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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

New Frontiers in Optimizing Patient Outcomes in Multiple Sclerosis: Strategies for Early Intervention to Address Progression Independent of Relapse

Announcer:
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Dr. Krieger:
Good afternoon, everyone. Welcome. Well, I'm glad we've got a full house. Welcome in everyone, grab some lunch, grab a seat, and welcome to our program here. This is called New Frontiers in Optimizing Patient Outcomes in MS: Strategies for Early Intervention to Address Progression Independent of Relapse, a topic near and dear to all of us here at ACTRIMS. So, my name is Stephen Krieger. I am a Professor of Neurology at Mount Sinai in New York. And I'm very happy to introduce our panel and my collaborative discussants today. We're joined by Dr. Gyang, who's an Assistant Professor of Neurology, and the Division Director of Multiple Sclerosis and Neuroimmunology at The Ohio State University in Columbus, and Augusto Miravalle, who's the Chief of the Multiple Sclerosis Center, the Associate Professor of Neurology in the Department of Neurological Sciences, now at Rush in Chicago. So, welcome to both of you, and to everyone, and to those of you watching and streaming online.

Here are our disclosures.

We've organized this program in three cases that illustrate subtleties and points that are important to all three of us and we're going to discuss them as we go. So, here's the first case. This is one of mine. This is a young woman whose backstory is in 2005, while she was in an MBA program, she'd noticed some numbness in her feet when biking or working out, but it would fade away within minutes to hours. She did have some persistent left foot numbness. In 2008, when she was 29, she developed significant fatigue, she needed naps in the middle of the day. She reported her boyfriend thought she had narcolepsy. She was always falling asleep. She saw neurology, no diagnosis was made. In 2009, the next year at age 30, she developed numbness and tingling on her left hemibody, arm and leg. It lasted for weeks and led to a workup. She had MRI, which showed lesions. She had a tap, which was positive for 10 oligoclonal bands. She was diagnosed with MS. And this being 2009, she was started on glatiramer acetate. She took some modafinil for fatigue, but her mood went into disarray. She was crying and just revved up, and so she stopped that and tried to improve her wellbeing and her sleep. So, that's her backstory.

I should say this is an absolutely true case. To be honest, I've changed no details. Probably I should have changed some, but this is an absolutely true story. She came to my practice in 2011, and at her initial exam, it was normal. She had a suggestion of a little numbness in her left foot but really barely. Interval MRIs done were stable for the next 10 years, during which time she remained faithfully on glatiramer acetate, except during her pregnancies. She delivered two children. Was promoted to increasingly senior roles where she works in medical marketing. And she had no relapses.

Here is a representative example of her scan, which I'll scroll through here like a PACS system. She has a pretty good-looking brainstem, good-looking cerebellum. But as we work our way up, you start to see her lesion burden, periventricular, subcortical, in the callosum, again, periventricular, maybe that left frontal one is juxtacortical, we could argue about it, a couple of others. That's it, a pretty mild lesion burden. And that was a 10-year interval where nothing changed.

So, with that in mind, we turn to our panel. This is a person who I've been seeing for a decade, stable MS. We're all here trying to do a great job for people with MS. How do we define success? Dr. Gyang, I don't want to have to call on you guys, but do you want to say a little bit? Is this success? How do you define success in treating someone with relapsing disease?

Dr. Gyang:
Yeah, I mean, overall, it looks like she hasn't had any relapses over the years. Her MRI scans have been relatively stable. Her lesion burden overall looks low. She doesn't - it doesn't look like she has a lot of lesions. So, you know, just listening to the story, I would say she seems to be stable, you know, over the course of 10 years.

Dr. Krieger:
Yeah. So, Dr. Miravalle, is this the promised land of NEDA, and have we achieved it? Can we always achieve this?

Dr. Miravalle:
Yeah, that's a great question, Stephen. And I think we all feel NEDA allowed us to have something measurable. So it was, in a sense, an improvement from the times in which we didn't have sort of those frameworks. However, we always feel that we might be missing a lot of clinical manifestations of subclinical pathology, that perhaps are not included in traditional NEDA. So, I feel that NEDA brought some value, but I think we are also ready to move beyond and try to see if there is anything we can measure, whether it is clinically or otherwise, to identify the progression of disease that perhaps may go beyond relapses and lesions.

Dr. Krieger:
And so, it begs the question, she is on glatiramer acetate, she has been on it since 2009. Do you typically change someone from a widely regarded as lower efficacy disease-modifying therapy, when we kind of feel the goal is being achieved? Dr. Gyang, you said this sounds pretty stable. Dr. Miravalle, you said maybe we should look beyond it. Would you change this patient's treatment at this point?

Dr. Gyang:
I would say it depends, right? Because the patient, there were some things that we've mentioned that, you know, patient was having a little bit of struggle. So, on the surface, it looks like she's stable. But we probably should look at other functional metrics to see if there are other things that could benefit from improvement.

Dr. Krieger:
Sure.

Dr. Gyang:
Yeah.

Dr. Krieger:
Dr. Miravalle?

Dr. Miravalle:
Yeah, I will probably use these as a perfect excuse to discuss with patients where we are in the care of MS care, whether, you know, our tools to measure disease progression perhaps are very insensitive. I also will use excuse to introduce the array of approved disease-modifying therapies and how perhaps they differentiate with each other and have an honest discussion about, you know, how we feel about her care, and perhaps the things that may be missing and have a true shared decision-making process.

Dr. Krieger:
Well, you guys are way ahead of me because all those years I did not change her disease-modifying therapy. She was on injectable glatiramer faithfully. She started complaining again about her fatigue, like it was a decade earlier, starting to interrupt her work, feeling cognitively overwhelmed. But I examined her, and I found her exam unrevealing; normal mental status, bright affect, this is a very positive, motivated person. I didn't see her fatigue. She told me about it, but this was not a person who comes into the room and really looks like they're struggling. So, she's telling you about this fatigue. Are there other questions you would ask her, like ways that you pursue that just in the office, in the room, either of you?

Dr. Miravalle:
Yes, so I see the Modified Fatigue Impact Scale as a way to, in a sense, quantify fatigue in something that is measurable. I also

appreciate the fact that it gives you a total score, but also different subscales, whether it's physical, cognitive, or psychosocial. So, it's not a perfect tool. But in a sense, I have been using that quite often to, in a sense, quantify that and have something to follow over time.

Dr. Gyang:
I also think it's helpful to ask the patient, just from a functional standpoint, on a day-to-day basis, are you having trouble with anything? Right? Are you having trouble with work? Are you having trouble with school, if it's a student? Because sometimes we're not picking up things on exam, but there are other metrics or other things that the patient may be experiencing that may not come up on the exam or may not come up when we just ask them questions in clinic.

Dr. Krieger:
Yeah, you asked about work. My favorite question is, have you had your annual performance review yet this year? And how's it going? Because we all get reviewed, our performance is always being evaluated. And so that, to me, is a good way of opening the door for someone to say, 'Well, yes, I can't quite keep up with what I used to,' or 'My boss says that I'm not quite hitting my metrics,' or 'I'm asking for too many breaks,' or things of that nature. It starts to give you a sense that that person is not achieving at their existing level. So, I say here, how would you further assess her? I think you both mentioned other tests you might do.

And here's what we did. So, this was a couple of years ago now. This is summer 2019. She had been stable for a decade, and we had just started our Neuropsychology Comprehensive Care Program at our MS center led by Jim Sumowski. And so, we had her evaluated. And I'll say this was like a 10-page long thing that I distilled into a couple of high points, so I'll read you the high points. So, she reported forgetting familiar people's names like coworkers, this would sort of happen when she was rushing. It resulted in her feeling embarrassed. She felt some difficulty with cognitive flexibility when trying to focus. She described her mood as good and positive, but she did feel more fatigued. So, we assess her. The baseline level of educational and occupational attainment placed her at a 79th Percentile of premorbid cognitive status, hugely important. Where is somebody starting from when you assess in what ways they have changed or are worsening? So, this is a very high-functioning person. So, the SDMT, our cognitive screener, 28th Percentile, that's not great for somebody who's coming in at a high level. Auditory attention, information processing speed was average. But symbol search test was in the 34th Percentile, decision speed was in the 18th Percentile. And if any of you have worked with medical marketing folks before, these are quick-thinking folks, so decision speed at the 18th Percentile is not normal. Problem solving with the Tower of London was 1st Percentile. So, really not normal. A couple more, word generation, she says she's having trouble finding words and names. Word generation was 1st Percentile, memory was low, upper extremity function was not perfect, gait and balance was okay.

So, I'll pull back and I'll say, really, honestly, this was a very humbling case for me. This is a person I knew really well who had been stable, NEDA, doing great, achieving the goal for a decade. And I missed all that, because I hadn't looked for it. And it really did change the way I've started to think about looking for early signs of the disease.

You know, I kind of pose this question to you guys. Would you call this PIRA, progression independent of relapse activity, even though her EDSS hadn't changed at all?

Dr. Gyang:
I would. I would, because there is something that's different. I mean, the metrics we use right now can only measure what we can have them measure. There are many other ways to assess a patient that captures things that we miss in between, big leaps in an exam or on an MRI scan.

Dr. Krieger:
Agreed.

Dr. Miravalle:
Yeah. Even though you do not have longitudinal change to assess progression, I think by all means, this constitutes clinical evidence that MS is affecting cognition, which is ultimately one of the most important functions of the brain. So, I think certainly, I would take these as an evidence of progression.

Dr. Krieger:
So, I would no longer consider her burden of disease to be all that mild, even though the scan didn't reveal things. And considering she's a high-functioning person, a mother of two, I was concerned about the trajectory for years to come. I imagine both of you are as well here based on what you've already said. Would you continue glatiramer acetate in this patient based on what you know now?

Dr. Miravalle:
Well, again, I will use now we have evidence. We have a neuropsychological testing assessing cognition, and I will certainly emphasize the importance of being proactive about it. I will present options that we have with the limitations that we currently have on all or most of

the approved medications that we have very limited evidence that they may directly affect cognition. But perhaps we'll have a great opportunity to discuss alternative therapies.

Dr. Krieger: 1
Dr. Gyang, how about you?

Dr. Gyang:
Yeah, I mean, I would definitely have a discussion with the patient because we know we didn't have disease-modifying treatments. The way in which they affect progression independent of relapse is different when we look at different disease-modifying treatments. So, definitely have a discussion with her about considering other treatments that may be able to target, you know, the subtle underlying progression that's going on.

Dr. Krieger:
So, you know, I'm going to take you for a minute here through, or maybe 3 minutes through, my approach to this. This case informed how I look at the disease. It kind of informed how I've looked at the EDSS to think about what we're missing. So, here's our usual EDSS scale. But it's important to remember that we only detect what we look for. And this notion of normal is based on a clinical threshold, which is really an illusion. We talk a lot about silent progression in this field, and silent only if we're not listening carefully enough for it. And I think we need to look harder.

So, EDSS is 0; what's below the EDSS of 0? There are ways that we can get beyond that. And this is based on a paper we published a year or so ago called EDSS 0 is Not Normal: What's Below the Clinical Threshold? And what we did at Mount Sinai in our group is we looked at a group of patients with an EDSS of 0, and compared them to age-matched healthy controls, who also have an EDSS of 0, because they don't have a disease. Try to look under the surface using this visual, which is, you know, my life's work, trying to peer below the surface to see the disease below.

Let's think about how we assess cognition in a regular office visit. Do we ask our patients to do this? We do not. I will point out the Krieger here is not me, that's my dad. It's my dad's work. I finally get to put my dad's work on a screen. But we ask patients to remember that, and that, and that, and then we say, yeah, your cognition is pretty good. We don't ask people when we're doing a motor exam, and we're looking for strength, we don't ask them to do this. What we ask them to do is something a little simpler, like, could you please reach out and squeeze my hand? And then if it seems strong, we call it 5 out of 5. Similarly, for fine motor control, we're not asking people to play for coffee up in the office, we ask them to do a really challenging task, like touch my finger. So, I put these here, just to remind us how insensitive our routine clinical measures are. And when we studied this group of people with an EDSS of 0 with more challenging tasks, we found that there was disease burden there. These folks were not quite normal, that the idea that EDSS of 0 is normal, is wrong.

And to the question I posed to our panel at the beginning of our case, does this woman I'm describing have progression independent of relapse activity? Well, we struggle with that, honestly, in our field, because we talk a lot about progressive MS. This is something I wrote with our fellows Drs. Patel and Nichols last year, a little review thought experiment. If we call secondary progressive MS, the insidious development of disability and cognitive dysfunction, basically, always, you know, manifest gradually, wouldn't every patient with RIS or CIS or relapsing remitting MS in whom you find cognitive dysfunction be called secondary progressive? So, I'm not interested in the nomenclature. I don't care what we call it. I care that we look for it, and that we recognize the burden of that disease.

So, what happened with our patient? We were both alarmed, honestly, by her cognitive profile, but it validated a lot of her longstanding concerns. We used that as an opportunity to have a conversation that Dr. Gyang and Dr. Miravalle talked about, start to talk about what we can offer. We changed her disease-modifying strategy, put her on an anti-CD20. This was back in the fall of 2019. And over the last 4 years, she was cognitively more stable than she'd been before. She felt better. Her neuropsych profiles reflected her improvement. She also optimized her fitness regimen, changed a lot of things about her life and her lifestyle. So, I don't know exactly what the cause and effect was, but she's better now than she was 4 years ago.

And I think that has implications for what we do. The best way to treat progression is to prevent people from progressing in the first place. But while we wait for therapies that will get us there, what can we do to boost reserve, fill the tank? Which is what she was doing, exercise, physical, occupational, speech therapy, psychotherapy for mood, optimized diet and body mass index, get her cardiovascular health in shape. These things actually matter. You know, when I talk to general neurologists or others about this, I think they feel that this is soft. I think at this conference and in this room, I think we are committed to a lot of these things and to studying them.

I thank you for part one. I'm going to turn the podium to Dr. Miravalle, who's going to talk about aging and lifespan in multiple sclerosis. Thank you.

Dr. Miravalle:
Very good. Well, thank you, Dr. Krieger, for a wonderful case and presentation. And I'm going to take you to a different challenge that we have these days in the care of multiple sclerosis patients, which has to do with our understanding of how age perhaps impact outcomes.

So, this is a case of a 62-year-old man that was diagnosed with multiple sclerosis at the age of 35. And he had an initial relapsing course. This patient was placed on ocrelizumab in 2015 after he had a transverse myelitis, and he went initially on interferon and then switched to ocrelizumab. His EDSS remained at a 3.5 level which suggested moderate disability level, mostly residual deficits from his last relapse, something that perhaps today we will classify as RAW, or relapse-associated worsening. However, he's been experiencing sustained daytime somnolence. He has regular nocturnal episodes of urinary frequency and urgency that occurred for at least 12 months. He was hospitalized in 2022 due to complications of COVID-19 infection. And when you saw him in clinic, the neurological exam was unchanged.

So, I have a couple of questions for my esteemed panel today. And I have some options for you. So, option A will be continue ocrelizumab as his multiple sclerosis is stable, and advise him to start modafinil for daytime somnolence; continue ocrelizumab and explain that his symptoms are due to smoldering inflammation and current disease-modifying therapies are ineffective in preventing progression; order bloodwork, urinalysis, and bladder ultrasound, and discontinue ocrelizumab and don't start any other DMTs as his MS is going through immune senescence. So, Dr. Gyang, how would you approach this case?

Dr. Gyang:
Well, it seems like he has urinary dysfunction. He's had a few infections. He had COVID not too long ago. He's on an immune suppressive treatment. So, I probably would start with just doing an infection screen in this patient.

Dr. Miravalle:
Excellent. And Dr. Krieger, do you bring the topic of smoldering inflammation in your day-to-day care with your patients?

Dr. Krieger:
They bring it to me more than I bring it to them, which is a testament to medical marketing, actually. But, no, honestly, I try not to because I think that it raises questions that I can't answer. And I agree with you, you know, oftentimes things get ascribed to multiple sclerosis, and people in practice miss the fact that he may be harboring an infection. I recently had a guy that could have been progressing but turned out to have kind of a smoldering urosepsis picture. So, you really want to miss that – don't want to miss that, rather.

Dr. Miravalle:
And just to dive a little bit deeper, Dr. Gyang, so how do you screen for possible infections and complications, perhaps, of our therapies?

Dr. Gyang:
Yeah, so I mean, you can start with a general blood panel, a CBC. In this patient, I would get a UA to see if there's any evidence of an infection. Especially if the patient's on ocrelizumab, respiratory infections are common, so if they have any symptoms of a respiratory infection, maybe a chest x-ray would be helpful. And then just depending on the way the patient presents, you could, you know, tailor your workup based on what the presentation is.

Dr. Miravalle:
Excellent. And Dr. Krieger, if you have a patient with similar characteristics that is currently clinically stable on a disease-modifying therapy in which you suspect repetitive infections or recurrent infections, would you consider changing disease-modifying therapies to a safer option?

Dr. Krieger:
Yeah, I mean, remembering that this gentleman is 62, and if you're worried that he's starting to have repeated and breakthrough infections, if they're on a B cell depleter, this is a circumstance where you might look at their immunoglobulin profile. But even not, if somebody's having recurrent infections on a medicine that increases risk for infections, which is true for so many of our medicines, I think you do have to reevaluate the risk-benefit ratio, and think about de-escalating or giving someone a bit of a drug holiday, depending on the mechanism of action, to see if their immune system can reconstitute what it needs to fight off those infections.

Dr. Miravalle:
Excellent. Well, that's a perfect segue to discuss what we know about aging in multiple sclerosis. And I have to be honest with you that as I get older, I tend to push the definition of older forward. So, that's a moving target in my life at least. But one of the struggles that we have is that most of our information that we got from phase 3 clinical data is based on a population of patients that is not truly what we

will define as aging population. So, most of what we know comes from real-world studies, perhaps by using analogies with what we know is happening with the immune system. But these are some definitions that I find are helpful which chronological age is defined by our birthdate, and there is nothing we can do to change that unless we lie about it. However, biological age is defined as the functional decline and loss of homeostasis that is occurring over time. And this is the area that we can modulate or influence based on our lifestyle choices. And Dr. Krieger already spoke on behalf of the importance of this lifestyle choice, whether it is through exercise, through symptom management, through nutritional strategies that has a profound effect in not only perhaps disease processes, but also in how we age, how our patients are aging.

And then there is another definition that I felt was helpful to include in today's discussion, which is the definition of senescence, which is the state in which cells will lose the ability to replicate; however, they can still function. And in the case of multiple sclerosis, they are known to continue to produce inflammatory or proinflammatory molecules that may have a profound effect in disease processes.

On the left side of your screen, you can also see what are some of the consequences of aging. And some of those we can test, some of those we can just simply see the clinical consequences of it, which has to do with weakened antimicrobial immunity, also increased susceptibility to certain infections, mostly respiratory or urinary tract infections. But we also see reactivation of latent infections, particularly in our patient population mostly is viral infections, like in the case of VZV reactivation or shingles, we also see that in aging population, there is an impaired response to vaccines. And also, we've been seeing over the decades that there is an increased risk of neoplasms, or cancers that perhaps speak to a decreased ability of the immune system to provide immune surveillance.

So, diving a little bit deeper into the mechanisms behind immune senescence, we know that age affects many things in our lives. And I will not go into detail on that. However, we also know that in the immune system, it has a profound effect in pretty much every player, whether you look at innate immune responses, but also adaptive immune responses. One of those consequences is we know that the progenitor cells as we age may have a shift in the way they differentiate into the myeloid versus lymphoid, with an increased proportion of cells differentiated more into the myeloid-producing cells that we know that will lead into platelets and red blood cells and perhaps microphages with a decreased proportion overall on cells differentiated into the lymphoid cell type.

We also know that when you look at the behavior of individual cells, there is a decreased function of the macrophages for example, on phagocytosis, there is a decreased cytokine response, as well as a reduced antimicrobial activity that happens just with aging with or without multiple sclerosis. If you look at what is happening in the adaptive immune cell system compartment, we see that the two main players, B cells and T cells, have also a shift in the way they can respond to certain antigens, certain stimulations. We know that both in the T cells, the T cell receptor and the B cell receptor, has a decreased ability or decreased diversity to be able to identify novel antigens. And we've seen them clinically during the pandemic in which we were all exposed to a novel antigen that we've never seen before or a novel version of an antigen. And we've seen that in elder/older individuals, they struggle to actually mount the proper response with more severe clinical manifestations of it.

We also know that there is a shift between this T cell subtype to reduce a proportion of CD8-positive cells. And one of the functions of CD8-positive cells play in our immune system is immune surveillance for cancer. And perhaps this is linked to an increased incidence of certain neoplasms over time. On the flip side, we also know that there is an increased proinflammatory response and increased proportion of memory cells. If we look at what is happening in the B cell compartment, similarly to the T cells, we also identify a decreased diversity in the B cell receptor that perhaps had to do with a decreased ability to recognize novel antigens. But also, when you look at the antibody responses, there is a decreased affinity to certain epitopes of certain antigens as well as decreased neutralizing effect.

And there is a subtype of cells. So, there's a subtype of memory cells called age-dependent B cells. And those age-dependent B cells, in general, they constitute approximately 1% of the total pool of B cells. We know that as we age, that proportion increases to up to 5%. But we also know that in multiple sclerosis patients and other autoimmune disorders like lupus, there is already a higher proportion of these age-dependent B cells. It's unclear the role that these cells have in the immune pathogenesis of MS, but perhaps because they are a subtype of the memory cells, they may play a role in continuing to perpetrate that chronic inflammation that is in response to perhaps an initial antigenic response, probably linked to Epstein-Barr Virus responses.

So, let's now try to put all of that knowledge into context. And we are shifting the way we look at the clinical pathological correlation in multiple sclerosis to introduce new topics and new terms. We are now looking at perhaps acute inflammatory responses, as well as chronic or smoldering responses. And we know that there are clinical and biomarker manifestations of those mechanisms, perhaps different. Traditionally, we'll look at acute lesions, relapses instead of worsening, and certain biomarkers as perhaps clinical manifestations of acute inflammation. Whereas, we look at things like brain atrophy, slowly enlarging lesions, brain lesions activating microglia as pathological manifestations of smoldering inflammation. Clinically, we usually assign that progression independent of relapse activity to be the clinical manifestations of smoldering inflammation. And certain biomarkers are becoming a little bit more

specific to represent the underpinning processes in smoldering inflammation like GFAP.

So, how will this knowledge go into timing as we age? So, it's been suggested that early on as our immune responses are healthier and younger, we see higher manifestations of acute inflammatory responses. And that's why, traditionally, natural history studies have suggested that the incidence and frequency of relapses of new lesions is maximal early on. And we also know that as we progress, as patients age, the clinical manifestations of progression independent of relapse activity, perhaps become more clinically evident. That doesn't mean that they start later in life, perhaps the process starts earlier, but it's been masked, as Dr. Krieger explained before, perhaps by brain reserve or other mechanisms. And if you put the same principle and framework around however therapies are affecting these responses, we have robust evidence that most, if not all, of these therapies, have been approved under the knowledge that they have a profound effect on markers of acute inflammation, whether it's relapses or acute MRI activity. It's less clear whether that effect is indirectly or directly correlated with markers of progression independent of relapse activity. And that's why we've traditionally been seeing that the clinical efficacy and benefits of these medications is maximal earlier in the course of the disease process.

So, when you approach the topic of aging in multiple sclerosis, how do you practically go about that? Do you ever find yourself that you adjust the dose or the interval in individuals that are older? Dr. Gyang?

Dr. Gyang:
Yeah, I mean, I think it depends on the patient. Because as you said, you know, there's a difference between biological age and chronological age. But I think it's definitely wise to reassess risk and benefit in patients. Because as we know, the efficacy of some of these DMTs is not as strong as patients get older, because that inflammatory activity is not there anymore. And then the risk of infection and malignancy goes up. And so, there's always that reassessment of risk and benefit with each patient. I don't think there's a magic number or magic life event, but with each patient, I think it's a matter of talking with them, you know, at each visit about what are we doing about this DMT? Do we need to de-escalate to a less potent disease-modifying drug? Or do we need to do a holiday from a DMT to see if that inflammatory activity is still there?

Dr. Miravalle:
Excellent. And Dr. Krieger, I have the million-dollar question for you here. When would you consider stopping disease-modifying therapies?

Dr. Krieger:
Yeah, mean, it is challenging. And even the DISCOMS study, which I applaud for being an actual randomized effort to answer this question, only could answer it insofar as risk of resumption of overt inflammatory disease activity in a relatively short period of time. And it was seen in some folks who are over 55. I'll tell you what it doesn't – that that doesn't answer for us, and the bigger picture problem is, are these medicines preventing gradual accumulation of disability in the older age group? And are we increasing their risk for further progression if we stop the medicines? And we really don't know the answer to that, or at least I really don't. The best I can do is to say, I try to keep track of when was the patient's last known disease activity. So, I usually have that in my note. If their last new lesion was in 2016, I might not be rushing to stop their medicine even if they're 65 years old, but if their last new lesion was in 1988, I might be a little bit more willing to do so.

Dr. Miravalle:
Excellent. And again, that speaks to our inability to clinically measure the signs and symptoms of progression that, perhaps, is the big concern that I have when approaching the discussion on stopping disease-modifying therapies is that are we going to miss a chance to perhaps affect chronic progression with the interventions that we are using if we stop therapies? And we don't have the tools perhaps to be able to identify that progression before it reaches a clinical threshold that results in disability.

So, there are now several studies that tried to look into is there any differential effect on the efficacy of disease-modifying therapies based on age? And as I mentioned before, one of the limitations that we have is that most of these studies, phase 3 clinical trials, did not enroll patients older than 55, or perhaps 60 years of age, so we are not truly capturing an older population. However, when you try to make a subgroup analysis into efficacy, it seems like certain interventions may continue to offer clinical benefits, when you look at for example, annualized relapse rate, whether patients are younger or older than 45 years of age. Perhaps some medications don't have that, whether that's a result of the number of patients enrolled that was not powered to truly look into the subgroup analysis, whether that represents a different mechanism, is yet to be determined. And when you look at, for example, the effect on the markers of smoldering or chronic inflammation like PIRA, for example, you see that the responses are all over the place, you can say that a certain mechanism perhaps is linked to a certainty that is going to affect disease progression, whether you're older or younger than a certain age. So, we are limited in terms of at least evidence based from clinical trial data on trying to answer that question.

This was another study that tried to look at a differential effect on a given medication based on age and timing. And what has been

suggested from the study is when you look at things like progression, that age does play a role. And the efficacy of these interventions, whether you look at any of the different mechanisms, appears to be maximal or higher, the younger the patients are.

How about infections? And how about side effects or safety? Well, not surprisingly, this study showed us that there are certain markers or factors that will play a role into an increased likelihood of infections, whether it's age, whether it's progression versus relapsing MS, or whether it's disability levels. And as we can see in this graph, patients that are older, patients that have a high amount of disability measured by EDSS, as well as patients that had a progressive onset of multiple sclerosis, they have a higher chance of having side effects or safety concerns when it comes to infection risk, based on disease-modifying therapies.

So, in summary, this is where we are. And we know that time and aging will play a role in different aspects of the disease. We know that earlier, and we didn't discuss that today, but the reparative mechanisms are more active, allowing for a higher chance of repair early on in life. And we've seen that with pediatric MS patients. We know that our mechanisms to provide immune surveillance are maximal early on in life. We know that also the markers to the inflammation are going to be more prevalent or frequent. And we know that the response to the disease-modifying therapies, at least if we are measuring traditional markers of acute inflammation, are going to be higher. As we age, we see almost the opposite, that the ability of the immune system to provide immune surveillance decreases over time, the risk of infections increases over time, as well as we know that the pathophysiological mechanisms underpinning MS may shift into more of a compartmentalized inflammation, that perhaps our therapies are, some of them, are inefficient in addressing.

So, all of that is to say that, in this case, what we decided to do is what Dr. Gyang recommended. A urinalysis confirmed the presence of infection, and he was started on antibiotic therapy. And ultrasound showed a residual urine and post void volume for over 150. And it's been suggested in different studies that this kind of like it's the cutoff in which we know that higher volumes than 120 increases the risk of subsequent infections over time, unless it's been addressed by other mechanisms.

So, after discussing different options, my patient opted to start oral cladribine. And the rationale for that was understanding that will hopefully continue to offer that high efficacy through a very similar mechanism, but with the added benefit of offering intermittent immune suppression and hoping to decrease the likelihood of infections over time.

So, in summary, we know that age results in increased risk of infections and complications from disease-modifying therapies. We also know that the mechanisms underpinning MS leads to more of a compartmentalized inflammation in the CNS, and we know that that may influence the efficacy and safety of our current disease-modifying therapies. So, all we can do now until we have markers to meaningfully measure these clinical outcomes, we have to be very careful in how we monitor and proactive. I have to be honest, in patients on anti-B cell therapies, I often do UAs, even in the absence of clinical manifestations, just to capture those subclinical urinary tract infections that perhaps patients may be developing over time. So, we have to be proactive and we have to be careful.

So, thank you for your attention. And now I'm going to invite Dr. Gyang to join the podium.

Dr. Gyang:
Alright, so I'm going to take us through the last case, and I'll try to get this done in a timely manner. So, the last case is a 30-year-old woman with relapsing remitting MS. She is coming to you for the first time. She's transferring care from a different provider. She was diagnosed with MS in 2011, but this highlights the MS prodrome. So, she had symptoms about a year before her diagnosis, brain fog, fatigue, mood dysfunction, and then had the first event in 2011 while she was on vacation. In 2013, had another event, was in the emergency room, had an MRI, had a spinal tap, everything was consistent with MS. You know, she was diagnosed with MS and started on glatiramer acetate.

And this is her MRI scan. So, we can see that she has MS typical lesions on the axial sequence. On the sagittal sequence, we can see, you know, periventricular lesions very typical for MS, and she has spinal cord lesions as well.

So, she's not had any more relapses over the past decade and, you know, she's establishing care with you for the first time. However, she reports that over the last 5 years, she's had some difficulty keeping up with her job as a store cashier. She falls about once a month while playing with her kids and her dogs, and she has poorly controlled anxiety and fatigue. And then, you know, your neurologic exam – and this is the first time you're examining this patient because she's, you know, she's new to you. Pertinent findings, reflexes are brisk generally, there's very mild proximal right leg weakness, mild width, but the gait is a little bit wide, and she has moderate ataxia. But then you go back into timed 25-foot walk that had been done serially over the years, and you notice that there's a 35% increase between 2013 and 2023. So, a 35% change. You look at her MRI scans, and there's nothing new in terms of T2 lesions or interval contrast-enhancing lesions over the last decade. But when you just review the scans between 2013 and 2023, you can see that there's a little bit of a volume loss. And so, overall, no relapses, no new lesions, but there's a definite change in this patient.

She tolerates glatiramer acetate very well. She, you know, wishes to remain on this therapy. She feels like she's very stable. Her exam

is stable as well. She's very apprehensive, and I see this a lot in patients where they do not want to do medications that they feel are risky. She doesn't want to consider any of the high-efficacy treatments, but overall acknowledges that her functional status is not as good as it used to be. She's falling often. She's having trouble with work, but at the same time very hesitant about switching disease-modifying treatments.

Alright, so this would be for the panelists, how would you approach the discussion about her disease stability or lack thereof?

Dr. Miravalle:
Yeah, I think I will similarly approach that in a sense of like we do have, in her case, evidence of progression. And her walking speed has declined, as well as some other markers of progressions have increased. So, I will certainly reassure her, and this is one of the areas in which perhaps more of a consultant and saying, hey, I don't expect the patients to have the correct answer, so that's when we have to perhaps a little bit more definite in saying this is a suitable moment.

Dr. Krieger:
Yeah, I mean, if we were concerned about the case that I presented, which has some superficial similarities to this one, but there's some fundamental differences here that you pointed out in terms of physical manifestations of progressing disability, and it points out why just comparing this year to last year, which we so often do on MRI scans or on timed 25-foot walk, is just too short a window of time. And I try to compare the current scan to the oldest scan to look for atrophy, and the current timed 25-foot walk to the oldest timed 25-foot walk to look for real change. And I'd be very concerned about her.

Dr. Gyang:
Yeah, so definitely some concern in findings. I think Dr. Miravalle already addressed if he would consider switching to a more potent DMT. Dr. Krieger, what do you think about that?

Dr. Krieger:
Yeah, I absolutely would. That said, if she is incredibly risk averse and worried, you know, you don't want to put a patient on a medicine that they're going to not be able to sleep at night because they're worried about what's going to happen to them. So, it's about getting them to understand what we understand, and trying to see eye to eye on it.

Dr. Gyang:
Good. Alright. So, I'm just going to talk a little bit about metrics of treatment, like how do we measure how effective a disease-modifying therapy is?

And on this side of the screen, I have the more commonly used metrics, you know, we see a patient in clinic, we're getting exams, we're asking them if they had a relapse. The MRI scan, you know, we're getting MRI scans very frequently on our patients. I know some centers do an annual EDSS or monitor that EDSS regularly, others don't. But these are metrics that most often we're doing in the clinic, you know, we're doing with our patients on a regular basis.

But there are other things that I believe would add a lot of value to assessing how well a patient is doing on a disease-modifying treatment. And something very easy is the timed 25-foot walk. You know, you get that done, you know, within the clinic, and you monitor that over time, and that tells you a lot of information. A patient's exam can remain the same, but yet there may be a difference in that metric. Same with the 9-hole peg test, you know, an increase of more than 20% is clinically significant between the two of them. And then I just put a few other tools that we should consider getting in patients, you know, over time. Neuropsychological assessments and symbol-digit modality tests, an OCT to measure, you know, your retinal nerve fiber layers. I'll talk a little bit about some advanced imaging techniques. Patient-reported outcomes, which you know, we can get in our patients. And then novel biomarkers, some places are monitoring neurofilament light chains. You know, we don't do that in our center, but there are places where you could get these done and monitored over time. Clinical significance is still being researched, so we are very careful about how we interpret these numbers.

So, how much does it really matter? You know, brain MRI is stable, no relapses, patient feels like she's stable. You know, do you really want to rock the boat? Do you really want to broke what – do you want to change what's not broken? So, I just want to talk about this paper that looked at association of early progression, independent of relapse with long-term stability in patients with relapsing MS. And the findings from this study are very interesting, like 1/4 of all patients presenting with first demyelinating disease will have a first PIRA event within the 12 years from the symptom onset. So, this is a lot more common, you know, than we know and something that we should always be aware of, and always be vigilant in looking at patients.

And then, you know, the last point that's highlighted, progression independent of relapse is associated with an even worse prognosis independent of inflammatory burden at the time of the first demyelinating event. So, regardless of how stable the patient is in terms of

relapses or new lesions, they can still have this early progression independent of relapses, and that is associated with a worse prognosis over time.

And another point, this is another paper that looked at, you know, disease-modifying treatments and progression independent of relapse. You know, this showed that a longer exposure to disease-modifying therapy was associated with a lower risk of PIRA. So, patients that were on disease-modifying therapy for longer had, you know, lower risk of progression independent of relapse. And then when we look at the pooled data from all the ocrelizumab studies, we see that when we compare ocrelizumab to interferon beta, there is a superiority in ocrelizumab in reducing PIRA compared to interferon beta. So, that tells us the disease-modifying therapies will influence this progression differently, some are more apt to do it than others.

So, early intervention is critical. You know, you want to think of highly effective disease-modifying therapies early in patients that start exhibiting signs of progression independent of relapse, think about escalation, think about that discussion about risk-benefits of our DMTs.

And just one slide about the advanced imaging techniques, they're not primetime right now, but progression independent of relapse has been associated with atrophy, being one, and also the paramagnetic rim lesions. And so, maybe this could become a metric that we could follow over time in patients that, you know, are experiencing progression independent of relapse.

So, back to our case. You know, we talked with the patient, we had further discussions, and she's JC negative, and we decided to switch to natalizumab, which offers her the benefit of not being systemically immune suppressed. So, she's not prone to a lot of infections, but yet on a very effective disease-modifying treatment. And then we get further testing or further metrics to monitor over time. And then other quality of life measures, psychiatry for her anxiety and mood issues.

So, the main take-home points, and I'll try to do this quickly because we're out of time. Insidious progression that happens in the absence of relapses, happens in a significant proportion of our patients with relapsing MS. And this is associated with unfavorable outcomes. And so, think about all the ways that you can measure and capture this because you don't want to wait until your exam has changed, because a lot of things can happen between that change in your exam. And think about high-efficacy DMTs in patients that may have progression independent of relapse.

Dr. Krieger:
Thank you. Alright, everyone, so we've had our key takeaways, we've done our questions, our time is up, but don't forget to complete the evaluation of the program. You're going to get an email with a link to it sometime this week. And you can also go to the website set up for this at globalneurologyacademy.org which is listed in tiny font on all of these squishy green brains that are for you to take. Thank you, guys, very much for joining us, and thank you to our panel.

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