looked at people who started high efficacy therapies either early on in their disease course or started them later on. And so times here in the top graph is when they actually started the high efficacy therapy. And we can see this separation and accumulation of disability that occurs over these patients with a really fairly long follow-up. It's interesting a lot of times to see that the first 2 years are very much – there's not a lot of separation in the curves. And if we consider that most of our clinical trials are 2-year studies, it helps us highlight the fact that we probably need to look longer at some of these measures.

I think the other piece that, to me, was interesting for this was at the bottom part of this where, if you kind of reset at year 6 in this case, and just kind of look at – and these were patients that were on that high efficacy therapy for the first 6 years, and then you kind of followed them afterwards, and you realize, like, there's a continued separation of the disability. So a decision you made 5 years ago has sort of this longer lasting effect, you know, downstream. And so I think early on, to kind of be able to kind of knock off the disease and take care of it, to me, becomes really fairly important.

Dr. Oh:
You know, I think it's very clear that most people with MS should at least consider high efficacy therapy from the beginning. And there are many people who absolutely should be on high efficacy therapy based on data that continue to emerge from many parts of the world, highlighting the importance of early disease control.

However, I would say, you know, there is a small proportion, it's not large, but a small proportion of people who really do have mild MS. It's just the problem is, as Enrique said, it's really hard for us to prognosticate accurately. And the tools that we use, you know, whenever you look at a neurology textbook or an MS review article, there's like, these giant tables of clinical features and demographic features and paraclinical features that help us to prognosticate, but it's pretty clear that we're not really that good at it.

So the bottom line is, you know, generally, I agree with Enrique and that in most people, at least consideration, should be given to high efficacy therapy. There are a large proportion of people where it really should be the standard of care and it's appropriate. But there is a small proportion of people where you may not need high efficacy therapy from the beginning, but the problem is we just don't know how to tell really well. And so I think in those situations, the key thing is to follow them closely, clinically and using MRI.

Dr. Shin:
Well, as you guys pointed out, there has been a shift, and I do think more and more individuals really agree with what's been expressed, that the early use of high efficacy therapies is beneficial for a large number of patients. And we've known this from the pivotal trials, right? Every pivotal trial showed that the placebo group or the group assigned to the less effective therapy, accumulate more disability. And even in open-label extension, they can never really catch up. You know, if someone's on a lower efficacy therapy and begins to develop disability, we can't really undo the disability that has accumulated.

Dr. Alvarez:
Yeah, I think the other piece is around, maybe the buzzword these days a little bit, of shared decision-making. But I think it becomes really important to kind of have that good discussion, right? I mean, I think some patients will be very afraid of the risk of the medications, and some people are going to be very afraid of disease. And, you know, to some extent, it's our job to kind of try and balance those out. But you may not be able to balance them out completely, and it's better that they end up on some treatment than no treatment, if you end up really kind of running them out of the clinic, to some extent. So I think it becomes important to have those big discussions and just, you know, guide the patient you know more so these days.

[CHAPTER 5]

Dr. Shin:
Alright. This question is diving into, maybe again, what we're talking about, sort of the future of MS therapies, specifically about this new

class of agents, Bruton's tyrosine kinase inhibitors. There was a recent readout regarding evobrutinib. And I think Dr. Kyle Smoot has a question.

Dr. Smoot:
More recently, we learned about the trial results from evobrutinib that it did not meet its primary endpoint when compared to teriflunomide. What thoughts do you have concerning the recent trial results? And do you feel that there is still a potential future for this class of medications, the BTKI inhibitors?

Dr. Shin:
And so we're fortunate to have Dr. Oh here with us, and maybe we can get it straight from your mouth. What are your thoughts?

Dr. Oh:
Well, I mean I don't think it's an exaggeration to say that many people were really surprised with the announcement. So my thoughts well, first, I was very sad to hear this just because I think we as a field have had a lot of kind of hope put into this class of therapy. And the reason for that is the BTKIs are a ubiquitous molecule, but they're involved specifically in many cells that we know are highly relevant to MS pathophysiology. So we know that BTK is an enzyme that is involved in B cell maturation, so if you inhibit BTK, we know that we can decrease B cells, which we know based on many of the existing therapies, play a pivotal role in relapse biology in MS. So that's part of the excitement.

But an additional part of the excitement of the BTKIs is that many of them actually do get into the brain pretty easily because they're small molecules. And it turns out, at least based on preclinical studies and some lab-based studies, that BTK is also a molecule that's heavily involved in the maturation of macrophages and microglia. And as we know, one of the major drivers of progressive disease biology, or CNS compartmentalized disease biology, which we think is a driver of the slow smoldering progression that we see in most people with MS, it turns out there may be potential for these BTKIs to beneficially modulate that process, which we know most of the therapies that we currently have probably do not have a major effect on.

So this was all of the excitement behind BTKIs. And I don't think there's ever been a time in the MS therapeutic field where so many of molecules from the same class of therapy are simultaneously being studied in MS. And so evobrutinib happened to be the first one that was evaluated in a phase 3 clinical trial. And despite the positive results of the phase 2 proof of concept study, where there was a significant reduction in gadolinium-enhancing lesions, the phase 3 trial did not meet its primary endpoint. And I think we're still waiting to hear about more detailed results from the study, but this was obviously a disappointment. And are there implications for, you know, the clinical development program of all of these other BTKIs? Probably. But we're fortunate, because the other two BTKIs that are front runners include tolebrutinib and fenebrutinib. And it sounds like we will be hearing results from the tolebrutinib clinical trials, hopefully, within the next year.

And so I think there still is hope. Just because evobrutinib did not show an effect on relapse rate versus teriflunomide, it doesn't necessarily mean that there is not an effect of the BTKIs on relapse disease biology, because there are a number of pharmacologic differences between all of these BTKIs, as you can see summarized in this table here. And it is possible that these pharmacologic differences, that we don't necessarily know if they translate to a clinical difference, but it is very possible that it may translate to a very meaningful or large clinical difference.

So I think bottom line is time will tell. And in the end, the proof is always in the clinical trial pudding. And so I think we're eagerly anticipating hearing additional results from the evobrutinib relapsing MS clinical trials, but also hearing about what happens with tolebrutinib and fenebrutinib, as well as the other BTKIs. And so I, for one, am keeping my fingers and toes crossed in the hopes that we'll be able to see an effect. And it's not really the relapse disease biology piece that excites me; it's getting into the central nervous system and maybe being able to decrease these pathologic microglia that we know cause these chronic active smoldering lesions, and are kind of diffusely present within the CNS, and are supposed to be driving a lot of this progressive disease biology. So we'll see.

Dr. Shin:
What was your reaction, Enrique, when you heard the results?

Dr. Alvarez:
Yeah, a little bit shocked. I mean, I think and by a little bit, I mean, probably a lot. And I think the extension data maybe might be a clue into some of the issues with some of these medications, where we're seeing that kind of in the long term, there's some ongoing MRI disease activity in these trials. And whether that has to do with something of upregulation of other tyrosine kinases after a prolonged period of maybe BTK inhibition, or things like this, and we might need to go after a couple of different pathways might be interesting.

The other piece that comes into it a little bit, I think, is that the number of attacks or relapses was really low. It was low on both sides.

And that gives us into a situation where the effect of the teriflunomide, for example, in these trials are almost as good as what we were seeing with B cell depletion in some of the other trials. And so you start to kind of wonder if we're starting to have effects from, you know, are we capturing all the events? Are we getting good reporting from the sites? We have to remember that the vast majority of these patients are coming in from war torn sort of areas, and in the middle of a war, it might be really hard to conduct a clinical trial. and so are the subjects able to go to the clinical trial site? Are they able to get assessed and things like this? And so are we underreporting some of the events that we saw? Now, that might be for the clinical side, but the MRIs, you think would tell us a little bit better difference and things like this. So I'm very curious to see where we go.

Dr. Shin:
Well, I think there's no question the community was disappointed by this result. On the other hand, I think it's interesting, because, as Jiwon mentioned, the excitement about this class of BTK inhibition was the idea that maybe we would have medications that would be more effective at slowing down or preventing progression, especially maybe progression independent of relapse activity, than the other tools that we have. And yet, the primary endpoint, the one that evobrutinib stumbled over, was about its effect on clinical relapses. And as Enrique mentioned, and I think it's actually really patient selection, you know, these over time, we've seen in all clinical trials that relapse rates tend to be lower, I think, because we tend to enroll patients who are otherwise fairly stable.

And so I think what we don't know, as Jiwon said, is does or did evobrutinib have an effect on progression? I don't know if we'll get a chance to sort of do a post mortem on this study and get some of that data. Again, the primary endpoint was not met. But was there any effect on any other parameter that's more specific to progression? And the clinical trials that are coming up, as you mentioned, do have slightly different designs. So as you said, maybe not all hope is lost.

[CHAPTER 6]

Dr. Shin:
Alright, we're sort of diving into clinical practice, an area that is of interest, because many people living with MS are young women. So this is a question about pregnancy planning in a newly diagnosed patient.

Dr. Geenen:
What is your treatment strategy of choice in a newly diagnosed female with MS who has active disease and considering pregnancy within the next 3 years?

Dr. Shin:
Well we'll start with Enrique, maybe. What are your thoughts here? What is your approach?

Dr. Alvarez:
Yeah, I mean, we have increasingly gone to a model of using B cell depletion kind of pre/post pregnancy now probably for about 6, 7 years, or something like that. I think that this diagram highlights a little bit of a lesson learned from the early rituximab trial, from the HERMES trial where the patients only really received one dose of treatment and then were followed for an entire year. and maybe conveniently you can fit a 9-month pregnancy really nicely into that 1 year to kind of allow for no real, you know, no further treatment during the pregnancy.

And I think the pieces that we've been adding in a little bit later is sort of, now, what do we do, sort of after the pregnancy? And that has involved doing other infusions. I usually will shoot for about 4 weeks after delivery. It allows breastfeeding, which I think becomes a really important part, with a lot of benefits for both mom and baby. And one of the things that we started to do early on was then start to look at some of the B cells in the babies to kind of see if we could detect decreases, you know, implying transfer. We had some early studies, led by Dr. Bove, that showed that some of these antibodies do make it into breast milk. But the question is whether the baby would be able to absorb them, sort of after the first couple of weeks, where you have the colostrum milk? And we have some data where we show that at least in 10 of our babies, that they all had fairly normal levels of B cells present, you know, giving us a little bit more comfort. And this was kind of what we were stuck with a little bit just because of the difficulties getting antibody levels for some of these. We can check for rituximab antibodies, but it's a little bit harder to check them for, like ofatumumab. And so this was kind of an end point result that we can kind of look at.

So I think this gave us comfort to do this, and we've seen really pretty good outcomes. There's also a lot of recommendations that we can use. And I think a lot of these become very reasonable as we talk, you know, about sort of the other options that we do have. I think glatiramer acetate is a very safe option throughout pregnancy. It's just, I worry a little bit about the efficacy for the post pregnancy, post-delivery bump that we tend to see a few months afterwards.

I think the other option that I consider a little bit is natalizumab. There's a little bit of concern about anemia in babies who are doing this.

There's been talk about trying to stop natalizumab for the last trimester. So there's different strategies. I just get concerned a little bit about rebound in that scenario.

You can look at some of the induction type options with alemtuzumab where you can deplete and then allow for the reconstitution of the immune system have sort of a, you know, good effect over a year or two afterwards, and then consider restarting therapies or maintaining monitoring afterwards.

So I think the nice thing is we have options now that maybe in the past we didn't have that allow us to you know, to encourage moms that, if they wanted to have kids, that it's still an option for them.

Dr. Shin:
Jiwon, do you agree? Do you practice any differently in Canada?

Dr. Oh:
I think Enrique has done a really nice job of covering it all. The other point I wanted to add is in somebody who's not in a rush to get pregnant, sometimes a non-continuous immune reconstitution therapy like cladribine tablets, can be useful. and I think, you know, obviously, if somebody's in a rush to get pregnant, it's always the B cell therapies that are probably easiest to use. But in someone who's thinking of pregnancy, you know, 2 plus years down the road who doesn't have extremely active disease, I think something like cladribine tablets are also really useful, just because you don't have to worry about stopping therapy and starting again postpartum, as long as disease is controlled.

Dr. Shin:
Yeah, I think that we didn't say it exactly, but, you know, there's always been this perception that, while women with MS are pregnant, they're protected from their MS. I think we've had sort of conflicting data on whether relapse rate goes up after delivery. But in the past, we simply, I think, mostly, just stopped MS drugs and sort of let people take their chances. But there's been increasing evidence, as you both mentioned, that there may be you know, scientific evidence that would guide us to give them additional protection through their pregnancy and beyond, using these strategies.

I feel like I have to say, maybe, for the purpose of this, that all of these conversations are off label, right? These medications are given labels that are very specific about not using them during pregnancy, giving them windows that are extremely conservative in terms of how long you'd have to wait before using the medications.

I think a takeaway message, as I think everyone's hearing, is that in practice we're trying to be guided by science and evidence to sort of optimize the protection of women during their pregnancy.

[CHAPTER 7]

Dr. Shin:
Alright, this question also from Sang, is about cognition.

Dr. Oh:
So how do you assess cognitive changes in patients with multiple sclerosis? In practice, we may use like an MMSE. Do you think that's enough? Or are there other forms of cognitive testing that you use? And if you do see cognitive changes, do you change medications? Do you consider using a different DMT?

Dr. Shin:
Well, I think Sang brings up an interesting point, because I feel like when I was first learning about MS, we often said that MS patients don't have cognitive impairment until very late in their disease course. He mentioned something, an assessment, like a Mini Mental State Exam, or these days, I think people may use a MoCA, a Montreal Cognitive Assessment. But we've learned that those tests are not very sensitive for MS type of cognitive dysfunction. And so in my practice, actually, I have been increasingly using Symbol Digit Modality Testing. What I like about it, it's extremely quick. By definition, it's a 90-second assessment. And some people have recommended doing this annually. I just sort of do it at every visit. When they come in, I'll just ask them to do this as a part of their assessment. And this is still a screening assessment, but it seems to actually identify slowing of cognitive processing speed, which is something that many people with MS are experiencing.

So he also asked the question, and what would we do with this information? And I think that, similar to maybe some of our conversations about OCT or brain atrophy, I don't know if I would think of this as something that I would use reactively. In other words, I don't want to wait until there's sort of a significant change in cognitive assessment.

But I do think an initial assessment sometimes highlights surprising impairment. In other words, I have patients who are professionals,

maybe physicians, you know seemingly without complaint, who do shockingly poorly on SDMT. and I use this actually – even though we talked about prognostic markers in passing, I use that to maybe prompt me to consider a higher efficacy therapy early. If I see someone who's already demonstrating this sort of impairment, it might prompt me to be a little bit more aggressive, if you will, in terms of treatment. I don't know Jiwon, what do you think?

Dr. Oh:
I agree. I think it's a useful kind of screen at the beginning, and it gives us a snapshot of how much damage there already has been. And so it does influence, I think, my perception of an individual's prognosis, and what sort of therapy they need to be on. And then, you know, I think there's emerging data on the fact that there are cognitive relapses. It's just that I don't think I know enough about it right now.

And in terms of the monitoring piece, I also think that's important. But again, you know, similar to that threshold discussion we had, I don't think I know enough about how quickly I expect to see a change with the DMT change and all of these things. So I don't necessarily incorporate it as a monitoring tool in clinical practice, but it definitely does sway my judgment about initially, how worried I am about a patient.

Dr. Shin:
Do you agree, Enrique?

Dr. Alvarez:
Yeah, I agree. I think Jiwon brings on an important point about sort of a learning effects of these tests and things like this. And when you do them over and over, then you start to see these improvements in the scores, and is it, you know, are patients getting better? Or is it the fact that they just got better at the testing?

And so I think it's important to recognize that. I think we all have, you know, sort of that case that we can remember in the back of our mind, where we got burned about how badly disabled somebody might be cognitively. When patients come in, you know, we ask about bladder, we ask about, you know, sleep, we ask about all these other things. And cognition has to be part of it. sometimes it's related to sort of true cognitive issues. And sometimes it's just the patient is so fatigued because they're not sleeping at night because of their pain, or they're up with urinary issues, that sometimes you may not be able to do something about it, but sometimes you can have an influence on them.

And I think from a diagnostic perspective, recognizing that sending some of these patients to get evaluated by our neuropsych colleagues can be really helpful in identifying comorbid depression overlying functional disorders and things like that, where they can kind of help tease those things out. And I think for those reasons, you know, it adds another thing that we may end up adding to the 2052 criteria for McDonald's in diagnosing MS. So I think we'll get there at some point, it's just, I think we need more information.

[CHAPTER 8]

Dr. Shin:
Alright, let's see what our next question is. Alright, the role of biomarkers, Dr. Smoot has a question here.

Dr. Smoot:
What role do you see biomarkers playing in the future, specifically, neurofilament light and GFAP? Are you currently checking these biomarkers in your practice? And if so, how often? And also in what situation?

Dr. Shin:
Jiwon, I'll see if you can tackle this first.

Dr. Oh:
So I believe Bob, last year, we had a battle about biomarkers. Enrique, and I know you were part of that as well. So we talked about a lot of things at the time. But you know, obviously there's many emerging biomarkers that I think may have clinical utility in the coming years. But all of these issues that we talked about with thresholds, and knowing what the clinically actionable threshold, that's pertinent to really every single one of these.

And then another key piece is access. And so I think Dr. Smoot asked the question am I checking NFL and GFAP in clinical practice? And I'm not, mainly because we don't have access outside of research settings. However, we are just about to start on a clinical project with an industry partner where for a few years in our clinic, we will have access to these tools. So I believe when access isn't an issue, we will probably figure out ways to use this.

But so far, based on the accumulating evidence it seems that neurofilament may be a useful tool to monitor for impending relapses or

new MRI lesions. And this may be a way that, with a simple blood test, we may not have to, like, bring patients all the way into the center to sit through sometimes what feels like a claustrophobic MRI. And so I think that's one way that potentially NFL, if access is not an issue, may be used.

And then there's some really intriguing data showing that maybe the combination of NFL and GFAP, or GFAP alone, may be helpful to monitor for progressive disease biology. But obviously we need a lot more data to help us validate all of this.

So bottom line is, right now, I'm not using NFL and GFAP in clinical practice. but there are also some really interesting imaging biomarkers that are emerging, including I'm sure many people have heard about paramagnetic rim lesions, or PRLs. We touched briefly on the central vein sign earlier what we talked about maybe some upcoming changes to the diagnostic criteria. So I do think there is going to be a lot of change in the coming years in terms of newer imaging and fluid biomarkers, as well as maybe digital biomarkers that we use in clinical practice. But we do need to keep in mind that just because something in a number of kind of research study shows benefit, it's a big leap between seeing how useful it is scientifically, versus being able to use these tools in the clinical setting, in individual patients. But again, some of the tools that we talked about, I do think, have a lot of potential, because it's clear that they may be easily accessible for many clinics, and they may be usable in the clinic because it doesn't require fancy technology and all of these things to say, generate an imaging measure that may be of utility, whether it's diagnostically or for disease monitoring. So look forward to having a panel of biomarkers that can help supplement our clinical judgment in the years to come.

And then just one last point, I think MS is such a complicated slowly progressive chronic disease that it's unrealistic to think that we're going to have one magical biomarker that will be the panacea for everything. And so in the end, I think we're going to have panels of biomarkers that we use in specific settings. And so I look forward to that date.

Dr. Shin:
Enrique, do you have any thoughts you wanted to add here?

Dr. Alvarez:
So many thoughts around biomarkers. The issue of thresholds is still a very important one, and what we need to adjust them. It is possible in the states to get things like NFL levels back, they're not fully adjusted for things that we know are very important, like some of the labs will adjust for age, but they may not adjust for like weight. And when we've looked at this, you know, it's a little bit counterintuitive, but small people will have higher levels of NFL just because they can't dilute them out as much. And so trying to, you know – so are we measuring disease activity? Are we measuring the size of the person? Those things become really important. And so I think we'll get there. I think we're learning a lot more about these markers. It's going to take a little bit of time, and I'm not sure they're quite ready for primetime yet.

[CHAPTER 9]

Dr. Shin:
Alright here's a question from Robert Sterling about assessing subacute changes.

Dr. Sterling:
For chronic multiple sclerosis patients who are already on a disease-modifying agent, what is your recommended approach when evaluating subacute neurofunctional worsening without really any clear imaging evidence of disease progression?

Dr. Shin:
Enrique, what do you think?

Dr. Alvarez:
Yeah, so when a patient starts to come in and they're having progression, and maybe taking a step back and kind of looking at that bigger umbrella in term of worsening. I think it's important to kind of take a step back sometimes and just make sure that we are ruling out other things. Whether a patient has spinal stenosis making sure that they don't have PML. And these sound like really obvious things, but we have to look at that the vast majority of PML cases, for example, on B cell depleting therapies, were on patients who came off of medications such as natalizumab, and not patients who develop PML while on CD-20s. And that just highlights a little bit of the fact that these patients probably had PML as their progression that led to the switch over to the B cell-depleting therapy. And so understanding the rates of progression becomes really important in understanding that. So ruling out those possibilities.

And then looking at other factors that can kind of contribute to that worsening. It's very common to see patients that are just not very active and are getting deconditioning and so encouraging exercise for some of these patients, and trying to have them lose weight or other things like this that might contribute to their ability to kind of balance out for those things.

I think this is then we're kind of left with this question of, like, what do we look at? I think NFL, as we talked about, was much more of an

inflammatory biomarker, so maybe not so helpful in progressive disease, but maybe GFAP might be better. Jiwon already talked about PRLs and cells, these paramagnetic rim lesions and slowly expanding lesions.

And so I think there's going to be a lot to look at these things. But I think at the end of the day, the problem that we're having is, I'm not sure that we really understand progression and sort of how to measure it, and clinically, we're kind of like, stuck. And this is the eternal question that we get from our patients, it's like, how am I getting worse if my MRI is stable? Well, it is, but it's not. You know, if we start looking at atrophy or other things like this, we'll recognize that there's changes there happening that are probably likely accounting for some of those changes. It's just we're not very good at measuring it at this point.

Dr. Shin:
So Dr. Smoot has a question about response to progression independent of relapse activity while on high efficacy therapy.

Dr. Smoot:
If you have a patient who is on high efficacy treatment, but unfortunately has experienced progression of their disease, do you consider switching to a different therapy with an alternative mechanism of action? For instance, if you have a patient that's on an anti B cell therapy, would you consider switching them to possibly an S1P agent to help slow down the progression of their disease?

Dr. Shin:
What do you think Jiwon?

Dr. Oh:
So I think a really good question, and highlights kind of probably the greatest unmet clinical need that we have right now. You know, I see this, and I actually now that we use high efficacy therapy in a large proportion of people, I think we see this more and more often. And I have to say I feel like the current therapies that we have, probably do not have a significant effect on the CNS compartmentalized disease processes that we think drive progression or worsening in MS.

So the bottom line is if I do see someone like this, I'm not convinced that any of our existing therapies have a major effect on decreasing CNS compartmentalized disease processes. And so I think I do my best to ensure that they're on a therapy that may have some benefit in progressive disease biology. And so I think the only trials that we have to support that are ORATORIO, which was ocrelizumab in PPMS, and siponimod in SPMS. And so these are therapies that I would consider, depending on what clinical phenotype I think the patient has, although we're recognizing that our clinical phenotyping is flawed.

But the bottom line is I don't really know what to do in these settings, because, again, I'm not really convinced that any of our existing therapies will have a profound effect on decreasing what we see clinically, which is PURA.

Dr. Shin:
Enrique?

Dr. Alvarez:
I totally agree. I mean, I think we're starting to see and recognizing PURA. It wasn't that it wasn't happening before; it was just the inflammation of relapses was so much bigger of an effect. You know, we took care of that, I think, really effectively now, and so now we're kind of left with this much more residual progression. And I still do not know how much of this is sort of, you know, progression related to MS versus aging, versus other things that kind of keep adding to it. In some patients, it's very clear that there's a progression phase to it. But in other patients, it's not uncommon to kind of see progression in 10 years, and they kind of look almost kind of the same as they were before, but you see changes that, you know, are noticeable.

And so I think how to tackle it becomes really difficult, and I summarize it in one word, in wellness. Because they're already on the drug, I kind of try and treat the relapses, and then you kind of try to address all the lifestyle things that might have an effect on it, that are really easy for me to talk about and really hard for the patient to do. But you know, at that point, that's what I got left, so I try and really push those things.

Dr. Shin:
Well, I agree completely. And when someone's on a high efficacy therapy but demonstrating subtle changes, that doesn't mean we can't do anything at all, it just means that we shift the things; making sure they're getting physical therapy, making sure we're focusing on pain management, making sure they're seeing a urologist for bladder symptoms, making sure that we're addressing pain and anxiety and depression while we wait for something like maybe the promise of BTK inhibitors or something like that to give us a better tool.

[CHAPTER 10]

Dr. Shin:

Alright, so we have one more question to tackle and tie it into what we're just talking about, which has to do with risks of using high efficacy therapy.

Dr. Smoot:
Many of our high efficacy therapies have a potential risk of infection, and I have some concerns about utilizing these medications long term, especially in my older patients. Are you considering extending the dosing, particularly for anti B cell therapy? Or possibly switching them to a medication that has maybe moderate efficacy in these situations?

Dr. Shin:
Well, this is a very important question, as we've been using high efficacy therapies earlier and in more patients. I think Dr. Smoot's question is, is there a point at which we should consider de-escalating? In other words, maybe moving to a therapy that we don't perceive to be as effective, but perhaps could be safer? And in this case, actually, I rely on a paper and work from Dr. Alvarez, who with his group, has given us a little bit of information here. Maybe, Enrique, I should turn it over to you to maybe talk a little bit about what you guys have been thinking.

Dr. Alvarez:
Yeah, I mean, I think just because of the use of high efficacy therapies early, the question, then, does become, how do you invert the treatment paradigm a little bit so that you can sort of take advantage of these medications? And so some of the work that we did looking at comparative effectiveness between different medications at our center, we kind of started converting over to be able to understand a little bit about the natural history of MS on treatment. And so we could see, for example, on the panel on the left, that the number of attacks definitely decreases with age, that as we look at sort of higher efficacy therapies in blue versus those in red that we could see a difference. And early on in young patients, there's a big difference between these groups of therapies. But you get to a point where there's not much of a difference. As the number of attacks go down, you may not need those high efficacy therapies to kind of match the intensity. So for us, that confidence interval, the dashed lines, kind of crossed over at like, something like 54 years of age. If you look at the clinical trial data, it's around 44 years of age.

And I think the point is that you do get to a point where these high efficacy therapies aren't high efficacy therapies; they become sort of our standard run-of-the-mill therapies. So if you do sort of a de-escalation approach, it kind of matches the disease process a little bit better.

One of the things that when we balance this out with risks you know, it's age might be the better prognostic factor for disease activity. But for risk, it really becomes disability from some of the other work that we've done. And so as the patient accumulates disability, the risks kind of keep going up and up from infections. So a 70-year-old who's out still running marathons, versus a 50-year-old who is in a wheelchair, that person in a wheelchair has a much higher risk. And we've seen that again with some of our work, but we saw it during the pandemic, where patients in wheelchairs during the pandemic were 25 full times more likely to die than patients who didn't need any aids for ambulation. So for me, that's a little bit of a clue sometimes when I'm seeing somebody in a wheelchair, to be like, hey, maybe we need to consider taking a step down and kind of de-escalating from there. so I think it's important recognition, you know, it's okay to start those high efficacy therapies, but it's good to have an exit strategy at some point as well.

Dr. Shin:
Alright. Well, we covered a lot of ground. I want to thank, actually, the providers who sent us these questions. But I especially want to thank my colleagues, so Drs. Oh and Alvarez. It was a lot of fun. Every time we do this, it's actually very enjoyable. so I hope those of you listening got a lot out of this, and maybe we'll do this again, and I'm sure there'll be new topics to discuss at that time.

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