Individualizing Therapy and Optimizing Treatments in MS

A **Neurology Exchange** Grand Rounds Program

FACULTY SLIDE REVIEW

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Slide 1 – Title Slide

Aaron Miller, MD: This is Dr. Aaron Miller, and I'm happy to be speaking with you in this talk that is titled "Individualizing Therapy and Optimizing Treatments in Multiple Sclerosis."

This activity is jointly provided by the Potomac Center for Medication Education and Rockpointe, and it was supported by an educational grant from EMD Serono.

Slide 2 – Program Information

Slide 3 – CME Information

Slide 4 - Educational Objectives

The educational objectives now appear before you, and I'll leave you to read them on your own.

Slide 5 – Polling Question

Slide 6 – Polling Question

Slide 7 - Multiple Sclerosis: An Immuno-genetic Disease

Let's talk a little bit about the etiology of multiple sclerosis. This is regarded now as a rather complex immunogenetic disease that results from the interplay between a number of genetic predispositions and a number of environmental factors. The exact role of each of these elements is not quite clear.

We regard MS to be an autoimmune disorder and there are a variety of genetic factors – now more than 100 different alleles have been implicated as risk factors for MS – and almost all of these relate to the immunological system. The most important genetic factor remains the presence of the HLA-DR2 (DR ß1*1501) allele.

Twin studies indicate that there's a high rate of concordance between monozygotic twins. If one twin has MS, there's about a 35% chance that the other twin will have it. But, on the other hand, since there's a 65% chance that the other twin will *not* have MS, there clearly are environmental factors at play here, as well.

And we have a number of factors that have been identified as risk factors. I don't believe any of them are specifically causative but they probably play a role in determining whether or not a susceptible person is likely to get MS; these include some microbial agents, perhaps Epstein-Barr Virus. We know that low vitamin D levels increases your risk for multiple sclerosis. Smoking increases your risk. And some more recently emerging and less well-established risk factors such as high salt intake and high body mass index seem to be risk factors. There's a lot of interest now in the role the microbiome of the gut may play, and this is something we're going to hear much more about in the near future, I think.

Slide 8 – Additional Disease Modifiers

So there may be a role, also, a diet that's rich in polyunsaturated fatty acids. I've already mentioned the role of body mass index. And melatonin levels may also play a role.

Slide 9 - A View of MS Immunopathogenesis

Let's speak very briefly, about the MS immunopathogenesis. We think that the problems begin in the peripheral blood where there is activation of Th1, Th17 helper cells, perhaps through the process of molecular mimicry. And then these sensitized cells need to adhere to the wall of the vascular endothelial cell in order to penetrate through the blood-brain barrier, into the central nervous system. This may involve the role of matrix metalloproteinases in facilitating that entry. And once these cells do get into the central nervous system, they are reactivated, proliferate further, and result in tissue damage.

Slide 10- Pathology of MRI Gd-enhancing Lesion

This damage is readily visible in conventional MR imaging, both as T2 hyperintense lesions, as seen in the left-hand portion of these two MR images, and the active inflammation is indicated by leakage of gadolinium or contrast enhancement, and that reflects the perivascular inflammation, which is demonstrated in the histopathology here, and ultimately results in demyelination, as you see in this Luxol Fast Blue slide where the white area shows the demyelinated zones.

Slide 11 – Immunopathogenesis of MS

Now, ultimately, clinical outcome of multiple sclerosis probably involves the interplay of two distinct processes – one is inflammation, which we've talked about a moment ago; the second involves a neurodegenerative process. But it's not as if inflammation ceases altogether and neurodegeneration then takes place; rather, we think now that this neurodegenerative process is beginning even in the very earliest stages of MS.

There is also some capacity of the nervous system to remyelinate but we need to find better ways to promote this remyelination in order to heal the nervous system. So, in summary, we have an active inflammatory process at the beginning. This results not only in demyelination but also promotes axonal loss, which can be demonstrated in the very earliest stages of MS.

Slide 12 – Case Presentation

Let's turn now to a brief case presentation. This is a 27-year-old man who was previously healthy. He develops weakness and tingling in both legs, imbalance, and impaired bladder emptying two weeks after an upper respiratory infection and possible fever. His past medical history is positive for Lyme disease at age 12 that was treated with antibiotics. His family history is positive for MS in his paternal grandmother.

Slide 13 - Case Presentation *(continued)*

His brain MRI shows multiple T2 hyperintensities including periventricular ovoid-shaped lesions, juxtacortical lesions, and a cerebellar lesion. In addition, he has multiple very small gadolinium-enhancing lesions.

The cervical spine MRI shows multiple T2 hyperintense lesions, and the spinal fluid is positive for oligoclonal bands, which are not present in the serum, as well as an elevated IgG index.

Slide 14 – MRI Images

Here are examples of his MRIs. In the upper two panels, you can see images from the, T2 FLAIR sequences showing multiple hyperintense lesions and, in the lower panels, T1 gadolinium-enhanced images showing multiple small gadolinium-enhancing lesions.

In the latest version of the McDonald Criteria, which were published in 2010, this patient would now meet criteria for definite multiple sclerosis. He previously might have been considered to have a clinically isolated syndrome because this was his first clinical episode of symptoms, and he'd never previously had an MRI scan. However, with the 2010 iteration of the McDonald Criteria, one is now permitted to make a diagnosis of definite relapsing-remitting MS at the time of the first clinical presentation. If the MRI shows simultaneously the presence of T2 hyperintense lesions and a gadolinium-enhanced lesion with the caveat that these lesions not be the ones responsible for the patient's clinical symptoms. So, in this patient, who presents with clinical manifestations of a myelopathy, the presence of gadolinium-enhancing lesions in the brain, along with the presence of numerous T2 hyperintense lesions, allows one to label him as definite MS.

Slide 15 – Polling Question

Slide 16 - 1996 vs 2013 MS Phenotype Descriptions: Relapsing-Remitting Disease

Now, fairly recently, there has been some revision of our MS phenotype descriptions. For the last 20 years, we had been using four categories of disease: relapsing-remitting; primary progressive – those patients who get worse from the get-go; secondary progressive – those patients who had, initially, relapses and then gradually worsened; and, finally, a relatively rare category called progressive relapsing MS -- these were patients who began as if they were going to have primary progressive MS but then developed relapses.

In 2013, an international group revised these phenotypes and further clarified how we should best describe people with MS. So we still retain the term "clinically isolated syndrome" for those patients who don't meet the imaging criteria for dissemination in time at that first presentation, but those who do or patients who've had multiple clinical attacks will be called "relapsing-remitting disease." It's now recommended that we classify patients in terms of disease activity. So in looking at the category of relapsing-remitting disease, a person could be categorized as "active" if they have had either clinical relapse and/or MRI lesions, so this could be either gadolinium-enhanced lesions or a new T2 lesion compared to a prior scan. So you always have to specify the timeframe, so one might say, "A patient has relapsing-remitting disease that has been active on MRI scan within the past year." And the committee that made these revised phenotypic descriptions urged that patients in the inflammatory stage of the disease, in the relapsing stage, should have an MRI once a year.

Slide 17 - 1996 vs 2013 MS Phenotype Descriptions: Progressive Disease

When we turn to progressive disease, we still retain the terms "primary progressive" and "secondary progressive" disease, but now we classify these progressive phenotypes as either "active," again, meaning a superimposed clinical relapse, or "new MRI activity." And we also classify them in terms of whether or not they have had progressive disease based on a clinical evaluation. So a person who formerly would have been called "progressive relapsing disease" would now be called "primary progressive disease with activity."

Slide 18

This cartoon is going to show you the various stages of MS. So we know there's a preclinical stage and, sometimes, we see patients that we classify as having a radiologically isolated syndrome; this would be a person who has undergone an MRI scan with no expectations that they might have MS. They might have been imaged because they had a minor head injury or perhaps because of headaches, and we see a pattern on MRI that looks characteristic of MS, and we call that the radiologically isolated syndrome.

We've already talked a bit about the *clinically* isolated syndrome and, in that stage and moving on, then, into the relapsing-remitting stage of the disease, as you can see from the lower vertical lines in this curve, which indicates MR activity, that there are many more episodes of new MR

activity than we can see in terms of clinically recognizable, relapses, marked here in the orange circles.

As time goes on, the diagnosis is established, a patient's visibility may worsen because of unresolved relapses, *or* the patient may then transition to a stage of secondary progressive disease. At that point, characteristically the frequency of new MR lesions diminishes but brain volume shrinks, as you can see in this purplish line and the burden of MRI activity in terms of T2 hyperintense lesions increases. Also, the patient, not uncommonly, will experience some worsening cognitive function as the motor disability also tends to increase.

Well, that's a little bit of information about the categorization and the description of MS.

Slide 19 - Existing and Emerging MS Therapies

Fortunately, now, we've entered an era where we have a dramatic number of choices in terms of disease-modifying therapy, at least for relapsing forms of MS, and the next portion of this talk is going to focus on these disease-modifying treatments for relapsing MS.

At this point in time, we have not yet had any drugs approved for the treatment of progressive MS with the exception of mitoxantrone, which is approved for secondary progressive MS but is very, very seldom used because of toxicity. One drug that will be discussed later -- ocrelizumab – has now had a positive trial in primary progressive MS but is not yet approved by regulatory agencies.

Slide 20 - Predicting the Course of MS

Given that we have so many options, it would help to understand a bit about the prognosis of an individual patient because that might influence our choice of drug, whether or not we should begin with a more aggressive but somewhat riskier drug, or perhaps opt for an older, very, very safe but not quite as effective agent. And even though traditionally, we have been reluctant to give a prognosis in an individual patient, we do actually have a lot of clues, and I think on a statistical basis, we can have a sense as to whether a patient falls into a good prognostic category or a bad prognostic category.

We can learn a lot from the clinical features of the onset bout. So if the patient has motor symptoms, they're likely to do worse than if they have sensory episodes. If they have multiple lesions of the central nervous system affected from the get-go, that's worse than a monosymptomatic presentation. And although it's relatively uncommon, early bladder involvement portends a poor prognosis.

Virtually every series in the literature has demonstrated that these patients do not have nearly complete recovery from their initial attack, that is an ominous sign. And if they have a short interval between the first and the second attacks – and that usually means less than two years – that tends to herald a worse prognosis.

Slide 21 - Prognosis

More recently, we've begun to amass MRI evidence that may suggest a worse prognosis, and this is from a series from the National Institute of Nervous Diseases in London, a cohort that's been followed now out about 20 years. But this shows that, in these patients who initially had clinically isolated syndrome, if they had zero lesions at the initial presentation, they had only about a 5% chance of reaching an EDSS of 6, meaning they need an aid to walk by 20 years. In contrast, if they had 10 or more lesions by 20 years, nearly half of these patients needed assistance to walk.

And then *another* study showed that patients who met three out of four Barkhof Criteria – these are a set of criteria that were used in the early iterations of the McDonald Criteria to meet evidence for dissemination in space if you met three or four of those four criteria, you tended to

do worse at five years than if you met fewer criteria. So if one amalgamates the clinical information and the MR information, I think one has a reasonable sense of knowing a patient's potential destiny.

Slide 22 – Yogi Berra

However, keep in mind the words of my favorite philosopher, the late Yogi Berra, who said, "The future ain't what it used to be." And the reason I emphasize that is that all of these prognostic data have been obtained in patients who are not treated with disease-modifying therapies, and we think that the advent of the therapeutic era is making a change in this prognosis.

Slide 23 - Making Treatment Decisions: Considering the Benefits and Risks

When it comes down to actually making a treatment decision, there are lots of things to be considered in assessing the relative benefits and risks of a particular drug. So, of course, safety is paramount, and efficacy is critically important, but patients regard tolerability as an extremely important element and may rank it even higher than these other important elements. And then, sometimes, pregnancy will be an issue. Unfortunately, cost and insurance considerations all too often play a role. Issues of patients' convenience and ability to follow a monitoring regimen – all of these things can come into play in selecting the right drug for a particular patient.

Slide 24 – Polling Question

Slide 25 - BEYOND: IFNβ-1b 250 or 500 µg vs Glatiramer Acetate

Well, the conventional 20-milligram-per-day *daily* dose of glatiramer acetate has been compared in two trials head to head against high-dose, multiply dosed interferon beta.
I show here the data from the BEYOND Trial which compared interferon beta-1b to glatiramer, and similar results were obtained in a trial of thrice-weekly interferon beta-1a subcutaneously. And, here, you can see that there is no difference between the annualized relapse rate in the patients taking glatiramer compared to those taking interferon beta-1b, shown in the left-hand panels, and also no difference in progression. But, in the right-hand panels, you can see that the red vertical bar shows that there was more MRI activity and a greater change in T2 volume in the patients treated with glatiramer than in those treated with interferon beta.

Slide 26 - Interferon Beta

We're now going to review the respective agents that we have as options for disease modification. So, probably, most of you are familiar with the interferons which have been around now for 20-plus years in various preparations which you can read in this slide, varying in frequency, as well as route of administration.

The one new player on the block here is the PEGylated interferon beta-1a which now needs to be given subcutaneously only every other week. There is the possibility that the flu-like symptoms with this preparation may be a bit more persistent and perhaps a bit more intense than that with some of the other interferon preparations.

Slide 27 - Glatiramer Acetate

A relatively recent change in the administration of glatiramer acetate has occurred – a couple of recent changes. First of all, we have now seen the introduction of a 40-milligram three times-a-week preparation of glatiramer acetate and this was tested against placebo. And, as you can see in the lower left-hand portion of the slide, that there was a 34.4% reduction compared to placebo, which compared to what was obtained in the earlier 20-milligram-daily placebo-controlled trials. I want to emphasize there have been no head-to-head trials between the three times-a-week preparation and the daily preparation.

In the lower right-hand portion of the slide, you can see also that the 40-milligram glatiramer acetate preparation did reduce the number of gad-enhancing lesions and the number of new or enlarging T2 lesions, but this is a relatively modest decrease when you compare it to what we've seen with a number of other agents.

Another new wrinkle in the glatiramer acetate landscape has been the introduction of the first generic preparation and this preparation is only available in a 20-milligram-daily preparation. And the FDA has allowed this drug on the market following generic rules which require only a pharmacologic equivalence and now clinical trials in humans. We *do* expect the introduction of subsequent generic preparations but, so far, there is only one on the market.

Slide 28 - Fingolimod (FTY720): Mode of Action

Turning now to the oral agents, in the order in which they were approved by the U.S. Food and Drug Administration, we begin with fingolimod. Fingolimod is a sphingosine 1-phosphate modulator and activation of that receptor is required for lymphocytes to exit from peripheral lymph nodes. So what fingolimod does is results in the internalization of this S1P receptor and, therefore, traps the lymphocytes in the peripheral lymph nodes, so, as a result, one sees very low lymphocyte counts in the peripheral blood. This drug is quite effective. It reduced the relapse rate by about 54% in one pivotal Phase III trial and a little bit under 50% in a second Phase III pivotal trial, and also reduced the rate by 50% greater than weekly intramuscular interferon beta-1a.

Slide 29 - Managing Patients on Fingolimod

And the drug is quite well tolerated, but there are a number of steps that have to be followed before a patient can be initiated on this agent. So you need a baseline CBC and liver panel. You have to make sure that the patient doesn't have any problems in atrioventricular conduction or pronounced bradycardia. You need a baseline ophthalmological examination because about one in 250 patients will develop macular edema, which can impair vision; this is generally reversible if detected early so you need a baseline eye exam. Also recommended is a baseline dermatological examination and establishment that the patient has some varicella immunity. If there is no definite evidence of varicella immunity, the patient should receive immunization against varicella at least one month prior to initiating fingolimod therapy.

Then, when you initiate therapy, six-hour monitoring is required because of the potential for bradycardia. Once the patient begins treatment, you need to continue to follow the CBC and liver panel. You get an ophthalmological follow-up at three to four months and annually thereafter, and an annual dermatological examination because there is a slight increase in the risk of basal cell skin carcinomas. Also, one should periodically check the blood pressure because this occasionally becomes elevated with fingolimod treatment.

Importantly, there have now been five reported cases of progressive multifocal leukoencephalopathy, or PML, out of the roughly 125,000 patients treated with fingolimod worldwide. There have also been cases of Cryptococcal infection including rare cases of Cryptococcal meningitis, and there is an increased risk of shingles in this population.

Slide 30 – Teriflunomide: A Selective Dihydroorotate Dehydrogenase Inhibitor

Let's turn now to teriflunomide. Teriflunomide is an inhibitor of a mitochondrial enzyme known as dihydroorotate dehydrogenase. And, by selectively inhibiting this enzyme, it decreases pyrimidine in pyrimidine synthesis and proliferating lymphocytes. It spares, those lymphocytes such as memory T cells that operate through the salvage pathway.

Slide 31 - Teriflunomide for RRMS (Phase III TEMSO Study): Key Clinical Outcomes

This drug has been tested in several large, clinical trials two pivotal Phase III trials, the first of which is shown here – the TEMSO Trial. And, in this trial there was about a 31.5% reduction in the annualized relapse rate with the 14-milligram dose.

In this trial, there was a similar reduction in the relapse rate with a 7-milligram dose, but, on MRI parameters and as shown on the right-hand portion of this slide, in sustained disability progression, the results are better with the 14-milligram doses, so that's the dose that's generally prescribed. In the second pivotal trial known as the TOWER Trial, this difference between the doses became even more apparent.

Slide 32 - Tolerability Issues with Teriflunomide

We have a very good sense of security about the safety profile of teriflunomide because another drug – leflunomide – has been on the market for many, many years to treat rheumatoid arthritis, and that drug, which has way more than 2 million patient years of experience, has proved quite safe, and that drug is actively metabolized to teriflunomide.

In the clinical trials, about 2% of patients came out of the trial because of GI symptoms, mainly diarrhea. There is mild hair thinning at the beginning of therapy only; fewer than 2% came out of the trial because of hair thinning. The FDA has recommended monthly liver enzyme determinations for the first six months. The drug causes occasional neutropenia, so the CBC should be checked periodically. And, again, as with fingolimod, one should check the blood pressure.

Importantly, this drug has a Category X pregnancy rating. You need to make sure that women are practicing very effective contraception if they use this drug. When teriflunomide is discontinued, the drug remains in the body for a very long time under ordinary circumstances, on average, for about eight months but perhaps as long as two years. So if you need to get rid of the drug -- for example, if a woman *wants* to become pregnant -- you need to undergo an accelerated elimination procedure which usually involves the administration of cholestyramine for 11 days, and this gets rid of the agent.

Slide 33 - DMF Has Shown Nrf2 Pathway Activation

The third oral drug is dimethyl fumarate. The exact mechanism of action is unclear for this drug. It has been shown to have Nrf2 pathway activation which results in *diminished* antioxidant activity.

Slide 34 - DMF: Integrated Efficacy Analysis of DEFINE and CONFIRM

This drug had two very large clinical trials known as the DEFINE and CONFIRM Trial. Because the trials were essentially identical, they can be combined in analysis, and, together, they show a 49% reduction compared to placebo in the annualized relapse rate. And, as you can see in the bottom two lines in this chart that there was a very substantial reduction in the time to either 12-week confirmed disability progression or 24-week confirmed disability progression.

Slide 35 - Safety and Tolerability Issues with Dimethyl Fumarate

There are some tolerability issues with dimethyl fumarate at the initiation of therapy. A lot of patients get the prominent gastrointestinal symptoms which can include any combination of: abdominal pain, heartburn, nausea, vomiting, diarrhea. They may also get intense flushing at the beginning.

In my experience if you can get the patient through this early stage, the symptoms will become markedly better after about one to two months of therapy. So I've only, in my own practice, had to discontinue about 5% or 6% of patients because of these symptoms, and I think I have done better than the community at large simply because I spend a lot of time educating patients.

Importantly, now there have been four cases of PML associated with the use of dimethyl fumarate for multiple sclerosis. And, in all of these cases, there was a relationship to lymphopenia. In three of the cases, there was profound lymphopenia, below 500 for a prolonged period of time and, in the fourth case, there was a rapidly falling lymphocyte count.

Again, one should follow liver enzymes, but these are relatively infrequently elevated. This drug, unlike the two other oral drugs, is a twice-a-day regimen, and patients must be comfortable that they're going to remember to take the capsules twice a day because the drug probably will be ineffective if it's not taken for both doses. This drug has a Category C pregnancy rating.

Slide 36 - Natalizumab Mechanism of Action

Turning now to an infusion therapy, natalizumab is a monoclonal antibody directed against alpha 4 beta 1 integrin, or VLA-4, an adhesion molecule on the surface of lymphocytes. This adhesion molecule has to interact with a complementary receptor molecule known as VCAM-1 on the vascular endothelium. This interaction results in the lymphocyte being arrested against the vascular wall, which is a requisite step for penetration into the central nervous system. By blocking that adhesion molecule, natalizumab prevents the entrance of these lymphocytes into the central nervous system.

Slide 37 - Natalizumab vs Placebo Affirm Study (1801)

In its monotherapy trial against placebo -- the AFFIRM Trial – there was a *very* robust 68% reduction in annualized relapse rates. This is far better than we've seen in any other agent that's on the market, with the possible exception of alemtuzumab, which is a reserve for more severely affected patients. But I do emphasize that there have been no head-to-head trials between natalizumab and any other agents, and it's only through head-to-head trials that we know with absolute certainty that one agent is superior to another.

Slide 38 – Natalizumab-associated PML: *Overall Incidence by Treatment Epoch*

The big rub, of course, with natalizumab has been the occurrence of PML. And this slide demonstrates how I use this data. So we've learned a lot about PML in relationship to natalizumab, and now we know that the major risk factor for the development of PML is the presence of antibody to JC virus, the causative agent of that disease.
A second risk factor is the duration of therapy, and a third risk factor is the prior use of immunosuppressive agents. Now, virtually all the cases of PML have occurred in patients who are antibody-positive, and a little bit more than 50% of people *are* antibody-positive. So, as you look at this graph, you should *double* the risk estimates, if you have an antibody-positive patient. So, as you can see here in the left-hand portion of this graph, even if you're antibody-positive, your risk in the first year of therapy – this being a q 4 weeks infusion – is only about one in 10,000. In the *second* year of therapy, the risk would go up to approximately one in 800. So, for example, it would be 1.3 per 1,000 patients. And the third and subsequent years, the risk increases up to about one in 200 to one in 250 patients.

Slide 39 - JCV Antibody Status and Risk for PML

Recently, now -- in positive patients, we get back a report of a JC virus antibody index, and if it turns out that the index is very low – say, below 0.9 – then the risk for PML appears to be comparable to that for JC virus antibody-negative patients.

So, again, to emphasize how to use all of this data, including prior immunosuppression, if you look at the lower right-hand corner of this table, you can see that the risk for a person who's been on treatment for several years, had prior immunosuppressive treatment, and is JC virus antibody-positive, the risk is up around one in 100, a serious potential danger. In contrast, the patient who is negative may have a risk lower, even, than one in 10,000.

Slide 40 - PML Risk Stratification Using Anti-JCV Antibody Index and L-selectin

There is some recent additional information that may indicate the utility of another biomarker; this is L-selectin or CD62L. So if you have a low L-selectin level, you are also at higher risk for PML. So this data can be used in combination with JC virus antibody positivity to establish risks.

Slide 41 - L-Selectin and Risk of PML

This algorithm is presented for your information; although, to my knowledge, it is not possible or readily available to get a L-selectin level at this point.

Slide 42 - Choosing Therapy

Let me now tell you how *I* use all of this information in selecting a drug for a particular patient. I first ask myself, "Does this patient appear to have very aggressive disease?" based on those risk factors I talked about earlier. If the answer is "yes," then I look at the JC virus antibody status.

If that patient is antibody-negative, I will almost surely put that patient on natalizumab. If the patient is antibody-positive, then I'm going to look at, sort of, how aggressive that patient is and what the patient's risk tolerance is. I may start that patient, if it looks like very aggressive disease, even on alemtuzumab even though we usually reserve that agent for patients who have failed other treatments. Or I might use natalizumab, at least for a year to try to settle that disease down. On the other hand, if I'm slightly less concerned I might start with fingolimod or dimethyl fumarate and monitor that patient closely.

Fortunately, most of the patients don't fall into this very aggressive category, and if they look as if they have a little bit less severe MS, then I'm going to ask the patient if it's a woman, if she is contemplating pregnancy in the near-term; if she is, I'm going to tell her that glatiramer acetate is probably, almost surely safe even *during* pregnancy. She certainly may take it up to the time of pregnancy. And, by the way, that's probably true of interferon, as well. But, in my view, she may even wish to continue glatiramer acetate *during* pregnancy; although, the prescribing information does not recommend that at the moment.

If pregnancy is not an issue, then I'll ask the patient, or explore with the patient, their level of concern and tolerance for risk. If they are absolutely steadfast in wanting the safest drugs, then I recommend one of the older, established injectable agents – interferon or glatiramer – because these drugs are incredibly safe, and we've been using them for many, many years.

On the other hand, if they either want to opt for a drug that's somewhat more effective and, also, they're not really interested in an injectable agent, then we have the options either of teriflunomide, fingolimod, or dimethyl fumarate, *or*, if they're JC virus antibody-negative, starting right with natalizumab. Unfortunately, sometimes, insurance considerations will impact this decision.

Slide 43 - Are Stable MS Patients Who Stop DMT at Risk for Increased Relapses and Disability

We might ask the question, "Can we ever *stop* a disease-modifying therapy in a person with MS?" and we don't really know the answer to that. There has been some preliminary data presented by Ilya Kister at a recent international MS meeting. This is not a controlled trial in any stretch of the imagination, and he found that 36% of patients who did stop drug experienced relapses within five years; that was more likely if they were young and *less* disabled. And those who stopped showed more *disability* progression.

However, if you stop disease-modifying therapy in someone who has had *no* relapses for five years, it's possible that you will *not* increase their risk. This is a question that we really need, an

answer from a controlled clinical trial, and one such trial has recently been funded and is about to be undertaken.

Slide 44 - Ocrelizumab: Results of Opera 1 and Opera 2 Phase III Trials in Relapsing-remitting MS

I'm going to finish up my portion of the talk by speaking a little bit about ocrelizumab. This is an anti-CD20 agent that depletes B cells, and it had very dramatic results in two, simultaneously run trials – OPERA 1 and OPERA 2 – in relapsing-remitting disease. These trials were done against three times-a-week subcutaneous interferon beta. And there was a quite remarkable 46% and 47% greater reduction in the annualized relapse rate for the ocrelizumab-treated patients compared to the interferon beta-treated patients.

There was also markedly better performance and statistically significantly better results in the confirmed disability progression at either 12 or 24 weeks, and in the number of either T1 gad-enhancing lesions or new or enlarging T2 hyperintense lesions. So this looks like a potentially extremely effective agent, hopefully, to be added to our armamentarium early next year, 2017.

The drug appeared to be well tolerated. It's given by intravenous infusion every six months. There were infusion reactions but these were generally mild to moderate.

Slide 45 - Case Presentation (continued)

Going back to the patient that we introduced earlier in the discussion, that patient began subcutaneous interferon beta-1a three times a week. An exam eight months later was normal. The patient was feeling well. About a year after beginning interferon beta, still feeling well. He underwent an MRI scan which showed two tiny new T2 hyperintense lesions compared to the initial MRI.

Slide 46 - Modified Rio Score

Now, there have been a number of ways to try to determine whether or not to switch therapies, and one approach has been that promulgated by Jack Rio from Barcelona, and later in conjunction with a statistician Maria Pia Sormani. And they developed the Modified Rio Score which was looking at patients treated with interferon beta and developing a grading system based on whether or not they've had multiple new T2 lesions and/or relapses. And patients with a Rio Score of zero at one year, meaning four or fewer lesions and no relapses, they had a very good chance of not having any progression over the next three years of therapy. And, conversely, if you scored 3, meaning you had more than four lesions and at least two attacks, you had a very high risk of not doing well over the next few years.

Slide 47 - Algorithm for Identifying Nonresponders Based on the Modified Rio Score

They modified this so that patients with *some* degree of disease activity on MRI or clinically at one year were reassessed at 1.5 years with yet another MRI and were again moved depending on whether or not they had more relapses or lesions, as shown on this slide, to the category of "Responder" or "Non-responder." So this shows how early assessment of patients may influence whether or not you should switch therapy. Unfortunately, we don't have yet similar data for patients using drugs other than the interferons.

Slide 48 - Case Presentation (continued)

This patient returned six months later, still on the interferon, with double-vision and facial numbness. His brain MRI shows a new gadolinium-enhancing pontine lesion. He was treated with five-day course of steroids with significant improvement in his vision.

And you might ask yourself at this point whether you would switch therapy and what are the reasonable alternative therapies. Personally, I would switch therapy because of his continued disease activity on multiple occasions, and would discuss with him a number of other options.

At this point, I'm going to turn this presentation over to my colleague Dr. Suhayl Dhib-Jalbut.

Slide 49 - Case Presentation

Suhayl Dhib-Jalbut, MD: Thank you, Dr. Miller. Hello, I am Suhayl Dhib-Jalbut, Professor and Chair of Neurology at Rutgers University.

This segment will focus on biomarkers and risk factors in multiple sclerosis. I would like to begin with a case.

This is a 25 year-old white female who was diagnosed with MS two years earlier, when she presented with optic neuritis and numbness below the mid-thoracic area. She was placed on interferon beta-1a intramuscular weekly injections. She continues to have relapses and worsening of her symptoms.

Slide 50 – Polling Question

Slide 51 - Case Presentation *(continued)*

This patient's antibody titer to interferon was tested and turned out to be quite low. This tells us that neutralizing antibodies are not the reason for this patient's lack of response to interferon therapy.

The next question is whether this constitutes a case of treatment failure. Of course, the answer depends on where you set your threshold for relapses and disease progression. In general, our threshold for treatment failure is becoming lower and lower as new treatments for MS come out.

Then, would you place this patient on a higher dose of interferon beta or would you switch therapy? I think the MRI can be very helpful in this regard. There has been a number of studies examining the use of MRI as a marker of disease activity and response to treatment in patients receiving interferon beta therapy.

Slide 52 - Defining Interferon ß Response Status in MS

For example, the role of the MRI in predicting treatment failure to interferon was examined in a study from the Cleveland Clinic. This study included 172 patients who had received weekly intramuscular injections of interferon beta in a placebo-controlled trial. Those patients were followed up for 15 years. The conclusion from this study was that new MRI activity during interferon beta-1a treatment correlates with suboptimal response.

Slide 53 - MRI as a Surrogate of Future Disease Activity

A subsequent study by Prosperini confirmed the use of MRI as a predictor of response, or lack of, to interferon beta. This study included 370 patients whose relapses and disability progression were examined over a four-year period. At one year, if a patient had one or more gad-enhancing lesion or two or more T2 lesions, they carried the same risk factor for worsening over the course of the subsequent three years, as within the first year. So the conclusion from this study was that MRI activity after starting interferon has similar implications as the relapse.

Slide 54 - Case Presentation *(continued)*

Let's continue with this case. The patient had a follow-up MRI which showed two non-enhancing brain T2 lesions and a new enhancing spinal cord lesion between T1 and T4. This, of course, raised the possibility of Devic's disease, which we now call neuromyelitis optica.

Because of the history of the optic neuritis and the MRI finding of the spinal cord longitudinal-enhancing lesion spanning three vertebrae, the patient was tested for neuromyelitis optica antibody, and the antibody was positive.

Slide 55 - Neuromyelitis Optica

Neuromyelitis optica is a condition that can be confused with multiple sclerosis. It is an inflammatory demyelinating disease, but what's specific about it is that it predominantly affects the optic nerve and the spinal cord with very little involvement of the rest of the nervous system. It is characterized by a specific immunoglobulin G antibody marker called NMO antibody. This antibody is diagnostic. It is elevated in about 80% of patients who have the clinical phenotype of neuromyelitis optica. And it can also be detected in the spinal fluid, as well.

The target antigen for this antibody is aquaporin-4, which is a water channel widely distributed in the central nervous system. However, the prognostic role of NMO antibody in this condition remains uncertain at the present time.

Slide 56 - NMO Pre- and Post-treatment Median Annualized Relapse Rates

It is important to distinguish NMO from MS, as treatments can be different. This distinction is important because, if you treat NMO patients with interferon beta, for example, anecdotal experience suggests a worse outcome. This slide shows a retrospective analysis of various medications' efficacy in NMO. It is an uncontrolled retrospective study that compared different treatment modalities using clinical practice of treating NMO.

These treatment modalities included rituximab, which depletes B cells, and chemotherapeutic immunosuppressant agents including azathioprine, mycophenolate, and cyclophosphamide. Outcome measures included relapse rate, shown on the left, and disability progression, shows on the right.

As you can see, rituximab, azathioprine, mycophenolate, and, to some extent, cyclophosphamide all had a beneficial effect in reducing relapses. However, when you look at progression of disability, rituximab and azathioprine showed a significant effect, but not mycophenolate or cyclophosphamide. This is not surprising since NMO is believed to be antibody-driven. Antibodies are produced by B cells and, therefore, a drug that depletes B cells, such as rituximab, is expected to produce a beneficial effect.

Slide 57 - Promising Future Biomarkers

Now I'd like to talk about some of the promising future biomarkers of MS therapy.

Slide 58 - Glatiramer Acetate Binds to HLA Class II on Antigen Presenting Cells and induces Type-2 APCs

The first one is glatiramer acetate, a commonly used drug in MS that has been around for over 20-some years with excellent safety record. There is a lot of interest in predicting responders from non-responders before patients are placed on this drug.

Those studies were done in my laboratory. The rationale was based on the mechanism of action of glatiramer acetate, which is shown on this slide. Glatiramer acetate binds to HLA-class II molecules on antigen-presenting cells, changing their immune activity from pro-inflammatory to a type II anti-inflammatory cell that drives production of regulatory and anti-inflammatory cytokines. So the question we ask is whether the HLA-class II background of the individual has any bearings on the clinical response to glatiramer acetate.

Slide 59 - DR and DQ Haplotypes Predictors of Clinical Response to GA

Here, you see a snapshot of our results. We have identified four HLA-class II alleles to be significantly associated with response to glatiramer acetate. DR15 and DQ6 were associated with responders, whereas DR17 and DQ2 were associated with non-responders. We then examined the predictive value of haplotypes, that is, the combination of alleles. We found that, if a patient is HLA/DR15/DQ6-negative but positive for DR17/DQ2, this patient is likely to be a poor responder. This patient has only about 17% chance of responding to glatiramer acetate.

At the other extreme, at the bottom of the slide, you see the haplotype associated with a *good* responder. A patient who is DR15/DQ6-positive but DR17/DQ2-negative has a 71% chance of responding to glatiramer acetate. This study is being investigated now in other cohorts and, hopefully, will be confirmed; if so, it can be utilized as a biomarker that can predict the response of the drug before treatment is started.

Slide 60 - Potential IFN-β Serum Biomarkers

Another example of biomarker research in MS is with interferon beta therapy. This slide shows a number of molecules that have been identified in various laboratories to be associated with either good response or poor response to interferon. Among the markers of good response is an elevation in interleukin-10, reduction in Th1 and Th17 cytokines, increase in neurotrophic factors except in microRNAs and other markers on T cells.

In the interferon non-responders, a reduction in IL-10 is not a good prognostic feature. Also, high interleukin-17 and interferon beta levels, particularly at baseline, are believed to be associated with a poor response. Neutralizing antibodies to interferon beta, as discussed earlier, and molecular analysis involving the interferon response factor 8 and 5 have been associated with a poor response. However, all these potential biomarkers have yet to be reproduced and confirmed in prospective studies.

Slide 61 – Axonal Damage Markedly Reduced by Natalizumab

The third example is with natalizumab, a multi-infusion that is quite effective in reducing relapses. This study demonstrated a reduction in CSF neurofilament levels with natalizumab therapy. As you can see from the bar graph. The level of neurofilament, which was elevated pre-treatment, almost normalized and went down to levels very much similar to those seen in healthy controls. Now, of course, whether the degree of reduction in the neurofilament level correlates with the degree of clinical response or MRI response is yet to be investigated.

Slide 62 - Exploratory Biomarkers of Newer MS Therapies

Among newer drugs, there is also ongoing research to identify biomarkers of response before and during treatment. This table lists some of the promising prognostic biomarkers for each of these newer drugs. For example, with natalizumab, I mentioned neurofilament, but there are others such as modulation of the VLA-4 on T cells, which is the target for natalizumab. Mobilization of CD34 cells increase circulation, as well as other molecules just adhere.

With fingolimod, there is interest in naïve and T central memory cells as well as the CD4:CD8 ratio as prognostic markers in both the blood and the spinal fluid.

In the case of rituximab, decrease in T cells and B cells, particularly in the spinal fluid, as well as CXCL13 levels in the spinal fluid seem to have some connection to clinical response.

With daclizumab, there is interest in NKregulatory T cells or the CD56 bright cells. Those cells seem to be elevated in patients who respond to daclizumab. Finally, a decrease in Th17 cells has been associated with a good response in bone marrow-transplanted patients.

Slide 63 - Safety Biomarkers

Finally, there is also equal interest in safety biomarkers. The best example we have now is the JC virus assay, which, as discussed by Dr. Miller, is frequently used as a screen for patients at risk of developing PML during natalizumab treatment.

The other example is with alemtuzumab, a recently FDA-approved drugs for multiple sclerosis. Those patients are at high risk of developing autoimmune thyroiditis. It seems that an elevation of serum interleukin-21 is associated with risk of autoimmune, thyroiditis.
So that's the end of my presentation. I want to thank you for joining us today. I would like to remind you to fill out the post-test and evaluation to receive your certificate.

Thank you.

Slide 64 – CME Credit