Transforming MS Care Advanced Strategies in Multiple Sclerosis Management

CMEO Podcast Transcript

Tanuja Chitnis, MD:

Hello and welcome. On behalf of CME Outfitters, I would like to welcome you and thank you for joining us at today's CMEO briefcase entitled *Transforming MS Care Advanced Strategies in Multiple Sclerosis Management*. This activity is supported by educational grants from Novartis Pharmaceuticals Corporation and TG Therapeutics. A quick disclosure and fair balance note before we begin. We may reference data or clinical considerations that extend beyond FDA approved labeling. When that happens, we'll clearly call this out and encourage you to consult the full prescribing information and current clinical guidelines when making decisions for individual patients. To introduce myself, my name is Dr. Tanuja Chitnis, and I'm a professor of Neurology at Harvard Medical School and Chief of the Division of Neuroimmunology, Mass General Brigham in Boston. And I'm joined today by my esteemed colleague, Dr. Mitzi Joy Williams. Dr. Williams, please introduce yourself.

Mitzi Williams, MD, FAAN:

Yes, I'm so excited to be here with you. I'm Dr. Mitzi Joy Williams, and I am a Neuroimmunologist and the Medical Director at Joy Life Wellness Ms. Center in Smyrna, Georgia.

Tanuja Chitnis, MD:

Wonderful. I'm sure it's warmer there than it is right now in Boston.

Mitzi Williams, MD, FAAN:

Absolutely.

Tanuja Chitnis, MD:

So wonderful. Before we begin, I want to let our audience know that this is going to be an intimate, informal conversation and to facilitate that, Mitzi and I will be addressing each other on a first name basis. So to get started, today's first learning objective is to assess data on available anti-CD20 therapies to make appropriate recommendations for patients with multiple sclerosis. And our second learning objective is to utilize evidence-based guidelines for MS management and to optimize treatment selection and monitor therapeutic outcomes. And lastly, our third learning objective is to develop tailored MS treatment plans and address the unique physiological and social needs of older and pediatric patients. Mitzi, before we get into the first case, what are the real-world barriers that you see most often derail in an otherwise solid treatment plan?

Mitzi Williams, MD, FAAN:

Excellent question. So two big ones that I see in practice are feasibility and trust. When we think about feasibility, it's really a matter of can we actually follow through with this plan? So that includes looking at things like visit burden, infusion logistics, timing of insurance, transportation, as well as caregiver bandwidth. Trust is also important because it determines whether the patient and family really believe that this plan, that the

potential benefits are worth the risk of the trade-offs, especially when we're talking about safety monitoring or therapies that can seem a little bit intimidating.

Tanuja Chitnis, MD:

Mitzi, I absolutely agree with these sentiments and I think really the best plans are laid out, but it is both up to the patient and caregiver to decide that this is the optimal path forward for them. With that in mind, let's start with our first case, pediatric onset MS. So I'd like the audience to meet Emma. She's 14. She was diagnosed with pediatric onset relapsing multiple sclerosis six months ago. She has a very busy school schedule. She's involved in sports, she's doing SAT prep. She's also looking at colleges in the near future and her caregiver is worried about long-term cognition and disability and Emma also wants fewer clinic visits now that she's understood what an MS diagnosis entails. And what I'd like to do is I'll walk you through this case and provide some of the details. So as we talked about, Emma is 14. She had a recent relapse with optic neuritis.

She presented with eye pain, monocular vision loss, and also sensory symptoms. And her MRI shows about 10 new T2 lesions. She has three gadolinium enhancing lesions and also lesions in her spine. She did have a spinal tap, which was not pleasant, but she understood that this was very important and it did show oligoclonal bands. And her MS workup, we've also excluded other things that can be important to consider in pediatric onset patients MOCAD. So we checked MOG antibodies in her serum as well as AQP-IV antibodies and both her serum and CSF. And these were both negative. So now we had a long discussion when she was first diagnosed about different treatment options, what was available, there was an FDA or is an FDA approved medication for pediatric onset MS, and we initiated this medication fingolamod or gilenya about six months ago. But some patients do have breakthrough disease and she has had both a clinical relapse with new enhancing lesions.

Mitzi Williams, MD, FAAN:

So that's a very interesting case, Tanuja, and I'll just underscore the fact here that if we look at the quote at the bottom, which I won't read, Emma is very focused on wanting to live a normal life. So it's important that when we're talking about treatment options with our patients, particularly our pediatric patients, that we keep their goals at the forefront of the plan and not use them as an afterthought.

Tanuja Chitnis, MD:

Yeah, absolutely. And I think that really treatment discussions are both with the parents that's important to take their thoughts into consideration, but especially with the young teenager or adolescent who of course is at the center of all of this. So now let's move to our next question. For Emma, who has highly active relapsing remitting MS, despite adherence to fingolamod, what do you think is the next best step after this confirmed breakthrough disease? Is it to A, optimize adherence and support barriers and continue current therapy? B, intensify, treat to target monitoring i.e. earlier MRIs without changing therapy, and sometimes we do this for patients? C, refer for escalation planning, including pediatric trial eligibility and implement treat to target monitoring? D, the acute relapse and defer any disease-modifying strategy change until later follow-up? And E, other.

Mitzi Williams, MD, FAAN:

So those are all very plausible treatment options or plans for Emma who's apparently having issues with her therapy. And of course whenever we have some of our younger patients, particularly who are very busy, if

they're on a therapy that is a home-administered therapy, my first question is always, are we having any difficulty with compliance? So I think it's important to recognize that that can be a barrier as well. And these options really offer a mix of either continued treatment with extra monitoring or change therapy. And in MS, when we're having particularly the option to continue monitoring, we need to also make sure that we have some threshold that's actionable where we decide, okay, at this point we think that this is not the best plan and we need to make a new treatment decision.

Tanuja Chitnis, MD:

Those are all great thoughts, Mitzi. Let's zoom out briefly and discuss why early control matters so much in pediatric onset MS. So what do we know about this form of disease? We know that it's typically more inflammatory. There are higher relapse rates and more MRI lesion activity than adult onset MS. There's also a very long horizon to treatments. So these kids are going to be treated not only during their teenage years, but now we're going on to decades of treatments. We have to choose our first options wisely and think about that on this long horizon. And then also real world evidence suggests that starting high efficacy treatment, especially at a disease onset, might lead to better outcomes long term.

Mitzi Williams, MD, FAAN:

Absolutely. And also this is where the burden of treatment cannot be ignored. You spoke a little bit earlier about how yes, the patient is at the center, but we do also have to consider their caregivers who will have to get them to appointments, particularly if you're 14, you can't drive. And so we have to look at the burden of treatment. If this treatment or our option will cause that teenager to miss school on a regular basis, then that may affect adherence, which then would affect long-term control of their multiple sclerosis.

Tanuja Chitnis, MD:

These are all great thoughts. So this is what we face every day in pediatric MS clinic. How do we choose and personalize therapy for these young people? So let's start with phenotype and prognosis. High lesion burden, spinal cord involvement, early relapse and breakthrough therapy or breakthrough activity are all red flags that push us towards higher efficacy strategies. Then if we can align and really set up the family with a realistic understanding of what treatments would involve and what the various treatments offer. So things that are important to consider are route of administration, so oral IV, subcutaneous, visit cadence, what will this all entail both for the treatment as well as from monitoring whether the treatment is working?

So the number of MRIs and the frequency of MRIs, the number of neurological visits and also the child's developmental stage. So thinking about where they are in their life and activities and also where their goals lie for school for their personal lives. Shared decision-making is essential here because in pediatrics we're often balancing an adolescent's emerging autonomy with caregiver responsibility and that shift or balance is something that I see in clinic every day.

Mitzi Williams, MD, FAAN:

So I definitely see that also at home. I've got a preteen as well. And so that autonomy or that emerging autonomy is extremely important. And I think this is also important to underscore the importance of the silent deal breaker. So part of what we do is we do a lot of education, but also a bit of what we do is reading people in

their responses. And when you're talking to a patient, if I have somebody where I say the word needle and maybe they start to cry or have a certain look on their face, then that may indicate to me that they have some needle anxiety and maybe we need to do a little bit more education or maybe that's not the treatment for them. So making sure that we look at those deal breakers for them, which may be needle phobia, fear of infections, transportation, insurance, when we're in that shared decision-making process is really important for us to try to ensure as much adherence as possible to our treatment plan once they leave the clinic.

Tanuja Chitnis, MD:

I think Mitzi, those are really good thoughts and I think having also follow up in between clinics is very important to enhance adherence and just also to have a connection with the patient and their family. So in terms of other treatment options that are available, we obviously want to look at something that could offer at least equivalent or possibly more efficacy. We have anti-CD20 therapies that are now on the horizon. None of these are currently FDA-approved for pediatric MS. so all pediatric use is currently off-label and trial enrollment should be considered when available. There are several studies and trials that either have completed for these anti-CD20 therapies or are ongoing, and some of these are scheduled to complete fairly soon.

So OPERA-II compared eculizumab to fingolimod and this was a non-inferiority study and it showed that the eculizumab arm met its goal, it was non-inferior to fingolimod. Ofatumumab has a similar study design that is ongoing and this is a trial that hopefully will complete soon. This compared ofatumumab to fingolimod and also had a siponimod arm. And so we'll get information about the efficacy of these three drugs compared to one another. And ublituximab is another anti-CD20 therapy and this trial is ongoing in its early phase at this point, so hopefully more to come on that, but it is very exciting that we do have more therapies now either in trial or becoming more data becoming available very soon.

Mitzi Williams, MD, FAAN:

This is very exciting indeed, and I'm very encouraged to see that there's so many studies that are really trying to help us better target and treat our pediatric population. So if we bring it home to the clinic, if a provider, a neurologist, or someone who is caring for someone with MS in the clinical setting is considering an anti-CD20 approach for a pediatric patient, first we want to think, is there a clinical trial available either at your center or at an academic center such as yours, Tanuja? Otherwise, considering a referral to potentially a pediatric MS specialty center and having a careful conversation about the off-label risk versus benefit discussion as well as very concrete plans about monitoring and follow-up if they choose to go the anti-CD20 route off-label.

Tanuja Chitnis, MD:

Great. And I'm glad that you brought up monitoring because not only is it about choosing a treatment and also individualizing the treatment choice that might be influenced by comorbidities or laboratory tests or other factors, but also to monitor and reassess whether that treatment is actually working. And that could be done through a couple of things, neurological exams and visits and reporting any symptoms, but also MRI plays an important role and we know that lesions reflect relapses or are silent relapse activity. And so I recommend monitoring with MRI at least within three to six months after a new treatment start or switch and then repeating this at another six months. And then if things are good, then maybe switching that to every year.

But I think frequent MRI monitoring, especially in the beginning is very helpful. Then also thinking about treatment to or treat to target examples around how do we convey this to patients and what is the goal of treatment? The goals in my mind are to prevent relapses, to stop new lesions from occurring on MRI and not have any new lesions and over the next few months to years ideally on treatment, and also to monitor whether there's silent disability accrual occurring. Now, this is not very common in pediatric MS. Usually disability is associated with relapses, but we want to monitor for any other signs of disability accrual. Those are my top line items when I think about treat to target.

Mitzi Williams, MD, FAAN:

Absolutely. And I tell my patients in the clinic, we want to achieve the same end points that we see in our clinical trials, and they're exactly the three things that you mentioned. So it brings the clinical science into the clinic setting to let them know this is what we looked at in the clinical research and this is also what we look at in real life to determine if your medication is working.

Tanuja Chitnis, MD:

Absolutely. And I think juggling schedules and figuring out as a parent how to fit this all in is very important. And as caregivers, we have to be sensitive to those challenges and certainly as a parent myself, I can imagine and know how difficult this can be. I think with pediatric onset MS, this also comes with other unique considerations and we've talked about the fact that it's a more inflammatory disease, so watching out for relapses and new MRI lesions is very important as disease activity markers, but also thinking about school and cognitive function. Now, there's also data around the impact of MS on cognition, and we can imagine that lesions on a developing brain can also cause issues and putting that together with now you're in school in a really critical time, it's really important to monitor how that young person is doing in school and also help them as much as possible through things like neuropsychological testing if they require a 504 or individualized education plan.

This is also part of our armamentarium and something that we do on a regular basis. I also think that thinking about how to talk about disability and what that could mean for this young person is important, but also finding ways for them to do as much as they want to do. And many of our young people are involved in sports and activities and figuring out what is the right balance for playing soccer sometimes in the hot sun, cooling down when you need to, and having that discussion around what is their limits, but also what can we do to help them do everything that they want to do.

Mitzi Williams, MD, FAAN:

Absolutely.

Tanuja Chitnis, MD:

And I think that around some of the other questions that often come up, especially related to immunosuppressive treatment, especially when we're thinking about anti-CD20 treatment are the potential risks. And we know that when we suppress the immune system, that can cause an increase in infections. You're at more risk for infections and getting those treated as early as possible is really key. The other things that we think about is making sure that vaccines are up-to-date, that as far as possible, and then also screening for laboratory tests such as hepatitis B is also important before starting one of these anti-CD20 therapies. So these

are all things that are part of the regular guidelines we all think about as we're starting immunosuppressive treatments.

Mitzi Williams, MD, FAAN:

Absolutely. And to underscore several points that you already made, the guidelines are on paper, but they also have to live in our clinics, meaning that if there are barriers to getting accurate care such as getting MRIs on time, sometimes we need a workaround plan, we may need to schedule, have scheduling templates, reminders, care coordination, and then also this is where practice setting matters. A tertiary center such as some of our academic centers where you are may have a larger or wider variety of resources than some of our community clinics, particularly those that are not focused on neuroimmunologic disease. So if someone is in a lower resource setting, early referral to a tertiary center or specialized center is extremely important. And there are many shared care models where I will see a patient and they will also have a local neurologist and we share some of that responsibility, but ultimately we want to make sure that people get the best care in a timely fashion in a way that actually fits into their lifestyle.

Tanuja Chitnis, MD:

Absolutely, and I think thinking about our young person, Emma, finding the right fit for the right patient at the right time in terms of therapy is something that I think about a great deal for my young patients, my older patients, and in terms of her treatment choices. So given the breakthrough activity on fingolimod, we really currently don't have other FDA approved treatment options, but there's a lot of promise with the recent studies and trials and anti-CD20 therapy, they've also been used off-label for a number of years in countries like the United States and around the world. So we are accruing a lot of data on these treatments. I'm hopeful that we will have more approvals of treatments in the near future, and as practitioners, we need to make sure we offer our patients all options available.

Mitzi Williams, MD, FAAN:

Absolutely, and again, when looking at treatment goals, many folks, especially our young people, do not want to come into the clinic on a regular basis. So even though fewer clinic visits or fewer touch points with the clinical setting may be the goal, it doesn't mean that fewer visits equals less monitoring. So certainly there are things like telemedicine visit, which I employ with some of my younger patients, particularly those who are in college, and we want our plan to be realistic. So if we have laboratory monitoring that needs to be done, can we do those closer to that patient's home? Can we do those without them having to come all the way into our regular clinic?

And then if we're tracking symptoms, how are we doing that? Are there other ways we can communicate through the patient portal, have periodic check-ins with either the patient and/or their caregivers? And then how are we making sure that especially our young people do not get lost to follow up? So making sure that we keep them engaged as well as their parents and family members and caregivers who are providing that support to them. So we want to make sure they don't get lost in the system, but we also want to make sure that again, they're out there living their lives, playing all the sports that Emma wants to play and doing all the regular activities that teenagers do to the best of their ability.

Tanuja Chitnis, MD:

Mitzi, you brought up some great points and I think oftentimes use of the patient portal or technologies to help track and figure out what's going on. Sometimes our teenagers are actually very good at that compared to their parents. So introducing them to this practice to also thinking about transition of care. They're eventually, very soon going to become young adults and will be responsible for their own care and appointments. Introducing them to technologies and ways to work with the medical system early on is very important. So I think you made some really great points. This also helps adherence in general and really monitoring clinical visits, MRI, also the laboratory tests that are needed. I think communicating clearly, these are the tests that are needed. This is the timeframe, you can always call if you need to and get clarification from your team.

Mitzi Williams, MD, FAAN:

And again, the adherence piece is so important, which is why we want to participate in the shared decision-making process. We want our patients to have a stake in the decisions that we make, so that will encourage them to continue to follow up. So we can certainly incorporate things as you discussed earlier, coordinating with the school if there are any plans or any adjustments that need to be made for absences because we don't want that to eventually translate into missed visits and missed doses of their medication, which could affect their ability to function. So when we think about shared decision-making in pediatric MS, there is a triad of those who are involved in that process. There certainly is the adolescent, there is the caregiver and the clinician, very similar to what we'll eventually talk about with the older population. And so when we're looking at all of these principles, we want to make sure that we are using age-appropriate language.

I try to make sure that all of my patients understand their treatment plan to the best of their ability. Sometimes I draw pictures, I may make analogies. My youth lingo and slang is growing over time so that I can make sure I can relate to the patients, but we also want to discuss realistic expectations. And I think that's one reason that sometimes we lose adherence, particularly with our young folks. And I try to make sure that we discuss that this is to prevent further damage, but it may not fix what's already broken because some people will get disappointed if they feel that a medicine is supposed to alleviate the symptoms they already have and they don't have that expectation set up from the beginning. So making sure that expectations are very forward from the beginning of the decision-making process is really important as well as making sure that we start and try to incorporate their goals, things they want to accomplish into the treatment plan, as well as looking at some of those surface concerns as we discussed, like needle phobia, safety concerns, concerns about missing school and for parents concerns about insurance coverage.

Tanuja Chitnis, MD:

These are all really great points. And I think also just setting the young person up for success in terms of helping them, supporting them through their treatment journey, also supporting their goals outside of the medical system, making sure that school is optimized, that we're supporting them through IEP plans and also social work and psychological support might be needed in some cases. So offering all of these options to our young people is really going to help them succeed as much as possible.

Mitzi Williams, MD, FAAN:

So I often say to my patients, our goal is we want to protect your brain and keep you doing everything that you want to do to the best of our ability.

Tanuja Chitnis, MD:

Well said. Let's close with Emma's case and a very practical recap. Our practical plan is to make sure that we are in touch with this young person and that we reassess whether they are having new relapses or possibly pseudo relapses. If they're out in the hot sun and they're not feeling well or their optic neuritis gotten worse, we need to educate our young people about that. Also, to think about restaging disease activity and performing monitoring such as MRIs frequently, especially after switching treatments, and I say within three to six months after a treatment switch, then another six months later, and then we can probably establish an annual MRI plan if things are going well. We should also think about escalating, especially if there are breakthrough disease activity, lesions occurring or new relapses certainly. And then think about, I always tell my young patients and their families, let's keep an option in our back pocket.

What would we do next just in case something occurs? And we're also prepared for that. We do the blood tests ahead of time and think about those options. And then there are a number of safety essentials that we should think about. So if vaccinations are required for particular treatment, those should be administered of course before starting treatment. And then also reproductive counseling is very important, especially in our teenagers. So if that's something that you're not comfortable with referring to their pediatrician or even an adolescent clinic. So these are all options, and I've used them in the past and different variations. And if anti-CD20 is being considered, then there are very specific pre-screening tests that we should do. So screening for hepatitis B, quantitative immunoglobulins, counseling about infection risk, and also to make sure that this young person really understands how often laboratory tests are going to be required and also the MRI and clinical follow up so they don't fall off and they're lost to follow up for the next year and you don't understand what is happening.

And then I think also making adherence realistic is very important, especially in our young people who are starting college. I put them on what's called the college treatment plan or the college visit plan, and we try to schedule their visits with me in the summer and in the winter breaks, and ideally they're getting infusions during those time periods. And so we set aside slots for our college students who can only be here for those periods of time. I also recommend, especially if they're moving out of their parents' home and going to college elsewhere, we help them identify a neurologist in their local area. And this might be helpful for acute care that's needed or for tests that are needed. So we try to identify someone who can help in their care that's local to their college.

Mitzi Williams, MD, FAAN:

So all extremely important points with the shared decision-making process as well as the shared care model when we have our young people who are moving away and starting their unsupervised portion of their lives if they're going to college. So essentially we want to choose a therapy that matches their life and we want to make sure that we have explicit instructions on what monitoring should look like over time, as well as what breakthrough looks like over time. So they'll know when to call and they'll know when it's time to go in and be assessed.

Tanuja Chitnis, MD:

And breakthrough activity is so important, and sometimes our young people don't want to call or they minimize it, but it's very important to emphasize that they should contact their neurologist or doctor if there is breakthrough activity, and that way we can treat or consider escalation if needed. So it's really been a pleasure speaking about Emma, and hopefully these are some good takeaways in terms of treating pediatric onset MS.

Mitzi Williams, MD, FAAN:

Absolutely. So now we're going to shift gears a little bit and talk about older adults with MS. And I always caution because the older I get, the older old seems to me. So for the purposes of this talk, we will say over the age of 55, however, I will give the caveat that I do not think that 55 is old. So in pediatrics we are asking how fast do we need to control inflammation because as you said earlier, Tanuja, the disease is primarily categorized by a high inflammatory process rate. And so in older adults, the question becomes if someone has been very stable in terms of their disease, particularly if they're on high efficacy therapy, how do we then begin to weigh the risk versus the benefits of that therapy, particularly when we're dealing with issues related to aging, immunosenescence and other factors, comorbidities, which we'll get into a little bit further on in this discussion. So let's introduce you to Robert. He is a 68-year-old man with relapsing MS that was diagnosed at age 45. So he's a little over 20 years into his disease.

He has been both clinically and radiographically stable on an anti CD20 therapy ocrelizumab for about eight years. So no relapses, no new MRI lesions. However, he does come into the office for evaluation and state that he's having increased fatigue and falls. So when we look at his comorbidities, he's got hypertension, diabetes, he's got some chronic sinus problems as well as polypharmacy due to his multiple conditions. In terms of infections, over the past six months, he's been hospitalized twice for upper respiratory infections. So he's had pneumonia and bronchitis and his IGG, which has been monitored as part of his treatment is low at 480. His CD19 B-cells are undetectable, which we would expect with a anti CD20 therapy. His goal really when he comes in is that he wants to remain independent. He obviously does not want to fall and break something and he does not want to be admitted to the hospital, which is reasonable with these upper respiratory infections. He also would prefer fewer clinic visits if possible. So this is our setup to talk about this patient, Robert, who is an older gentleman with MS.

Tanuja Chitnis, MD:

Mitzi, this is a really classic scenario where stability is real, but risk is changing. So we really need a structured way to reassess this.

Mitzi Williams, MD, FAAN:

Absolutely. So we're going to go to an audience response question and given Robert's scenario, what is the best next step or the next best step? So A, continue his anti-CD20 with the same schedule and monitor more closely. We could also consider holding or extending his therapy, so doing extended interval dosing, reassess infection risk, as well as IGGs to see if he's having any B-cell reconstitution before redosing of therapy. We can also consider de-escalation and switching to a lower risk DMT and monitoring closely or discontinuing therapy with a structured follow-up plan. Another plan could be to refer to immunology or infectious disease and consider IG replacement depending on the severity infection, and that may facilitate him continuing on an anti-CD20 therapy.

Tanuja Chitnis, MD:

Mitzi, this is a situation that I see quite often. He's stable from an MS inflammation standpoint, but he's showing signs of vulnerability and recurrent infections, low IGG during B-cell depletion. And this is really a challenge both for the patient and the physician.

Mitzi Williams, MD, FAAN:

Absolutely. So in many cases, the reasonable next step would be to hold the next dose of therapy as the infection's clear, et cetera. And then after that, consider extended interval dosing, reassess infection risk, and then also considering any input from immunology or infectious disease would also be a reasonable option. But certainly this is something that we commonly encounter in the clinic setting and definitely something that we have to address on an individualized basis with each patient that's sitting in front of us.

Tanuja Chitnis, MD:

And this highlights why the risk benefit equation shifts with age compared to our younger patients with aging and longer disease duration relapses, new MRI lesions often decline while disability accrual increasingly reflects something called progression independent of relapses or PIRA as well as neurodegeneration. And I think this is an important change that we should note because as practitioners who are seeing older patients, we have to be on the lookout for PIRA and really rigorously monitoring for this worsening independent of relapses.

Mitzi Williams, MD, FAAN:

And one of the challenges is that measuring PIRA really is all about the patient history. So it shows up exactly like Robert mentioned, where he's not really having acute episodes or inflammatory events, but he is having more life events, so he's having more falls, he's having more fatigue, more infections, hospitalizations. And so it's important again to bring in the care partners when we're having these discussions because sometimes when our patients are in that 20 minute or 30-minute visit, they may forget some of those things and their care partners may be able to chime in and say, "You know what? Remember you fell five months ago." or, "You fell four months ago." and they may not remember some of those things that may have happened immediately close to their visit. So it's really important to measure these things and to talk to our patients, and that's how we get our best understanding of PIRA at this point.

So when we think about a framework to try to optimize treatment, because our goal is always to optimize that treatment and create as personalized a treatment plan as possible with our older patients or really with all of our patients with MS. So we can look at this framework. So versus confirming current inflammatory activities. So we want to check and see has there been any recent inflammatory activity which would help us strongly consider leaving them on a high efficacy therapy. So we look at their relapse history, have they had any relapses in the past five years? Have they had any new MRI lesions or MRI changes in the past three years? We can also look at their disability trajectory. Are they having primarily PIRA or have they primarily had relapse associated worsening? We can also look if they've had any new clinical concerns, whether they have brought them up in the clinic setting or have called in or sent messages to the clinic about those issues.

We also want to quantify as much as we can, vulnerability. So looking at their age, their level of disability, their comorbidity and the burden of those comorbidities. Does he have poorly controlled hypertension or poorly

controlled diabetes versus well controlled? Also, looking at other things like polypharmacy, which can affect cognition as well as things like fall risk and cognition as well as infection history and vaccination history. And then finally, we want to match action and a monitoring plan. So if they have active disease, then we may be more likely to continue close monitoring on a high efficacy therapy. If they're very stable and they have increased risk for infection, then we may look at things like extended interval dosing as well as de-escalation or discontinuation of therapy. So essentially we want to assess the inflammatory activity, look at their vulnerability for side effects, and then also match that action plan to what we think will be the best treatment for them moving forward.

Tanuja Chitnis, MD:

I think those are really important points. And I would also say the matching plan also includes feasibility. So some of these patients, they don't drive, it's hard to get to appointments. So really matching what is feasible from both a monitoring standpoint, laboratories visits, and also the caregiver support system, what is feasible for them. And something that often comes up is time away from work for caregivers, making sure that they're in touch with a social worker who can help to support any transportation needs. And so I think all of these support systems in clinic are really important to consider.

Mitzi Williams, MD, FAAN:

Absolutely. So there are a lot of parallels actually with our pediatric population depending on the person's age as well as their level of a disability or ability. So let's zoom in on the anti-CD20 therapy, and you covered a bit of this earlier, Tanuja, with the first case. In older adults, we can see that these agents are obviously highly effective at reducing relapses in MRI activity, but the treatment effect because inflammation tends to decline over time, can decline with age as well as longer disease duration. And on this slide, we look at the expected benefit for age, we know that they decrease inflammatory activity, but certainly the risk for things like infection can rise with age, disability and other comorbidities. Some of the key safety signals that we look at are infusion and injection reactions, which we tend to see very early on after initiation of therapy.

So for someone who is eight years into disease, if they've not had a lot of infusion reactions or injection reactions, those are not likely to occur after eight to 10 years on therapy. But certainly something to look into. We certainly want to look at hypogammaglobulinemia because we know that declines in IgM can occur over time, and then IgG levels which can occur also are linked to higher infection risk. And we did see this in our patient case. And then of course, before someone starts therapy, we want to do screening for hepatitis B, we want to look at their vaccinations, and we want to periodically monitor their IgG while they're on treatment so that we can again try to continue to mitigate any risk of side effects or risk of infection in this population.

Tanuja Chitnis, MD:

So I think mitigation really becomes part of treatment and things that you've mentioned, of course, the baseline hepatitis B, vaccine screening, checking for immunoglobulin levels and monitoring these, and also updating vaccines before initiation when feasible, and advising patients to avoid live vaccines during therapy and also to keep up with their laboratory tests since this really helps us to assess their potential risk for infections.

Mitzi Williams, MD, FAAN:

So the next slide looks at the current landscape of anti-CD20 therapies. I certainly am not going to read this in detail, but it gives the different therapies. We have four, three of which are FDA approved and one which has been used off-label for several decades in the field of MS or multiple decades. That's rituximab. We have the different routes of administration as well as the mechanism of actions listed here. For ocrelizumab, it is given both intravenously as well as subcutaneously. Ofatumumab is intravenous, ublituximab is an injection, and rituximab is an intravenous therapy.

Some of the key practical considerations are for ocrelizumab, which is given both intravenously and subcutaneously as well as our other infusion therapies. These have to be given in a clinical setting. So we have to factor in things like transportation and length of time in the infusion suites as well as where the infusion will be administered versus ofatumumab, which is home administered. And we would have to again look at things like compliance, which we can't measure as easily in the home setting as we can when someone is coming in for infusions. Also, we look at things like pre-medications, which need to be done prior to infusion, as well as observation that may be to be done depending on the infusion therapy that's being administered.

Tanuja Chitnis, MD:

So Mitzi, across all of these, the safety anchors are very similar. So pre-medication and observation protocols were applicable, hepatitis B screening, baseline IgG and ongoing risk surveillance, which should be tailored to the patient's age, comorbidity and infection history.

Mitzi Williams, MD, FAAN:

So if we look at a snapshot of the pivotal trial results, the big caution that we say upfront is that we cannot compare across clinical trials because these trials were done in different populations at different time points. Some of the comparators differed in the clinical trials and there were no, or currently are no head-to-head randomized clinical trials comparing our FDA-approved anti-CD20 therapies in MS. So we look at these descriptively, but you can see them listed here. We can see the data for ocrelizumab versus interferon and the pivotal trials for relapsing MS as well as the trial for primary progressive MS, which is ORATORIO, and that was ocrelizumab versus placebo. We see the ofatumumab, the ASCLEPIOS I and II trials was compared to teriflunomide and ublituximab in the ULTIMATE I and II was also compared to teriflunomide. And then there is another study called the RIFUND study that looked at rituximab versus dimethyl fumarate in relapsing MS and clinically isolated syndrome.

And so I think it's fair to say that these all had significant impacts on MRI activity in terms of decreasing new and enlarging T2 lesions as well as enhancing lesions. There are varying levels of effect on disability in terms of 12-week confirmed disability progression and 24-week confirmed disability progression. But even for those that did not reach statistical significance, there was a trend toward more or a larger decrease in clinical disability versus their comparator. So the data is there, these are effective drugs, but certainly we have to look at each individual patient and determine is this still the right thing to do for this patient or is the potential benefit not outweighing the risk anymore in that certain individual?

Tanuja Chitnis, MD:

Mitzi, these are all strong anti-inflammatory therapies for relapsing MS, and I think we have to assess whether it's the right choice for individual patients. And this often comes down to fit, route, cadence, monitoring, comorbidities, and patient goals, especially in older adults where safety risks can dominate the conversation. And this is, I put this front and center when I'm speaking to my older patients that these are the potential side effects. These are things that we have to consider, and I think it's very important for patients to understand that clearly.

Mitzi Williams, MD, FAAN:

So let's delve a little bit deeper into vaccination and guidelines for treatment selection in our older adults. So we know that vaccinations can be very important and there are vaccinations that we go through in the pediatric population, but also there are vaccinations that begin to be implemented as people get older, such as Pneumovax and the shingles vaccine, et cetera. So we want to review our patient's immunization status at the time of diagnosis as well as at the time of therapy, treatment switches or adjustment of therapy. We certainly want to prioritize non-live vaccines such as the influenza, pneumococcal, et cetera. But before we start an anti-CD20, we would like for them to obtain any live attenuated vaccines at least four weeks prior to initiation of therapy and any non-live vaccines at least two weeks before their first dose, if at all feasible. And then during therapy, we generally recommend that our patients avoid live vaccines and then we counsel them that the responses to vaccines when they are given can be blunted because of B-cell depletion.

So guidelines from the AAN really give us limited data and guidance on when to discontinue or deescalate therapy, and there really are no age-based thresholds. There are some clinical trials that have tried to get to the bottom of this and give us more guidance such as the DISCO-MS trial, which looked at people living with MS over the age of 55 who were stable on therapy, and there were some that discontinued therapy as well as those that continued on therapy. And so the discontinuation group did not meet non-inferiority, and there were more new MRI lesions in those who discontinued therapy versus those who continued. Although relapses were uncommon in either of those groups as we would expect in an older population.

So I think the key takeaway here is we look at each individual patient and if we have an older patient who is stable on therapy for some time, but they may have rising risk for infection, including recurrent infections or hospitalizations with severe infections, it certainly is worth having the conversation to consider de-escalation or discontinuation of therapy with very close monitoring as well as criteria in place to say, this is when we're going to reassess this plan as well as this is our boundary for where we will restart therapy or consider escalating back up on therapy. I think something else that's really important to keep in mind is the rebound effect with some of our agents because some of them, if we abruptly discontinue therapy, can lead to rebound disease and we certainly don't want that to occur in our patient population either.

Tanuja Chitnis, MD:

These are very important points. And I think just coming back to this whole question of vaccinations, this I think needs to be really reiterated. It's important I find to put this vaccination plan into writing. Patients often forget when they step out of your clinic and making sure that it's in their patient gateway or in a letter that's sent to the patient and also coordinating with primary care or pharmacies. So don't assume that it'll happen on its own and make sure that these vaccinations are indeed coordinated with all the right parties.

Mitzi Williams, MD, FAAN:

Absolutely. So coordination is key. Our older adults with MS as we discussed, bring a different set of day-to-day challenges. They may have comorbidities, polypharmacy, there may be frailty, recurrent falls, cognitive changes, as well as caregiver strain. So a practical approach is being multidisciplinary and proactive. So I often say it takes a village to take care of a child. It sometimes also takes a village to take care of MS. And so we want to incorporate things such as medication review to reduce any avoidable risk. We want to look at a falls risk assessment and engage physical therapy and occupational therapy early to try to prevent falls and to try to stabilize ambulation.

We also want to incorporate cognitive and mood screening because these can impact a patient's adherence to therapy as well as their safety. And we also know that cognitive and mood changes can sometimes overlap or compound with other MS symptoms such as fatigue and difficulty sleeping. We want to coordinate, as you said, Tanuja with primary care, sometimes immunology or infectious disease when infection risk is rising. And most importantly, we want to revisit that disease burden at each visit and make sure that it's included in the overall treatment process and treatment plan.

Tanuja Chitnis, MD:

And I think also monitoring intensity should match the risk as you've so well stated, Mitzi, if you're changing dosing strategy or considering discontinuation, increasing follow-up and monitoring and then space it out maybe when you've demonstrated that there's been stability under the new plan.

Mitzi Williams, MD, FAAN:

Absolutely. So let's take it back to our patient, Robert. So let's look at a stepwise decision pathway for his particular case. So first, we want to confirm stability, which we've done. We know he's had no relapses and no new enhancing MRI lesions and at least the past two to five years. Then we want to try to stratify risk. Looking at his age, he's 68, his comorbidities, hypertension and diabetes, as well as his infection history with two episodes of hospitalizations for upper respiratory infections in the past six months. We also want to match option to risk, and our options are to continue anti-CD20 with enhanced prevention or monitoring to consider extended interval dosing to de-escalate or to consider structured discontinuation with monitoring. And then of course, we want to pre-define restart triggers if we decide to discontinue therapy such as if he had a relapse or if he had new enhancing lesions on MRI as well as inflammatory progression.

And we want to establish that follow-up so that we have close monitoring three to six months after that type of change in MRI and six to 12 months after a change. And then of course, looking at the evidence, we talked about some of the data with DISCO-MS, where patients who stopped therapy tended to have more new MRI lesions, although relapses were uncommon. There also is observational registry data looking at the relapse risk after stopping therapy by different agents as well as those that may have risk for rebounds such as natalizumab and fingolimod. And then the bottom line is we want to individualize treatment decisions and we want to pair any change that we make with a very specific plan for monitoring follow-up as well as plans to consider re-escalating or restarting therapy if needed.

Tanuja Chitnis, MD:

And I think this whole discussion around discontinuation or de-escalation is really critical and there are times when that might be the appropriate choice. There are some studies in DISCO-MS suggests that in some people MRI activity can recur or increase after stopping treatment. So even though mostly discontinuation can be safe in some patients, in some older patients with MS, you really need to continue monitoring with frequent MRIs with visits and even laboratory tests. So you're not just continuing care, you're just continuing the treatment.

Mitzi Williams, MD, FAAN:

Absolutely. And I love what you just said. We're not discontinuing care even if we potentially discontinue that particular treatment. So this slide is just a reminder that we have to look at response to therapy as well as safety and try to balance those two in our older patients. So we look at the clinical aspects, if there's inflammatory activity, we look at adherence. Are they able to come to their visits or is that a difficulty for them or their care partners? We also look at MRI surveillance, and if we consider deescalating or stopping or discontinuing therapy, we want to have some type of MRI fairly close after we make that decision to monitor to see if there's increased activity. So within six to 12 months.

And then of course we want to have a plan in mind for if we see new lesions, enlarging lesions or enhancing lesions. That would be a reason to change our treatment plan or adjust it. And then of course, anti-CD20 safety monitoring. There are screening labs that we do for hepatitis B before start of therapy. We monitor for infections at each visit and monitor IG periodically. And then of course if they have recurrent or serious infections or clinically meaningfully low IgG, then we want to reassess the treatment plan and see if we need to get any input from our immunology or infectious disease colleagues or if we need to deescalate or discontinue therapy.

Tanuja Chitnis, MD:

And I think this monitoring is so important. And even signs that might not show up on laboratory tests such as complaints of frequent falls or weight loss or illnesses or not bouncing back as they normally would. This might also indicate that this is time to reassess and rethink their treatment plan.

Mitzi Williams, MD, FAAN:

And so what that may look like in the clinic setting is oftentimes actually my patients will bring it up to me, "Hey, Dr. Mitzi, I've been on this treatment for 10 years." Often the question is, how do I know it's still working? How do I know that it's still doing anything? Or they may say, "Due to this factor, whether it's insurance or getting to visits, I'm having difficulty with this, can we reassess?" And so I think that it is a proactive decision on the patient part, but as well as our part to say, "You've been stable, we're having issues with infections, let's reassess." And I always look at every visit as an opportunity to reassess treatment to say, are we still doing the right thing or do we need to consider another option? So the key discussion points when we talk about this conversation is looking at their current stability or lack of stability, so to speak, looking at the benefit to risk ratio depending on their age, comorbidity as well as their other risk factors.

And then comparing what options we have available and then agreeing on the plan for monitoring as well as clear triggers to adjust or reassess the plan. And then of course, we want to support our patient's values and

goals. We want to look at what they would like to accomplish. Obviously staying out of the hospital is a very reasonable thing for our patients to want. And then look at their preferences, make sure they understand to the best of their ability the plan that we have put into place and make sure that if there are clinical trials available for this population, that we also offer that as an option. Because we do know that inclusion matters in clinical trials, and often many of our MS clinical trials have groups such as those from different backgrounds, but also those of certain ages.

Tanuja Chitnis, MD:

That is very true. And I do think we need more trials and more data in older people, and that's really where the questions around risk benefit and efficacy do matter. So I think also communicating risk and really making sure that the patient understands what you mean by these treatments could increase your risk for infections or around other side effects. So one thing I make sure I do is to both say it very clearly and plainly to write down potential adverse events and also refer them to literature and let them know what to do if they feel that things are not going correctly and if they're going down that slippery slope. So making sure they know who to reach out to in our clinic and that they can always contact me if they have a question.

Mitzi Williams, MD, FAAN:

I think it's also important to address fears of discontinuation. I have many patients who feel like they've been fairly stable on therapy and they're actually afraid to stop because they're like, "I've been doing good. I don't want to mess with the plan." And they're concerned that their disease will recur or that they'll have issues when they continue therapy. So it's important again to have those written plans in place in very specific instructions for what are our actionable items, what are we going to be looking for? We're going to closely monitor you. And then if there are issues that arise, we're going to reassess the plan. So in kind of wrapping up this case with Robert. In our older patients with stable MS, we want to make sure that the benefit of the treatment certainly outweighs the risk. And so we want to individualize their plan, look at their goals as well as look at their comorbidities and be open to reassessing the plan if they're having issues with treatments such as increased risk of infection, hospitalizations, et cetera.

So we want to discuss their options in a structured way, whether it is extended interval dosing of treatment, whether it is de-escalation or structured discontinuation, which are all viable options. And then we also want to make sure that we have that follow-up in place, that we have a plan for imaging, whether it's six to 12 months after changing the treatment plan and we want to compare that to their previous imaging. And then we want to have those actionable items. When should they be calling us? When should they be coming in? What are we looking for to determine if we're going to reassess treatment and either re-escalate or re-initiate therapy? And of course, making sure that they're keeping track of infections and that we're checking their IgG on a regular basis and determining if we need our other colleagues to come in and give some input from infectious disease.

Tanuja Chitnis, MD:

And I think a key message around all of this is that changing treatment is not abandoning care. Any change requires a follow-up plan and a rapid path back to effective therapy if there is new inflammatory activity. So we can always switch. There are different options out there and working together is really key.

Mitzi Williams, MD, FAAN:

Absolutely. So we covered a lot of material in a very short amount of time. So we're going to summarize our discussion with our SMART goals, which are specific, measurable, attainable, relevant, and timely. These major points are what we hope that you will take from this presentation and now apply to your practice. And so what can you do in the clinical setting to try to facilitate these conversations and treatment plans with your patients? So within one week, there could be implementation of an anti-CD20 checklist, which talks about all of the different things that need to be done at baseline, when vaccine timing needs to occur, as well as logistics and perhaps target greater than 80% completion in eligible visits by one month. Within two weeks there certainly could be a panel review to flag if there are older patients that exist in your practice on anti-CD20 therapy who've had serious infections or low IgG and/or those who've had breakthrough MS activity and target 100% of flagged cases being reviewed within 30 days.

Within one month, one goal could be documenting a monitoring plan for patients on DMT and target may 90% of those with a documented plan, which looks at clinical function cognition as well as MRI cadence. And within three months, you could consider standardizing shared decision making plus de-escalation documentation and target greater than 75% of de-escalation discussions to include all of those elements in your clinical setting. And then ongoing something to strive toward could be quarterly check-ins to track four metrics including vaccines, IgG monitoring, missed visits and doses as well as serious infections. And then set and report a local improvement target for each quarter. It's important to recognize that solutions are local. These are certainly some suggestions of things that can be implemented, but we want to make sure that we are taking the information that we receive and trying to implement it as much as possible in the clinic setting, which is why these cases were so practical.

So I want to remind our audience that this activity and a wide variety of activities and resources on MS are available on the CME Outfitters website. We would like to thank CME Outfitters for their partnership in creating this education, and we are grateful to Novartis and TG Therapeutics for their independent medical education grant that makes this activity possible. To receive credit for this activity. Please complete the post-test and evaluation. We appreciate your feedback and want to hear from you, tell us what you liked, how we can improve, and what additional topics you would like us to address. Tanuja, thank you for sharing your expertise and experience today.

Tanuja Chitnis, MD:

Thank you, Mitzi, and thanks to everyone for joining us.

Mitzi Williams, MD, FAAN:

Yes. Thank you to our audience and we look forward to seeing the ways you are able to translate this into action in your own practice.

