Understanding Progression in MS

Presented by:

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Marie LeGrand:
Hello and welcome to MSAA's live webinar: MS Awareness Month - Understanding Progression in MS. I would like to take this opportunity to thank you for joining us. I am Marie LeGrand, Senior Director of Mission Delivery and Health Equity for MSAA and your host for the program this evening. We are extremely grateful to have Dr. Carrie Hersh with us, who will be presenting on this topic. Dr. Hersh will provide us with a deeper understanding of the markers of progression and effects of progression for people living with M.S., as well as discuss the importance of early treatment.

This program is for educational and informational purposes only and does not constitute as formal recommendations. Please do speak with your doctor or health care provider if you have any questions or concerns.

As you may know, MSAA is a national nonprofit organization dedicated to improving lives today for the entire MS community. Now, some of our free services include a national helpline, equipment and cooling products, we also have MRI funding, we have an online community, webinars and many more free programs available to people living with MS nationwide. To speak with one of our specialists, so you can reach our helpline Monday to Friday from 8:30 AM to 8 PM Eastern. And to learn more about MSAA's programs and services, please do visit us at mymsaa.org, or you can also give us a call.

Now, throughout tonight's program, you will have the opportunity to ask questions by typing them into the chat box. And we encourage you to submit questions throughout the program, and we'll do our very best to answer your questions during the Q&A portion of tonight's webinar. At the end of the program, we ask that you please complete a brief survey. Your feedback is extremely important and will help us in developing future programing and content. A link to the survey will also be included in the chat box.

Without further ado, I would like to introduce our speaker for this evening, Dr. Carrie Hersh. Dr. Hersh is a Neurologist and Assistant Professor of Neurology at the Cleveland Clinic, Lou Ruvo Center for Brain Health in Las Vegas. She also serves as chairperson for MSAA's Health Care Advisory Council. I will now turn it over to Dr. Hersh. Welcome, Dr. Hersh.

Dr. Carrie Hersh:

Thank you so much. It is a privilege and an honor to be speaking to you all today. And I'm going to go ahead and I'm going to share my screen with everybody, and so that way we can get going with what I hope will be a very educational opportunity and hopefully some stimulating communications and conversations at the end of the program.

So tonight's program is on Understanding and Treating Progressive Multiple Sclerosis, which is a very hot topic in the MS scientific community. And I hope tonight's program will be able to share some important information on being able to recognize progressive MS, how to prevent progressive MS and how to treat progressive MS.

So these are my disclosures, which should have no impact on tonight's program. So the overall objectives for tonight's lecture is to understand some basic information about MS, including the epidemiology, pathophysiology, what we call MS phenotypes, which are the clinical presentations of MS, and the natural history of MS, which will nicely segue way into how we diagnose progressive MS, and certain markers of progressive MS, such as clinical findings, imaging markers and biomarkers. We're going to discuss treatments for progressive MS and review the importance of symptomatic therapies, neurorehabilitation and health and wellness. And lastly, we're going to address personalized treatment decision making in real world practice to overall improve long term outcomes.

So let's start with what I call the basics. So MS is an autoimmune, demyelinating, inflammatory and neurodegenerative disorder of the central nervous system, which is made up of the brain and spinal cord. It is the leading cause of non-traumatic disability in young adults, and it significantly impacts general health, physical and cognitive functioning, and overall quality of life

So multiple sclerosis primarily affects women to men in about a 3:1 ratio. And the onset of MS is quite heterogeneous, but most patients are coming in somewhere between 20 to 50 years old with symptom onset. But there is quite a high variability of age onset anywhere from two years old, that's the youngest reported case of MS, all the way up into their seventies. And the projected estimate of the incidence of MS in the United States is now about a million people, with about 2.8 million people being affected worldwide. And folks of caucasian descent tend to be affected more than other racial and ethnic minority groups. But folks of black, LatinX and Asian Pacific Islander populations tend to have overall worse disease outcomes. So it's really important for us to be able to recognize disease early in these populations so that way we can start treatment earlier.

So when it comes to MS, there is a combination of non modifiable and modifiable risk factors that can increase someone's risk of developing MS if they have a genetic predisposition. So the folks that are not modifiable, meaning that we can't change, are certain genes, sex and viruses. And recently there was a very compelling scientific article that was published in Science Journal, which showed that the Epstein-Barr virus actually has a pretty significant impact in determining the onset of MS in people who are genetically predisposed. Now, this isn't new information, we've actually had an understanding of this based on prior epidemiological reports and studies, but this was a very nicely executed study that showed some pretty compelling data that now we're factoring into some of our education when we're talking to patients and maybe some additional either vaccination talks or treatment talks in the near future.

And then modifiable risk factors, these are risk factors that one can change, that someone can take control over to actually improve their overall prognosis when it comes to MS. Such modifiable lifestyle risk factors include vitamin D deficiency, tobacco smoking, being overweight, certain vascular comorbidities such as high blood pressure, type 2 diabetes, high cholesterol

and physical inactivity. And we do have an understanding in terms of the global distribution of MS, that in those locations that are further away from the equator, specifically in North America, certain locations in Europe and Asia, and then Australia, New Zealand, as we get further away in the Southern Hemisphere from the equator, that these folks tend to have a more increased prevalence or risk of developing MS. And we seem to think that that is related to the vitamin D hypothesis. So folks who have less exposure to vitamin D may have an increased risk of developing MS if they have the appropriate genetic predisposition.

So what happens in MS? What propagates this from happening? So in folks who again, have that genetic predisposition, there is a trigger that gets turned on and it can be either the modifiable risk factors, the non modifiable risk factors, or a combination of the two that kind of flips-on an on switch. So someone goes from being predisposed to actually having the condition. And what happens is that there is this autoreactivity of certain players of the immune system, specifically our T lymphocytes and our B lymphocytes that then become activated in the periphery or the bloodstream. And then through a leaky blood brain barrier, these lymphocytes are actually able to traverse through and become activated again and start this very complicated series of cascades of inflammation that can then start affecting the nerves and neurons that are in the central nervous system. And if we start getting into this piece by piece, I'll kind of lay out to you where this pathology leads to and why folks with MS tend to get the symptoms that they do, and then eventually a disability progression.

So let's start with inflammation. So this is what we call a characteristic lesion on a brain MRI for MS. And if we look at this at the microscopic level, and this is what we call a hematoxylin eosin stain, we can see that around this little venule is what we call this inflammatory cell cuff. This is a group of activated B and T lymphocytes that were able to get through from the blood stream, through this venule, and start causing an area of inflammation that, on a macroscopic level, manifests at this inflammatory lesion right here.

And then when that happens, it leads to what we call demyelination. So that means that you have this protective sheath or layer that surrounds this axon, kind of like a wire that allows neurons in the brain and spinal cord to communicate with each other. And in a healthy neuronal system, you have this beautiful propagation of electrical activity that goes from one neuron to another neuron to communicate information. But when there is that inflammation going on, so that area where there are more B cells and T cells that are activated and they're starting to create that cascade of inflammatory events, It starts sloughing off pieces of this myelin. So that way the electrical signaling is no longer as fluid or as fast as it was before. And the electrical signaling starts becoming very choppy and messy.

But where we really have to start paying attention is... well, sure, maybe there's some repair, and when people have early MS and that myelin sheath may be able to repair itself, but what happens when there is this chronic area of inflammation and demyelination that can't repair itself? Well, then that leads to what we call axon loss, and another term for that is neurodegeneration, where you actually have these axons that then become completely transected, meaning that they get cut off. And this is actually an example of what this looks like. So in a demyelinated axon, you have these areas that are kind of not working very well, but they're still intact, the wire is still intact. Here, the wire got chopped off. And that's because of this chronic demyelination that's scarred down and just created this chronic area of inflammation where it just got cut off completely. And there are a number of reasons why that can occur. And I'll be able to go into this in a little bit more detail in a later slide. But we feel that some of this is related to a mismatch of energy demand, where your body needs more energy because there is injury to what would otherwise be a normal neuronal system. And because it's injured, your

body needs more energy in order to create a signaling. And when the energy demands are not really being met because the body just can't keep up with it, that can lead to neurodegeneration. So, we have to pay particular close attention, especially when we're talking about progressive disease, because this is an important component of that disease progression.

So as that neurodegeneration occurs, there can be what we call brain atrophy, and this is otherwise known as brain shrinkage. And we can actually see this not only on gross specimens, so this is actually a gross specimen of a brain, but we can see this on MRIs, and that's why it's important to monitor not only disease activity but progression with MRIs, because we can see it, we can see the pictures quite clearly. So this is a person who has MS when it was initially diagnosed, and then over the years you can see that they had this brain shrinkage. And we can see this by seeing very deep cuts into the brain tissue. And then we can also see a bienlargement of what we call the ventricles, which are fluid filled spaces. And these get larger when there's not a lot of brain tissue to compensate for it. So this is what we're looking at when we're trying to see whether or not there is brain shrinkage or brain atrophy going on. And unfortunately, this is irreversible. So the key is to try to prevent this from happening from the very beginning.

So this is a schematic diagram of what the natural history of MS looks like. And the vast majority of patients, and I would say about 85% or so develop this relapsing-remitting disease phase in the very beginning, where folks have a period of newer worsening symptoms and then they either resolve completely or they only partially resolve where a person is left over with what we call a little bit of baggage. They have a little bit more numbness, they have a little bit more right sided weakness because they didn't recover all the way. And overall, when that happens, when this is not treated, there can be this increase of disease burden, meaning that the person is slowly accumulating disability because of lack of recovery from each of their relapses. But, for the purposes of this talk, we're going to focus in on progressive MS.

The secondary progressive MS occurs when a person has already had relapsing-remitting, meaning that they have the periods of worsening and then the periods of recovery, but then they reach this critical threshold where they're no longer able to compensate for that inflammatory disease. And when that happens, they start slowly getting worse. So they start to slowly accumulate disability irrespective of whether or not they're still having relapses, and I would say about 60% of patients may go on to have secondary progressive MS if their relapsing-remitting disease is not appropriately treated.

And then we have primary progressive MS. So this is what we call progressive MS from the very beginning, meaning that they never had these peaks and troughs, but they only had this, what we call, insidious slow decline from the very beginning. And about 10% of individuals, when they are first diagnosed, are diagnosed with primary progressive MS.

So this is an example of a series of MRIs that are taken from a patient who was initially diagnosed with relapsing remitting MS and had quite the bit of disease activity. So we can see this by seeing all of these white spots. These are all of the MS lesion burden, it's called T2 lesion burden, because we look at it on a T2 scan, and this is a marker of how much inflammatory disease there is on the brain in this particular individual. This would be a moderate amount of what we call inflammatory lesion burden.

This is what we call a post-gadolinium scan, meaning that every lesion that is showing up bright is an active lesion, meaning that these lesions are newly inflamed and causing activity. So this individual was treated and when they were treated, you could see that the amount of MS lesion

burden kind of stabilized here and there was no more activity. But then the person stopped treatment and they developed more lesions and large lesions. And not only that, but if we look at this graph down here showing what we call the percent brain parenchymal fraction, we can see that as the person came off of treatment, their overall brain volume started decreasing and it actually significantly increased over the years that that person was off of treatment. So this is really important to show because it's not just the number of new lesions, but what about the brain matter itself? The brain volume, because that is your brain reserve, that's your neurological reserve or cognitive reserve. And when you start losing that brain tissue, it's irreversible. It's not going to come back.

So this is a a summary of an oldie but a goodie of, what I call, a very important paper that came out in the late 1980s that showed that untreated persons with MS are at risk of disability accumulation. And this is going to nicely segue into, well, how are we going to prevent MS and how are we going to treat MS? So basically, this was what we call a life history epidemiological study that looked at nearly 1,100 patients with MS. And what they were able to show was that for patients who remained untreated, the mean time for them to reach a level of disability where they were using a cane was only 15 years, and that 6 to 10 years from their symptom onset, 30 to 40% of those with an initial relapsing-remitting disease course transitioned into progressive MS.

So this is a teaching opportunity, a teaching opportunity to show that treating early is a very important way to prevent secondary progressive MS. And in the MS space, early diagnosis leads to early treatment. And I have this schematic diagram, kind of like a timeline, of disease modifying therapy approvals in the United States, just to give you an overall view of how many disease modifying therapies have exploded, especially over the past five to seven years of the past. And what we're able to see is that in the beginning, we had a lot of these self injectable therapies. And then we started moving on to some highly effective infusion therapies. And look now at all of the oral disease modifying therapies that we have available. So this is basically an opportunity to show that the MS treatment landscape is rapidly evolving with a number of differences in terms of how well they work and how they're administered and safety. And it's kind of like what I call Baskin-Robbins - there are so many different treatments that are available. And of course, choosing a disease modifying therapy in an individualized manner with your healthcare provider is important. But the overall teaching point here is to treat early.

So let's get into a little bit about progressive MS, once someone is looking like they are transitioning into progressive MS. So I'm going to start with a case, and I do this with my medical students and with my residents and fellows and even when I'm teaching other general neurologists and advanced practice providers. But I feel that this nicely sets the stage. So I'm going to do that here too. And you can give us feedback on whether or not this style is helpful.

So we have Mr. Jones. Mr. Jones is a 56 year old Caucasian gentleman with a 25 year history of MS who presents to the clinic. He has been on multiple disease modifying therapies in the past, including two self-injectable medicines and two oral disease modifying therapies. He's been off the disease modifying therapy for about three years because of the previous side effects on his other medications, and "they just stopped helping".

So he previously averaged about one relapse, every one to two years. But over the past five years, his walking has slowly become more labored because of weakness in his legs, and he had to stop working and go on Social Security Disability last year because of gradually worsening cognitive impairment and fatigue. He now walks with a cane and continues to struggle with right foot drag, and his last relapse was four years ago.

So he denies depression. He has an excellent support system through family and friends. He gets about 8 hours of good quality sleep every night, wakes up feeling refreshed in the morning. But still, he continues to feel very tired during the day. And a recent brain MRI showed that he had a lot of MS lesion burden, but there were no new MS lesions compared to an MRI that he had two years ago.

He has one non-enhancing lesion in his cervical spinal cord and he has one non-enhancing lesion in the thoracic spinal cord, which is also stable compared to two years ago. And his current Expanded Disability Status Scale score is 6.0, meaning that he walks with a cane, and I will talk to a little bit about what the EDSS is and how we measure it.

So the reason why I brought this case up is to show you a quintessential patient coming in who is clearly transitioning from a relapsing-remitting MS phenotype to a secondary progressive MS phenotype. And basically, this is a little drawing showing what that looks like. So you have someone who is clearly having peaks and troughs and peaks and troughs and maybe slowly developing some disability accumulation along the way. But then after a while, the relapses started becoming more spread out, and then eventually they stopped occurring altogether. And during this very important phase, this transition from relapsing-remitting to secondary progressive, there tends to be less brain capacity or brain reserve, less cognitive reserve, meaning that there are fewer compensatory mechanisms that your body is able to instill to try to make up for the fact that there is this ongoing disease in the brain and the spinal cord.

And when that happens, there tends to be more brain atrophy and more disability progression because of that critical threshold being present where the individual is no longer able to repair and heal on their own. So there tends to be this more slow, insidious progression of this disability accumulation over time. And then unfortunately, as the person is transitioning into this progressive MS stage, there tend to be fewer treatment options available.

So this is the traditional view of what relapsing versus progressive MS looks like. So here on this side, we have what we call relapses. Well, what does that manifest as on an MRI level or a microscope level? So that basically means that there are new T cells, new B cells and other players of the immune system that are actively getting into the brain and spinal cord and causing that new inflammation, which we kind of already went over. And that manifests as new lesions on the brain and the spinal cord, whether or not they're enhanced and with contrast. But disease progression, on the other hand, at some point may occur independent from that inflammation where new MRI lesions eventually are not common and active lesions are only occasionally encountered, and that leads to what we call that progressive neurodegeneration and progressive loss of brain and spinal cord volume.

So how do we measure this clinically, right, where we're talking a lot about pathophysiology, what we can see under a microscope, what we see on an MRI, but how do we diagnosis this clinically in a clinic? So there is something called the Expanded Disability Status Scale, or EDSS for short, and this is a numerical scale ranging from zero, meaning the person has normal neurological function, all the way to ten, which is death. And then there is a series of levels of disability in between that is numbered from one to nine. And this is kind of like the quintessential measure of disability in MS and it is the most commonly used clinical outcome measure in trials that quantifies physical disability. However, there are multiple caveats when we are using and interpreting the EDSS.

So one, it does not comprehensively reflect disability status. So meaning that once you get to a certain point, about 6.0 or so, when the person starts using a cane or a walker, some sort of assistive device to get around, it starts becoming harder and harder for that person to increase in their EDSS. Meaning that it's not truly reflecting other aspects of the functional systems that are equally, if not more, important in measuring progression, such as upper extremity function in your hands, how well you can use your hands, and cognitive function. The EDSS is not very good at picking the nuances up with these particular functional systems, and it also shows very little sensitivity to change, especially, again as I mentioned, when someone starts walking with the device and it's difficult to administer in routine care because it's pretty timely.

Okay, so because of those limitations, we in the clinical space have adopted other ways to measure disability. So some of these are measures of the, what we call, functional composite system, which makes up different measurements of different aspects of disability, including walking. We have to include walking here and we do that through what we call the timed 25-foot walk. So basically how long does it take for a person to walk in seconds 25 feet, either independently or with an assistive device.

And then we also want to measure other things. Manual dexterity is one of them that is measured through a nine hole peg test, where someone is tasked with having to put little pegs into little holes one by one, and then take them out, one by one, and time how long it takes for them to do that.

We also want to make sure that we're measuring cognitive function. So that includes what we call the PASAT or the Symbol Digit Modalities Test. So each of these are administered a little bit differently. So the Paced Auditorial Serial Addition Test is an auditory test where an individual is tasked with adding up a series of numbers that are presented, the last two, and then you have to keep at it. So the last two numbers, you have to add them up. And then, the next two numbers, you have to add them up. And it can be quite difficult actually. So there is another test that is available, called the Symbol Digit Modalities Test, which is a visual test where the person is tasked with matching a number to a geometric shape based off of a legend that is provided and there are paper forms and there are digital forms that are available. And then we also want to take a look at someone's vision, low contrast letter acuity. So the person is tasked with having to read a series of slowly transitioning numbers from a dark print to a very, very light print.

So there is another kind of tool that we can use in the clinic called the Multiple Sclerosis Performance Test. And this is actually available to about ten different centers that are participating in what we call the MS PATHS program, the MS Partners Advancing Technology and Health Solutions program, which is essentially a demonstration project that is sponsored by Biogen, and what it is, it's an iPad based software program where an individual comes in on the day of their visit and self performs all of these different tests, all of the components of the MSFC that I showed you on the previous page. And we're able to digitally measure all of these assessments every single time the person comes in. So not only are we standardizing the way that we are measuring clinical activity and clinical progression, but we're using it at the point of care so we can actually talk about any changes with our patients and make any treatment decisions right then and there. So it's pretty cool.

But then there are other markers of disease progression as well, in addition to the clinical measures that we had talked about. So on an MRI, we kind of talked about this a little bit already, we're looking at how much, what we call, T2 lesion burden there is, how many MS lesions are there on the brain and spinal cord MRI, and then looking at atrophy of both the brain

and the spinal cord. The spinal cord can atrophy as well. That can lead to significant disability accumulation and can be a risk factor for early disease progression as well. And then also looking at not only the white matter but the gray matter. So there are very important structures in the brain, specifically the thalamus, which is otherwise known as our central processing unit. And if they're getting smaller, then there are higher chances that the person may progress earlier over time.

And then other areas that we can use for measuring progression, one is called the Optical Coherence Tomography, or OCT for short, which is a very simple test. It's kind of like an eye ultrasound that takes about 10 minutes using an OCT machine, where we are measuring the back layer, called the retinal nerve fiber layer, the ganglion cell/inner plexiform layer, which is shown here on this map. And if we're seeing that the layers are getting thinner and thinner and thinner over time, there is pretty ample research showing that that actually might be a risk of disease progression. So we can use that as a marker for progression as well, especially if an MRI may not be available at that time or may not be financially feasible.

And then there's something called neurofilament light chain. So neuralfilament light chains are essentially these structural proteins that make up the backbone of neurons. And when there is injury, there is a release of this NFL into the cerebral spinal fluid and blood. The problem with this, however, is that it's not just restricted to MS because there are a lot of things that can cause injury to the brain and spinal cords. There can be traumatic brain injury. There are other neurodegenerative conditions like Alzheimer's disease and Parkinson's disease. So we have to be a little bit careful of how we use it, especially when we're measuring markers of progression. But what we have been able to show is that we can actually measure them in a blood sample. We don't actually have to do lumbar punctures, and that, it's a nice marker of MS inflammation predictors of relapses and then measuring how someone is doing on a disease modifying therapy. So currently it's being investigated as an outcome measure in newer progressive MS trials. And we still require a lot more information on how we can use this effectively when we are talking about progressive disease.

So this is just another radiographic demonstration of what brain atrophy looks like over time. So we have someone's brain MRI at baseline. And then as the years go on, we can see that not only are there more MS lesions that are being developed, but there's this more confluency, meaning groupings, together, growings together, of these MS lesions, and then eventually leading to the beginnings of some brain tissue loss as well.

But what about your voice? So, the person with MS's voice really matters here. And we collect this specifically through patient reported outcomes. And these can be through a variety of different questionnaires that can be administered at the time of a person's visit. And we are actually doing it at the Cleveland Clinic as part of that MS PATHS program, as I had mentioned before. But what is really important here is that we want to be able to obtain perspective from the person with MS on a variety of different things: everyday function, their neurologic disability or their concept of neurological disability - how do they feel that things are changing? We want to know about their symptoms, any psychosocial distress, satisfaction with treatments and quality of life. This is really important when it comes to the day to day care.

So we talked about a whole lot of different ways that we can diagnose progressive MS or how we use different markers of disease progression. But how do we put all of this together? What is the best way to measure progression? Well, it's not always easy and very straightforward. So, there are lots of challenges and it's summarized on this graph here, but basically what it's trying to say is that there really is no best approach right now when it comes to the clinical every day

demonstration of progressive MS. So do we use the EDSS? Well, we talked about some of the intrinsic challenges there are. Do we do the other screening tools that we had talked about? Well, maybe in some clinical practices it's not really feasible to do all of them. Well, how do we define progression? Is it over one year? Is it over two years? Or is it over three years? You know, there are a lot of different limitations and questions that we have in terms of how we are defining progressive MS.

But this is kind of a way that we are starting to implement some of our knowledge. So there's the old way and the new way, and specifically in the new way, what we're really trying to focus in on is whether or not the person is still active, meaning are they still having relapses, still having new MRI lesions, are they progressing, meaning are they slowly worsening or are they not active but are progressing? And that's the tricky part.

So what does that mean? So there is an emerging concept called PIRA or Progression Independent of Relapsing Activity. And this was first introduced in 2018. And basically what it means is that it's not really a person who is accumulating disability because they just didn't recover from a prior relapse. It's the individual who is progressing because irrespective of the fact that they're not having relapses and they're not having new MRI lesions, and they're not having inflammatory disease activity, they're just slowly worsening. And there are a lot of theories of why that might be happening. Some of it might be related to the fact that it's related to this, what we call, chronic smoldering inflammation that is going on specifically in the brain without new immunological immune cell types coming in and creating new activity, it's just happening kind of slowly and it's smoldering in the central nervous system. And that can lead to what we call slowly expanding lesions. It could be related to that axonal degeneration, which we had talked about, that transection because of that chronic demyelination, or because of mitochondrial injury and chronic oxidative injury, which is related to that mismatch of energy demand and energy availability. And then as folks get older, as folks get older their MS gets older and they are more at risk of neurodegeneration over time. So there are a lot of theories as to why that might be happening.

So let's focus a little bit on treatment of progressive MS. So there are a variety of things that can be considered. One is whether or not a person is still amenable to disease modifying therapy, and then there are non disease modifying therapy options available. So one includes neurorehabilitation. There are symptomatic therapies (medicines to help with symptoms), health and wellness. And then we're going to talk a little bit about BTK inhibitors and some neuroprotective and remyelinating agents that are currently being studied. And then there is the concept of autologous hematopoietic stem cell therapy. We're not going to get into detail today, because this is a whole other topic, but there are current studies that are actively available that are essentially evaluating when is it best to use stem cell therapy in MS? And should we be using it in relapsing disease and progressive disease? And when is it appropriate in the disease modifying therapy schema?

So let's talk a little bit about a treatment. So we have ocrelizumab. That is the only disease modifying therapy approved to date for primary progressive MS. And this is based off of the clinical trial ORATORIO, that evaluated only patients with primary progressive MS and it showed that overall there was about a 30% reduction in what we call clinically definite progression, meaning that they continue to have disease progression over a period of time that was confirmed by their participation in the EDSS. And we could also see that there was also a reduction in other measures of progression, such as a timed 25-foot walk. But we have to be very careful about the interpretation of the findings. Younger folks, less than 55 and maybe who are still having inflammatory activity, were included in this study. So we have to kind of, you

know, take this with a grain of salt here. They were younger, maybe a little bit more inflammatory.

So what about secondary progressive MS with activity? So it's very similar to how we treat relapsing-remitting MS. The goal, overall, is to decrease inflammatory activity and delay disease progression, and the most available DMTs that are approved are for, what we call, relapsing forms of MS, and that includes secondary progressive MS with relapses and MRI activity.

But what about the folks who are not relapsing and they have stable MRIs, they have secondary progressive MS without activity, what do we do about those guys? Well, that's where things get a little bit tricky. So there was a clinical trial called the EXPAND Clinical Trial that looked at a population of patients with secondary progressive MS, and we considered them to be a typical population of secondary progressive MS, most of them are relapse free in the two years before they entered the study, at baseline only a small portion of them had active enhancing lesions on a brain MRI, and more than half of them needed walking assistance. But what they were able to show was that there was a reduction in their overall risk of developing disability over time. So this was considered a positive trial.

There is another study in a Phase II clinical trial looking at a small molecule called ibudilast, which is currently still being studied in clinical trials, in larger clinical trials. And this particular study looked at progressive MS patients, both primary and secondary, who had an EDSS that did show that they had disability at baseline and they ended up having to walk with a walker, a bilateral assistive device. And this is what we call a dose ranging study. So they were looking at different doses of the medication and it was placebo controlled. So in particular, what this trial showed was that it overall decreased the rate of whole brain atrophy, meaning that the decrease in brain atrophy and brain shrinkage actually was reduced compared to patients who were treated with placebo. So again, this was considered a positive result.

So I had mentioned to you that we are now looking at what we call BTK inhibitors. So this is a class of medicines that has a very unique mechanism of action and is actually quite popularized in the MS scientific community. So BTK, Bruton's tyrosine kinase, is a series of enzymes that are expressed in a number of different immune cells. And that particular enzyme is required for signaling across these different molecules, specifically B cells, which are very important MS pathology. And by bringing in an inhibitor, we essentially allow B cell modulation without depletion, meaning that we're changing the ways that the B cells that are activated from signaling to each other and creating MS disease pathology. But what makes it really unique is that it actually plays a part in microglia, which are very important immune cells that play a part in neurodegeneration and chronic smoldering lesions, so that very tight inflammation that is going on just in the central nervous system. And these BTK inhibitors can impact those microglia as well. This is a really exciting new mechanism in neurologic pathway.

So there were a series of Phase II studies looking at different kinds of BTK inhibitors. Evobrutinib is one of them. And this was a dose ranging study that showed that, overall, it reduced the number of active MRI lesions. And again, this was in a Phase II study. But we were seeing that overall there wasn't a really significant impact on annualized relapse rates compared to placebo. So it does require a little bit more information here. And then in terms of safety, overall, there were no significant safety concerns. There was some increase in alt which is a liver enzyme, but we were able to see that the liver enzyme elevations were resolved once the medication was taken away. So we'll have to make sure that we're studying this a little bit more closely in bigger trials.

Tolebrutinib is another kind of BTK inhibitor that was looked at in a phase two clinical trial. Again, a dose ranging study, meaning you were looking at different doses of the medication. And we were able to see in a short study that at 12 weeks it reduced the number of MRI enhancing lesions by about 85%. So this is considered to be pretty significant, at least in being able to decrease the amount of inflammation going on when the person first starts the medication. So there were no safety concerns that were found, and maybe there was some nausea and diarrhea.

But what we really need here are our Phase 3 clinical trials. So these are our bigger studies that are looking at more patients, and this is the phase clinical trials that come right before the medications go to the FDA for approval. So this is like the big kahuna. These are the Phase 3 clinical trials that are going to show whether or not there is significant effectiveness for these medications. And right now there are three of these BTK inhibitors that are being actively studied, Evobrutinib, Tolebrutinib and Fenebrutinib. And not only is it being tested in relapsing-remitting MS, but it's also being tested in primary progressive MS and secondary progressive MS, including non-relapsing secondary progressive MS - remember the type of secondary progressive MS that really doesn't have anything available at this time.

So I'm going to be going through the rest of the slides a little bit quickly, because I'm just paying attention to the time. But I want to focus in a little bit on DMT discontinuation, because this is becoming an even hotter topic than it was a couple of years ago. So is this a possibility in progressive MS? Well, guidance on when and if to discontinue treatment remains largely unavailable and currently there are no consensus guidelines. But questions do come up when the patients are wary of being on the medication. They're bothered by side effects, and they really don't feel like it's being helpful anymore. And then clinicians start becoming wary of it when someone has been on medicine for a long period of time and they've been stable, there hasn't been any more activity, but they're starting to be concerned about safety, especially as folks get older because of immunosuppressive effects and risk of infection.

So because of these questions, there is a big clinical trial that is currently active called the DISCO-MS Study that is being headed up at the University of Colorado. And this is basically looking at a patient population that is older, over 55 years, who have essentially been stable for a number of years and basically looking at whether or not they had disease activity if they come off of medication over a two year follow up period. And this particular study is based off of a number of observational studies that have previously been studied that try to answer these questions but are limited because of inherent biases of, what we call, an observational study. So this is a prospective placebo controlled randomized study that hopefully will be able to give us information on older patients and whether or not they can come off of medication in the right circumstance.

So many questions still need to be answered, but because there are no consensus guidelines having a conversation with the healthcare provider is mandatory; to have a conversation on whether or not it's the right circumstance for you and to discuss the evidence to support when and how to make that recommendation. But, you know, here are some... maybe some, I don't want to say guidelines, but maybe some guidance factors to keep in mind. So, one, if someone has been activity-free for at least five years in an aging population that has a progressive disease course, and maybe there are potential risk factors that challenge safety.

But of course, it does require monitoring. So again, because there's no algorithm, surveillance MRI should probably be adopted to make sure that there are no MRI lesions that are developing when someone comes off of treatment. Making sure that routine clinical visits are being held to

evaluate for any symptoms that sound like relapses, measure progression, and of course, maximizing function and quality of life through health and wellness, nutrition, exercise and neurorehabilitation.

So let's go back to Mr. Jones. So, he comes back and after having a very lengthy conversation, he decides that he actually wants to start siponimod based on the conversation that you had regarding the EXPAND clinical trial. But six months later, he... yeah, he reports, stabilization of his cognition, walking, but he's still struggling with right foot drag and spasticity, shooting pain, fatigue, overactive bladder symptoms. So because of these things, it's very important to discuss symptomatic management that either involves the medicine or is non-medicinal So some of that can be physical therapy, can be occupational therapy, maybe a neuropsychology test battery in order to gauge what his baseline cognitive assessment overall is, and maybe have to do another neuropsychology test battery later on to see if there has been any further worsening over time. And then in this particular case, he was mentioning that he does have continued spasticity. So there are things like physical therapy that can be employed, other oral medications, sometimes botulinum toxin injections, can be helpful. And then in refractory cases, a Baclofen pump assessment can be considered. Neuropathic pain management, some of it involves medicines, other strategies involve therapy, exercise, stretching, mindfulness, acupuncture.

And then bladder management. So there are different ways to manage the bladder depending upon whether or not it's a storage dysfunction or an emptying dysfunction. And this can include medications, It can impact lifestyle modifications. And then when in doubt, a urology referral might be needed to evaluate how much urine is left over in the bladder after a person empties through urination or a urodynamic study to evaluate urine flow.

And then fatigue management. So addressing secondary risk factors is really important - depression, medication side effects, other sleep disorders, inefficient mobility and deconditioning, pharmacotherapy, behavioral change interventions, occupational therapy, cognitive behavioral therapy and exercise. And then complementary strategies like yoga, tai chi, and mindfulness.

And then health and wellness. We couldn't have an MSAA talk without going over health and wellness a little bit. So not only as a preventative strategy for progressive MS, but also can be used in folks who have already developed progressive MS, specifically making sure they're getting ample doses of vitamin D, getting routine exercise, physical activity. There is no best diet that we've been able to establish so far, but a good Mediterranean anti-inflammatory nutritional regimen is probably a good idea. Good sleep hygiene and mental health management.

And of course, physical health. So making sure that vascular risk factors are either being prevented altogether or appropriately managed through a primary care doctor or another healthcare provider, such as hypertension, type 2 diabetes, and hyperlipidemia.

And ultimately having a good clinician-patient relationship is so important because given the complexity of MS and treatment options, the clinician and the patient must work together harmoniously to understand the problems and find successful solutions. And overall, we find that by establishing an open and honest clinician-patient communication, it will help foster mutual trust, enhance accuracy of the diagnosis and treatment, improve adherence, increase person satisfaction, and promote the best possible health and overall quality of life.

So in summary, MS is a chronic demyelinating and neurodegenerative disease of the central nervous system. Secondary progressive MS is a form of MS that follows relapsing-remitting MS. Persons with MS may still experience relapses in MRI activity, but gradually worsen over time in between relapses. And the transition from relapsing-remitting to secondary progressive MS can sometimes be elusive and take time to recognize. Primary progressive MS is a form of MS where patients develop slow clinical decline from the onset of symptom development. And an updated classification was proposed for progressive MS that categorizes the disease state as active or progressive or stable, not active or progressive. And this classification helps healthcare providers recognize whether or not a disease modifying therapy might still be helpful. We discussed that ocrelizumab is the only disease modifying therapy approved for primary progressive MS in the US, but data suggests better outcomes in folks who are younger with more inflammatory disease. Siponimod demonstrated benefit for secondary progressive MS in a pivotal clinical trial. And multiple novel neurotherapeutics for progressive MS, including BTK inhibitors, are currently in investigative stages. Discontinuing disease modifying therapy may be appropriate. Having a conversation with your MS team is important when considering this as an option. Symptomatic therapy, rehabilitation and health and wellness practices are key in managing progressive MS to improve function, safety and quality of life.

So with that, I would like to thank everyone for their attention, and I would be happy to take any questions

Marie LeGrand:
All right. Well, thank you so very much, Dr. Hersh, for the wonderful presentation. As always, you gave us so much information for us all to think about. And as you can imagine, you can see the activity in the chat, folks asking questions. And there are a number of really good ones. I'll try to get to as many as I possibly can. But for the sake of time, we're just going to touch on a few. So the first question is: I have trigeminal neuralgia, which I understand is a symptom of MS. Is there a way to address TN pain by addressing MS progression?

Dr. Carrie Hersh:
Wow, that is such a great question. So in trigeminal neuralgia with MS, someone can continue having recurrent trigeminal neuralgia attacks without having evidence of active MS disease. And we see that actually quite commonly. And it may not necessarily mean that you're progressing or you're having active MS, although maybe having a new set of MRIs, if they haven't been done recently, would help answer some of those questions. But the underlying treatment, which is pain management, or whether or not someone might be a candidate for gamma knife or micro vessel decompression or microvascular decompression, those things can certainly be discussed with the healthcare provider. But it doesn't necessarily mean that the person's MS is out of control or progressing. This is actually quite common in MS.

Marie LeGrand:
Okay, good to know. Now, in your case study, it is implied that should the person have continued taking DMT, they would have had less disease progression. What are your thoughts about that?

Dr. Carrie Hersh:
So in the case that I talked about, Mr. Jones, we were only looking at six months. Right? So six months, as we had talked about before, is still a very small period of time, especially in progressive MS, to determine whether or not someone is going to continue to reap benefits from that particular disease modifying therapy. Mr. Jones just happened to have felt a little bit more

stabilized by the time he got back to his six month evaluation. So continued monitoring, bringing him back into the clinic, doing MRI's, making sure he doesn't have any superimposed inflammatory activity going on in the background. But, doing certain kind of clinical tests may be components of the MSFC patient reported outcome questionnaires to help determine whether or not the patient and the clinician both feel that the progression is slowing down.

Marie LeGrand:
Okay. Now, does neurodegeneration occur without inflammation?

Dr. Carrie Hersh:
Yes, that's an excellent question. Yes, exactly. So in later stages of progressive MS, when the patient is no longer having new relapses and new MRI lesions, they can have neurodegeneration by itself, and that can manifest as non-active secondary progressive MS, which is really at this point the biggest unmet need in the MS scientific space. And this is why there is so much attention to BTK inhibitors to see if we have identified a mechanism and neurologic pathway that can actually really benefit our patients who have progressive neurodegenerative disease without inflammation.

Marie LeGrand:
Okay. Now, what is the best way to treat MS symptoms that are getting progressively harder to control with medications?

Dr. Carrie Hersh:
Oh gosh, that is such a good question. It really depends on what the symptom is. So, things like neurorehabilitation, physical therapy, for instance, can be really good for folks who are continuing to feel like they're slowing down or they're getting more weak or they feel like they're getting more spastic or tight. Occupational therapy can be good for folks who need fatigue management. for folks who have progressive cognitive impairment, cognitive rehabilitation through occupational therapy can be helpful. And then of course, the health and wellness that we had discussed, being physically active, eating well, getting a good night's sleep, being active in the community, all of those things are non-medicinal ways that might be approached for certain symptoms.

Marie LeGrand:
Okay. And this will be the last question, unfortunately. I wish we had more time to get through all of these. Why are some neurologists reluctant to confirm or modify a patient's diagnosis from RRMS to SPMS when it's obvious the progression has been increasing and relapses have been minimal to none over the years?

Dr. Carrie Hersh:
Excellent question. Gosh, I wish I could stay on the line for longer. These questions are fabulous.

Marie LeGrand:
They really are!

Dr. Carrie Hersh:
So good I would say that there's probably a couple of at least big answers to those questions. One, the healthcare provider may or may not be able to recognize it. So as I mentioned before, you know, it can take a while to recognize when a person is transitioning from relapsing

remitting MS to secondary progressive MS, and it can take a few years to recognize that. And if the proper tools are not being used to help the clinician identify if a person is transitioning, it might get missed.

The other might be because of the lack of FDA approval for disease modifying therapies for progressive MS, and they might be using certain language to make sure that if they feel an individual should still be on a disease modifying therapy, that they're able to get that approval through their insurance companies. So that might be a couple of different reasons why that terminology is not appropriately transitioning.

Marie LeGrand:
Okay. Well, thank you so much, Dr. Hersh. This was an excellent program, as always. We're so glad that you were able to join us tonight. Again, this has been an amazing and insightful program, and thank you to the viewers for your wonderful questions. As mentioned, I wish we could get through each and every one of them, but we're short on time.

So this concludes the webcast for tonight. Tonight's webinar was recorded and will be made available on our website at mymsaa.org. Please visit MyMSAA's calendar of events for some of our upcoming webinars. And on behalf of MSAA, once again, we'd like to thank you, Dr. Hersh, for the great presentation. And we'd like to thank you for joining us this evening.

Please consider completing the brief survey, which will appear on your screen momentarily and know that we are thinking of the entire MS community and hope that you and your families continue to stay safe. Thank you and have a good night.