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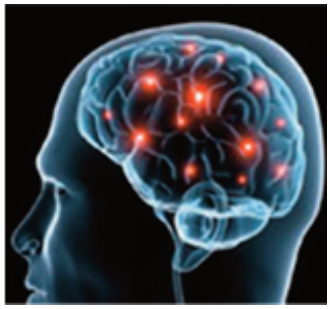

VOLUME 1 — ISSUE 2: TRANSCRIPT

Featured Cases: Personalizing DMT Regimens/The Risks Of Medication Non-Adherence

Our guest authors are Arun Venkatesan, MD, PhD, Associate Professor of Neurology and Scott Douglas Newsome, DO, at the Johns Hopkins University School of Medicine.

After participating in this activity, the participant will demonstrate the ability to:

- Identify when patients with MS should start or switch disease modifying therapies.
- Recognize important clinical and paraclinical factors of disease activity in MS.
- Describe the factors that may play a role in non-adherence to MS treatment.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topics of personalizing DMT regimens and the risk of medication non-adherence in the format of case-study scenarios for the clinical practice. This program is a follow up to Volume 1, Issue 1 *eMultipleSclerosis Review* newsletter — Personalizing DMT Regimens/The Risks of Medication Non-Adherence.

Unlabeled/Unapproved Uses
Dr. Venkatesan and Dr. Newsome have indicated that there will be references to unlabeled/unapproved uses of drugs or products in today's discussion, including specifically rituximab, daclizumab, ocrelizumab, and anti-LINGO therapies.

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Guest Faculty Disclosure
Dr. Venkatesan has indicated that he has served as a consultant/advisor to MedImmune. Dr. Newsome has indicated that he has served as a consultant/advisor to Biogen, Genzyme, and Novartis, and that he has received grant/research funding from Biogen and Novartis.

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CME INFORMATION ⇩ **PROGRAM BEGINS BELOW**

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MR. BOB BUSKER: Welcome to our first *e*MultipleSclerosis Review podcast.

Today's program is a follow-up to our newsletter issue *on Personalizing DMT Regimens and the Risks of Medicine Non-Adherence*. With us today are that issue's authors, Dr. Arun Venkatesan, associate professor of neurology, and Dr. Scott Newsome, assistant professor of neurology. Both our guests are from the MS Center at the Johns Hopkins University School of Medicine.

*e*MultipleSclerosis Review is presented by the Johns Hopkins University School of Medicine. This program is supported by educational grants from Mallinckrodt Pharmaceuticals and Novartis Pharmaceuticals Corporation.

Learning objectives for this audio program include:

- Identify when patients with MS should start or switch disease modifying therapies,
- Recognize the important clinical and paraclinical factors of disease activity in MS.
- Describe the factors that may play a role in non-adherence to MS treatment.

Dr. Newsome has indicated that he has served as a consultant/advisor to Biogen, Genzyme, and Novartis and that he has received grant/research funding from Biogen and Novartis. Dr. Venkatesan has indicated that he has served as a consultant/advisor to MedImmune. The faculty have indicated that will be references to unlabeled/unapproved uses of drugs or products in today's discussion, including specifically rituximab, daclizumab, ocrelizumab, and anti-LINGO therapies.

MR. BUSKER: I'm Bob Busker, managing editor of *e*MultipleSclerosis Review. Dr. Venkatesan, Dr. Newsome, thank you for joining us today.

DR. ARUN VENKATESAN: Really glad to be here, Bob.

DR. SCOTT NEWSOME: Yes, thank you, Bob. We look forward to this program.

MR. BUSKER: Our focus today is on personalizing DMT therapies for patients with MS and how patient non-adherence to DMT regimens can affect outcomes. Dr. Venkatesan, let's begin with a patient scenario.

DR. VENKATESAN: This 23 year old woman presented with several days of right eye pain with horizontal eye movements, along with some blurring of the right eye. She had not had any previous neurological symptoms and reported no relevant medical or family history. On examination she was found to have a right afferent pupillary defect, and decreased visual acuity in the right eye — 20/200 — along with some asymmetric hyperreflexia in the extremities. A brain MRI was ordered and it demonstrated two hyperintense T2 lesions, one in the periventricular area and one in the juxtacortical area. In addition, she was noted to have enhancement of the right optic nerve on MRI.

She underwent some serologies, which included ANA, ESR, CRP, SSA, SSB, vitamin B12, TSH and Lyme, all of which were negative or unremarkable.

MR. BUSKER: Dr. Newsome, your impression of this patient — and what would determine your decision to start disease modifying therapy?

DR. NEWSOME: This type of patient, whom we refer to as having clinically isolated syndrome, is very common in the clinic. The purest definition for clinically isolated syndrome is an initial and isolated episode that occurs within the central nervous system and is often associated with inflammation and demyelination. CIS is synonymous with the first attacks of multiple sclerosis, which is extremely important because studies in this group of patients have shown that the earlier we can get them onto disease modifying therapies, the better they will fare over the long haul. Some of the decision-making whether we start someone with CIS on a disease modifying therapy is whether their CIS is classified as low risk or high risk according to what the MRI is demonstrating. In this patient, not only did she have an enhancing right optic nerve that was causing her symptoms, she also had two hyperintense lesions in regions of the brain that are typical for a demyelinating disease, and specifically multiple sclerosis. So this patient in my mind would be categorized as high risk CIS.

MR. BUSKER: And low risk CIS?

DR. NEWSOME: Low risk CIS is someone who presents similarly to this patient but has a normal brain MRI. The differences between the two are important to differentiate because of treatment. For our patient, who is at high risk of developing clinically

definite multiple sclerosis that untreated could result in disability, we would strongly consider initiating disease modifying therapy; whereas with a patient who is at low risk, we may take a watchful waiting approach, repeat MRIs over time, and if new lesions appear or the patient has a clinical attack, we would likely start them on a disease modifying therapy.

MR. BUSKER: So in the patient you just described — ?

DR. NEWSOME: With this patient I personally would pursue a disease modifying therapy because she has high risk CIS and eventually will go on to develop a clinical attack or new MRI lesions that will confirm that she has clinically definite MS. From some CIS treatment studies, we know that getting people on treatment earlier will help prevent them from developing clinically definite MS and thus decrease disability over time, as we've seen clinically.

MR. BUSKER: Dr. Venkatasan, if a disease modifying therapy is started in this patient, which DMT agent would you choose and why would you choose it?

DR. VENKATESAN: In a situation like this, the patient clearly does have CIS, and the data suggests that early initiation of treatments would likely be beneficial. For choice of agents, several double blind, placebo-controlled trials in CIS have demonstrated a reduced risk of conversion to clinically definite MS. The interferons glatiramer acetate, teriflunomide, as well, have been demonstrated to reduce this risk of conversion. Several interferons, as well as glatiramer, have been FDA approved specifically for CIS. So I think in a situation like this, one of those platform injectables would be a reasonable option to begin with.

MR. BUSKER: Dr. Newsome, what would prompt you to do to that in this patient?

DR. NEWSOME: Given this patient's low disease burden from the start, one may consider not switching early unless there is evidence of another relapse that she doesn't recover well from, she starts to have frequent relapses in short timeframes, or her next relapse targets an eloquent area of the nervous system like the spinal cord, then one would certainly want to switch therapies.

When we are discussing switching therapies with all the currently available treatments, it's important to have at least six months of continuous treatment on any of the agents before you can say that the patient has a treatment failure. Of course, that doesn't include people who are have poor tolerability to the medication — for example, if someone has injection site reactions or they're on a medication that's being taken more than once a day and they're forgetting their second pill during the day and they're not adhering to the medication, that certainly is in my mind a treatment failure because of nonadherence and poor tolerability.

If we look at the clinical and paraclinical disease markers, switching therapies sooner makes sense in the more aggressive phenotypes of MS. A number of studies have shown that males, older age at onset, African-American, spine involvement, frequent relapses from onset, poor relapse recovery, high lesion burden on MRI, and multiple spinal cord lesions would be key factors in determining that we need to watch this person closely and have a low threshold to switch. I'm curious, Arun, if we should consider other factors if we're going to switch therapies.

DR. VENKATESAN: Thanks, Scott. I think many of the factors you refer to fit nicely into a framework for reasons to switch disease modifying therapies. Those reasons could include factors surrounding efficacy or they could include factors surrounding safety. They could include patient related factors, as you mentioned, difficulty with adherence and so on, or there could be payer related factors that might necessitate a change in treatment.

And one of the other major pieces to consider is patient preference and the need to treat each patient as an individual. This is underscored by one of the studies we have included in our newsletter, by Salter, et al, "Patient Perspectives on Switching Disease-Modifying Therapies in the NARCOMS Registry."[1]

I want to highlight one of these factors, safety, because some interesting data on safety is coming out for some of the newer agents, specifically about dimethyl fumarate and its association with leukopenia and lymphopenia.

The data suggest that patients who have prolonged leukopenia or lymphopenia might be at risk for opportunistic infections such as PML (progressive

multifocal leukoencephalopathy). One case of PML has been reported in the literature and another one many of us have just heard about in which patients treated with medication have this prolonged low white blood cell count and developed PML. That's just one example of safety factors and safety concerns we need to consider. We've laid out a number of safety concerns for some of the newer agents in the newsletter, as well.

MR. BUSKER: Thank you for that case and that discussion. We'll return, with Dr. Scott Newsome and Dr. Arun Venkatesan from the John Hopkins MS Center in just a moment.

MR. BOB BUSKER: Hello. This is Bob Busker, Managing Editor of *e*MultipleSclerosis Review.

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MR. BUSKER: Welcome back to this *e*MultipleSclerosis Review podcast. Our guests are Dr. Scott Newsome and Dr. Arun Venkatesan from the MS Center at the John Hopkins School of Medicine. And our topic is personalizing DMT therapies and the risks of medicine non-adherence.

Let's continue with the same patient we've been discussing — a 23 year old woman with an original diagnosis of high risk CIS who was started on a DMT. Dr. Venkatesan, please give us a follow-up on this patient.

DR. VENKATESAN: Initially the patient did well and followed up with her clinician regularly; however, three years later she had a partial attack of transverse myelitis that resulted in a foot drop and poor penmanship, as well as some dysfunction of her bladder. This was not in the setting of a preceding or current infectious trigger, and her MRI revealed a new enhancing lesion in the cervical spine with otherwise stable lesion load. She reported strict compliance with her disease modifying therapies.

MR. BUSKER: Dr. Newsome, is this patient now considered to have MS?

DR. NEWSOME: This patient would fulfill the revisement criteria for making a diagnosis of clinically definite multiple sclerosis, because she now fulfills both separation in time and space for a clinical attack and a new lesion on MRI. So yes, she does have multiple sclerosis now. With the revised criteria, if someone presents with clinically isolated syndrome, we can make a definitive diagnosis of MS based on one clinical attack and one brain or spine MRI. If someone has an asymptomatic enhancing lesion that's not in the area that's causing the person's isolated symptom or syndrome, then with the revised criteria we can say this person has multiple sclerosis. Of course, that's if we've ruled out the mimickers. I mention that because it speaks to the data showing that people who start treatment earlier may do better long-term.

MR. BUSKER: Does she need at this point to switch therapies?

DR. NEWSOME: This is a bit tricky because we know that the current therapies we have are not cures, and some are more effective than others. If someone is put on a disease modifying therapy and doesn't have an attack for three to five years, maybe we don't necessarily need to switch them, and just have a lower threshold to switch them on their next clinical attack or they have symptomatic breakthrough disease activity on MRI.

For this person, though, given the location of the clinical attack, the spinal cord, that makes me quite nervous moving forward that if we don't switch her to a more effective therapy and she has another attack to the spinal cord that could leave her with disability.

My personal bias for this patient, especially since we have more than 10 FDA approved therapies, is to switch her to a different disease modifying therapy.

MR. BUSKER: How would you identify disease progression and what would determine actual treatment failure?

DR. NEWSOME: I already touched on some of the important clinical and paraclinical factors that help us stratify someone's risk of having a more aggressive MS phenotype. Generally, I will think of these same

factors when someone presents with the possibility of having disease progression or treatment failure. For example, if someone who is on a disease modifying therapy has not recovered well from a transverse myelitis attack and now has a foot drop, that could be a treatment failure —depending, of course, on whether they're adhering to the drug.

A number of groups have tried eloquently to define what suboptimal treatment response is, and I will pass it over to Arun to speak to that.

DR. VENKATESAN: Thank you, Scott. So just a few words about suboptimal treatment response. It's tough, trying to define this. MS is highly variable in its clinical course and progression, and monitoring disease activity is not easy, so it can be difficult to define suboptimal treatment responses.

Having said that, a number of experts have tried. In fact, a consensus statement was published a few years ago in an article whose first author was Dr. Coyle, C-O-Y-L-E, in *Multiple Sclerosis*, that tried to identify what was consistent with suboptimal response.[2] They concluded that if there was a relapse at a year after treatment, and especially if there was a second relapse while on treatment, that would certainly prompt evaluation for a possible suboptimal response. In addition, there were MRI findings that could prompt consideration, including what they considered to be a significant increase in T2 lesion load of 20% to 30%, or the development of several new enhancing lesions while on treatment. Those again could be considered markers of suboptimal response.

Finally, the consensus participants felt that a one point per year increase in progression on the EDSS (expanded disability status scale) would be an appropriate signal for treatment failure, as well.

DR. NEWSOME: I agree, Arun, that it's very challenging to discern what is suboptimal treatment response.

More recently at one of the large MS conferences, a survey went out looking at the consensus of US neurologists and seeing their practice patterns. That study looked at individuals from a practitioner point of view threshold to recommend switching therapy. There was wide consensus that if a patient had two or more new T2 lesions or one or more new gadolinium enhancing lesions one year out from starting a treatment, the majority of practitioners would recommend switching.

In the past, I think MRI was underused for monitoring treatment response in following patients over time. I think the MRI is a very sensitive tool to help us define whether someone has a treatment response or suboptimal treatment.

MR. BUSKER: I want to note to our listeners that the topic of using MRI — not only in making the diagnosis of MS but also in following patients over time to determine medication response —will be the focus of an upcoming issue of *e*MultipleSclerosis Review. Now I'd like to turn our discussion to medication adherence. Dr. Newsome, what does the evidence show about patients not complying with their prescribed DMT regimens?

DR. NEWSOME: Several large disease modifying therapy adherence studies over the years have looked at adherence. In reference to injectable therapies specifically, three studies that I'm aware of looked at this question: Treadwell and colleagues, Devonshire and colleagues, and Arroyo and colleagues.[3-5] Those studies had very large sample sizes, with the lowest in the 200s and the highest almost 3,000 patients.

These studies showed that anywhere between 18% to 39% of patients were nonadherent, which has huge implications for a patient. We've all seen the consequences of nonadherence to a medication. Some of those consequences include relapses, sometimes more severe relapses because available therapies can help not only prevent relapses, but if a relapse occurs, there is an observation that the relapse is not as severe.

New lesions shown on MRI can translate into long-term disability, so there are huge implications for nonadherence. MS is analogous to hypertension or diabetes, in terms of nonadherence to treatment, because nonadherence in those conditions could result in a stroke, a heart attack, or kidney disease.

I'd like to ask Arun, are any studies out there that can help us understand better what are the impacts of adherence in clinical and economic domains?

DR. VENKATESAN: I'd be glad to speak to that, but first I want to build on what you were mentioning

about MS being analogous to some of these other chronic conditions such as hypertension or diabetes. I think the other analogy there is that patients who are not adherent to medications may not immediately feel the consequences of that nonadherence, and it may take some time for serious clinical manifestations to arise as a result of nonadherence, and I think we can say the same about MS.

I want to highlight one study published by Tan and colleagues a few years ago that looked at the impact of adherence to disease modifying therapies in MS.[6] They identified about 2,500 patients with MS in an administrative database and used some of the data in that database to estimate the degree of patient adherence, using something called the medication possession ratio, which is a metric for estimating adherence. I won't go into the details here, but suffice it to say that they found a very clear correlation between adherence to DMTs and several clinical outcomes.

First, they found that compared to the nonadherent group, those who were adherent were much less likely to have MS-related inpatient hospitalization. The odds ratio was about .63 for patients who were adherent. The second major finding was that relapses were also significantly decreased in those who were adherent, and the odds ratio there was .71.

These are very important findings, and I think that they clearly speak to the need for adherence to disease modifying therapies in this chronic condition.

MR. BUSKER: I want to remind our listeners that links to the studies our guests have been mentioning are available in the transcript version of this podcast. To continue, Dr. Newsome, what are some of the most common reasons for nonadherence among the patients on DMTs?

DR. NEWSOME: One of the more common things I hear — and a number of studies have supported this — is forgetting to take the medication. Studies have shown not just in MS but in other disease states that the more frequent the medication administration, the higher the nonadherence rate.

With respect to injectable therapies, because there still are a lot of people on injectable therapies, injection site reactions, seem to be one of the main culprits for nonadherence.

One other point that I'd like to mention is a lack of perceived benefits. This probably trumps many of the other things that I've already mentioned and it goes back to educating patients about what these therapies are there for. The therapies that we currently have are not going to necessarily improve someone's function; they're preventative agents. We need to be very clear to patients up front that the point of these therapies is to prevent new things from happening, they're not going to make your numbness and tingling better.

If we're upfront with patients and honest how these therapies are supposed to work, at least in my own practice I've seen that improve adherence.

MR. BUSKER: Dr. Venkatesan? Your thoughts.

DR. VENKATESAN: I want to speak briefly about the importance of patient education, which is highlighted by a nice study that looked at patients with relapsing-remitting multiple sclerosis who had been receiving immunomodulatory therapy for three or more months. It turns out that those who considered themselves well informed about their disease and about treatments for their disease were much more likely to adhere to the regimen. This issue of communication between the physician and the patient, and making sure that everybody is on the same page about expectations for the medications, is absolutely crucial for adherence.

MR. BUSKER: One final question, doctors: Patients who have failed or can't tolerate any of the currently available DMTs. Dr. Newsome?

DR. NEWSOME: Unfortunately, a group of patients will fail or be unable to tolerate the majority of currently approved FDA therapies, and given the patient demographics and the disease severity in those individuals, we will often use therapies that more broadly suppress the immune system, including B cell monoclonal antibodies like rituximab. But if someone has failed therapies, then looking into clinical trials, a number of stem cell therapies are being done even here in the US, more options are available outside of the current FDA approved therapies.

DR. VENKATESAN: Scott, I'd like to mention a couple of other treatments are in the pipeline. One is daclizumab, a humanized monoclonal antibody against CD25 which is expressed on immune cells.

The mechanisms of daclizumab are incompletely understood, but at least one of the mechanisms is by expansion of a natural killer cell population that seems to provide efficacy for this drug in the setting of MS. A couple of phase II studies and a current phase III study have demonstrated efficacy in reducing relapses and on MRI measures.

Another treatment is ocrelizumab, a humanized monoclonal antibody against CD20. Similarly to rituximab, it depletes circulating B cells. It may be safer and less immunogenic than rituximab, but like rituximab it does appear to reduce both clinical and radiological measures of disease in MS.

Finally, I want to mention anti-LINGO therapy. This is quite exciting and targets a completely different pathway than many of the immune modulatory agents. The pathway targeted here is remyelination. LINGO-1 is a key negative regulator of differentiation of oligodendrocytes and of myelination. If you overexpress LINGO, oligodendrocyte differentiation and myelination is inhibited. And if you interfere with LINGO-1 activity, the converse occurs, so oligodendrocyte differentiation and myelination are enhanced. This has been shown in animal models and cell culture and in experimental autoimmune encephalitis, one of the prominent animal models for multiple sclerosis, where blocking LINGO function can promote functional recovery in EAE, improve axonal integrity, and improve axonal myelination.

This has spawned a lot of interest in these types of approaches in MS. A current study, the RENEW study, is looking at the efficacy of anti-LINGO-1 antibody in patients with a first episode of acute optic neuritis. The initial reported results do look promising for visual function and some other secondary endpoints of visual measures in the setting of anti-LINGO therapy. So there's going to be a lot of excitement about the possibility of such approaches in MS.

MR. BUSKER: Doctors, I want to thank you for today's discussion. Let's wrap thing up now by reviewing the key points of today's podcast in light of our learning objectives. So to begin, Dr. Newsome — identifying when patients with MS should start or switch disease modifying therapies.

DR. NEWSOME: Without a doubt patients with high risk clinically isolated syndrome and clinically definite multiple sclerosis of the relapsing phenotype should start on a disease modifying therapy. This is based on not only our experience in the clinic but also on supporting clinical trial data. Starting therapy earlier rather than later does seem to help prevent disability and relapses.

With respect to switching therapies, you have to look at the individual person. If they are recovering poorly from an attack, or if there's a number of new lesions on MRI despite being adherent to a medication, one needs to consider switching therapies. Of course, if someone is poorly tolerating a therapy because of a side effect, or they're just not adherent for reasons that are not clear, that would also be a reason to switch therapies.

MR. BUSKER: And our second learning objective: recognizing the clinical and paraclinical factors that determine disease activity in MS.

DR. NEWSOME: When we look at the clinical factors of disease activity, we're considering primarily relapses, specifically what is the severity of someone's relapse, where is the location of the attack, does an individual recover from a relapse, and how often do these relapses occur — once every few years or multiple relapses even within the same year.

Most of the paraclinical factors surround imaging, specifically MRI. The first thing we think when we see a person is, what is their lesion burden at presentation? Also, are there lesions that are in eloquent areas of the nervous system like the spinal cord? We look at the clinical and paraclinical factors, especially up front in someone who has multiple sclerosis, because that can direct how we treat a patient, how aggressive we will be based on these factors. The higher the lesion burden, the more severe the relapse with poor recovery, so I'm thinking from the get-go we need to be aggressive and maybe use a more potent therapy from the start, because down the line we want to prevent disability.

MR. BUSKER: And finally: factors that might play a role in the non-adherence to MS treatment.

DR. NEWSOME: A number of factors play a role in nonadherence, some of which are driven by the patient. Some of those factors could include just forgetting to take a medication, or a patient's lack

of perceived benefit for a medication. If someone is on an injectable therapy, maybe they're having unpleasant adverse injection site reactions, so they decide to stop. The important thing from a provider perspective is to try to identify each individual's roadblocks to adherence. Once you can identify those one or two factors, you can help address the adherence issue. This speaks to the strength of the physician/patient relationship; the more education we can provide to the patient and the expectations for the treatment moving forward, the improved adherence will be.

I have had personal experiences where the more time I've spent educating a patient, the better they seem to do with adherence over the long haul. We know from the studies presented today that when a person adheres to their medication, are improved outcomes; fewer, less severe relapses; fewer hospitalization; and lower overall medical costs.

MR. BUSKER: Dr. Scott Newsome, Dr. Arun Venkatesan, thank you both for participating in this *e*MultipleSclerosis Review Podcast.

DR. VENKATESAN: So glad to participate.

DR. NEWSOME: Thank you, Bob.

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