OVERVIEW

Multiple sclerosis (MS) is a chronic, progressive, and disabling inflammatory neurologic condition that causes more disability than any other nontraumatic neurologic condition. Early diagnosis, treatment, and monitoring of disease progression is fundamental to optimizing management of patients with MS. Join Edward Fox, MD, PhD, and Matthew Schindler, MD, PhD, in an interactive case-based roadmap for improved outcomes in patients with MS. In addition to addressing diagnostic challenges, Drs. Fox and Schindler share their insights into integrating advances in the pharmacologic treatment of patients with MS, focusing on the safety and efficacy of targeted therapies.

CONTENT AREAS

- Diagnostic principles and criteria
- Prognostication
- Treatment planning
- Treatment selection
- Treatment monitoring
- Adverse event management

FACULTY

Edward J. Fox, MD, PhD
Director, MS Clinic of Central Texas
Central Texas Neurology Consultants, PA
Clinical Associate Professor
University of Texas Dell Medical School
Round Rock, Texas

Matthew Schindler, MD, PhD
Assistant Professor
Division of Multiple Sclerosis and Related Disorders
Department of Neurology
University of Pennsylvania
Philadelphia, Pennsylvania

TARGET AUDIENCE

This activity was developed for neurologists, physician assistants, nurse practitioners, and allied healthcare professionals who diagnose and manage patients with multiple sclerosis (MS).

This activity is supported by educational grants from Genentech, a member of the Roche Group, and Novartis Pharmaceutical Corporation.

CE INFORMATION

Learning Objectives

- Apply the diagnostic criteria and diagnostic algorithms to diagnose a patient with MS
- Select a treatment plan for a patient with MS that is consistent with the state-of-the-art in MS care
- Recognize a patient with a highly active MS presentation or a poor prognosis
- Recognize adverse event prevention, monitoring, and/or mitigation strategies

Accreditation and Certification

The Annenberg Center for Health Sciences at Eisenhower is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Annenberg Center for Health Sciences at Eisenhower designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Annenberg Center for Health Sciences is accredited as a provider of nursing continuing professional development by the American Nurses Credentialing Center's Commission on Accreditation.

A maximum of 1.0 contact hour, including .25 pharmacology hour, may be earned for successful completion of this activity.

Disclosure Statement

It is the policy of the Annenberg Center for Health Sciences to ensure fair balance, independence, objectivity, and scientific rigor in all programming. All individuals with the potential to impact the content of an accredited education activity are expected to identify and reference off-label product use and disclose relationships with ACCME-defined ineligible companies.

The Annenberg Center for Health Sciences assesses relevant relationships with its instructors, planners, managers, and other individuals who are in a position to control the content of CE/CME activities. All relevant relationships that are identified are thoroughly vetted by the Annenberg Center for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. The Annenberg Center is committed to providing its learners with high-quality CE/CME activities and related

materials that promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.

In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center for Health Sciences policy, the following disclosures have been made:

Faculty

Edward J. Fox, MD, PhD

Advisory Board:	Alexion, Biogen, Bristol Myers Squibb, Genentech, Horizon, Novartis
Consultant:	Alexion, Biogen, Bristol Myers Squibb, Genentech, Horizon, Novartis
Speakers Bureau:	Alexion, Biogen, Bristol Myers Squibb, Genentech, Horizon, Janssen, Sanofi Genzyme

The following have no significant relationship to disclose:
Matthew K. Schindler, MD, PhD

The faculty for this activity has disclosed that there will be discussion about the use of products for non-FDA approved applications.

Additional content planners

The following have no significant relationship to disclose:
Sunali Wadehra, MD (Medical Writer)
Kam Newman, MD (Peer Reviewer)
Amber Lea Lambert, MSN, FNP-C, DNP (Nurse Reviewer)

Annenberg Center for Health Sciences

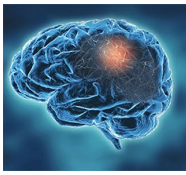
Staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.

The ideas and opinions presented in this educational activity are those of the faculty and do not necessarily reflect the views of the Annenberg Center and/or its agents. As in all educational activities, we encourage practitioners to use their own judgment in treating and addressing the needs of each individual patient, taking into account that patient's unique clinical situation. The Annenberg Center disclaims all liability and cannot be held responsible for any problems that may arise from participating in this activity or following treatment recommendations presented.

This activity is supported by educational grants from Genentech, a member of the Roche Group, and Novartis.

This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in your practice, and completing the assessment component. The estimated time to complete the activity is 1.0 hour.

This activity was released on June 22, 2022 and is eligible for credit through June 22, 2023.



KEEPING UP WITH ADVANCES IN MS:

CASES IN DIAGNOSIS AND TREATMENT, A CASE-BASED ROADMAP FOR IMPROVED PATIENT OUTCOMES IN MULTIPLE SCLEROSIS

StudyCompanion

Our Policy on Privacy

Annenberg Center for Health Sciences respects your privacy. We don't share information you give us, or have the need to share this information in the normal course of providing the services and information you may request. If there should be a need or request to share this information, we will do so only with your explicit permission. See Privacy Statement and other information at https://annenberg.net/pages/privacyPolicy.php

Contact Information

For help or questions about this activity please contact Continuing Education: ce@annenberg.net

---

Editor's Note: This is a transcript of a presentation on May 17, 2022. It has been edited and condensed for clarity.

Introductory Content

Multiple sclerosis (MS) is a chronic, progressive, and often disabling inflammatory demyelinating neurologic condition that may cause irreversible damage to the central nervous system (CNS).[1] It has a heterogeneous presentation with a wide range of symptoms, potentially impacting cognitive and motor function, activities of daily living, and quality of life. It is prevalent among young adults and is a common cause of nontraumatic neurologic disability in individuals between 10 and 65 years old.[2] Early diagnosis, treatment, and monitoring of disease progression is fundamental to optimizing management in patients with MS.

Case Scenario 1: A diagnosis-centric case: A patient presents with MS, but what subtype?

Case content: A 41-year-old White man, Johnny, is evaluated for progressive exercise intolerance. Six years ago, he regularly ran in 10-K races. However, he notes that he can now walk no more than 1 mile, which becomes more difficult in warm weather. He has no significant medical history.

1. All the following evaluations would provide information leading to the diagnosis of multiple sclerosis in this patient *except*:
    a. Clinical history
    b. Physical examination
    c. Lumbar puncture
    d. Brain magnetic resonance imaging
    e. Evoked potentials**

Rationale

Multiple sclerosis (MS) is a clinical diagnosis that requires a comprehensive assessment of the patient, during which clinical symptoms are evaluated by history and physical examination, testing is ordered, and conditions on the differential diagnosis for MS are excluded. The McDonald criteria, revised most recently in 2017, integrate clinical and paraclinical findings to aid in establishing the diagnosis in the context of a typical MS clinical event, such as Johnny's progressive neurologic decline. Specifically, clinical evaluation, magnetic resonance imaging (MRI) findings, and cerebrospinal fluid (CSF) testing are used to assess a patient for MS. Evoked potentials may be used to provide additional information about a patient, but are not included as part of the diagnostic criteria for MS.[3]

Case content:

In Johnny's case, physical examination reveals increased tone bilaterally in the lower limbs, as well as weak left ankle dorsiflexion with bilateral Babinski signs. The results of standard laboratory tests are normal. MRI shows multiple periventricular T2 hyperintensities. Analysis of CSF shows 3 oligoclonal bands.

Johnny is diagnosed with primary progressive multiple sclerosis (PPMS).

2. All the following characteristics of Johnny's case meet the criteria for PPMS *except*:
    a. At least 1 year of progressive disability
    b. Presence of multiple periventricular T2 hyperintensities on MRI
    c. Presence of Uhthoff phenomenon **
    d. Presence of oligoclonal bands on analysis of CSF

Rationale

As part of the diagnosis of MS, determining whether a patient evidences progression at onset is an important step toward defining clinical subtypes and determining treatment planning.[3] **Table 1** shows the 2017 McDonald criteria for MS in patients with an attack at onset, that is, relapsing MS (RMS), and **Table 2** shows the McDonald criteria for diagnosing MS in patients whose disease course is characterized by progression from onset, that is, PPMS.[4] It is important to keep in mind that at least 2 of the following are needed: CSF-specific oligoclonal bands; typical MS lesion in the periventricular, juxtacortical, or infratentorial brain regions; or 2 or more spinal cord lesions. Note that Johnny presents with at least 1 year of disability progression independent of clinical relapse, multiple T2-hyperintense lesions in the periventricular brain regions, and CSF-specific oligoclonal bands.

Table 1: 2017 McDonald Criteria – Attack Onset[4]

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥2 clinical attacks and objective clinical evidence of ≥2 lesions	None
≥2 clinical attacks and objective clinical evidence of 1 lesion	**DIS** demonstrated by an additional clinical attack implicating a different CNS site **OR** by MRI
1 clinical attack and objective clinical evidence of ≥2 lesions	**DIT** demonstrated by an additional clinical attack **OR** by MRI **OR** CSF-specific oligoclonal bands
1 clinical attack and objective evidence of 1 lesion	**DIS** demonstrated by an additional clinical attack implicating a different CNS site **OR** by MRI **DIT** demonstrated by an additional clinical attack **OR** by MRI **OR** CSF-specific oligoclonal bands

*DIS: Dissemination in Space; DIT: Dissemination in Time

Table 2: 2017 McDonald Criteria – Progression from Onset (PPMS)[4]

Clinical Presentation	Additional Data Needed for MS Diagnosis
At least 1 year of disability progression independent of clinical relapse	**Two** of the following criteria: One or more T2-hyperintense lesions in the periventricular, cortical or juxtacortical, or infratentorial brain regions Two or more hyperintense lesions in the spinal cord Presence of CSF-specific oligoclonal bands

Uhthoff phenomenon is common in some, but not all, patients with MS, and therefore is not a part of the diagnostic criteria. The phenomenon consists of a temporary deterioration of neurologic symptoms that occurs when the body temperature is elevated, either from ambient temperature or the presence of fever. When body temperature is elevated, electrical conduction occurs more slowly in areas that are demyelinated. In these circumstances, any neurologic symptoms are not considered relapses, as they do not represent new inflammatory events.[3]

3. The International Advisory Committee on Clinical Trials in MS of the US National MS Society created a Task Force on Differential Diagnosis of MS, during which major red flag clinical and paraclinical findings were identified that are suggestive of diagnoses other than MS.

   All the following neurologic findings are major red flags for a diagnosis other than MS *except*:

a. Peripheral neuropathy
b. Hypothalamic disturbance
c. Extrapyramidal symptoms
d. Lower urinary tract symptoms**

Rationale

Patients suspected of having MS may present similarly to patients with other conditions. It is important to differentiate these patients, as diagnosing patients early and accurately is important toward optimizing management. The International Advisory Committee on Clinical Trials in MS of the US National MS Society created a Task Force on Differential Diagnosis of MS which developed a list of major, intermediate, and minor red flags suggestive of a diagnosis other than MS in a patient presenting with a clinical event. The major red flags are shown in **Table 3**. Note the importance of excluding other diagnoses before making a diagnosis of MS.[5] However, up to 85% of patients with MS experience nerve-mediated lower urinary tract symptoms.[6]

Table 3: Major Clinical and Paraclinical Red Flag Findings of Patients with Central Nervous System Disease, Suggesting a Diagnosis other than MS[5]

Cardiologic
- Cardiac disease
- Myopathy

Dermatologic
- Livedo reticularis
- Rash
- Tendon xanthomas

Endocrinologic
- Diabetes insipidus

Gastrointestinal
- Mucosal ulcers

Hematologic
- Hematological manifestations
- Hemorrhages/microhemorrhages
- Recurrent spontaneous abortion or thrombotic events

Neurologic
- Abnormal calcification on CT scans

- Cerebral venous sinus thrombosis
- Cortical infarcts
- Extrapyramidal features
- Headaches or meningismus
- Hypothalamic disturbance
- Lacunar infarcts
- Large and infiltrating brainstem lesions
- Meningeal enhancement (though small leptomeningeal enhancement has been described in MS)
- Multiple cranial neuropathies or polyradiculopathy
- Persistent (> 8 weeks) gadolinium-enhancement and continued enlargement of lesions
- Persistently monofocal manifestations
- Predominance of lesions at the cortical/subcortical junction
- Selective involvement of the anterior temporal and inferior frontal lobe
- Simultaneous enhancement of all lesions
- T1-hyperintensity of the pulvinar
- T2-hyperintensity in the dentate nuclei

Ophthalmologic
- Retinopathy

Pulmonary
- Lung involvement

Renal
- Renal involvement

Rheumatologic
- Amyotrophy
- Arthritis, polyarthralgia, myalgias
- Bone lesions

Other
- Increased serum lactate level

Faculty Commentary

Matthew Schindler, MD, PhD: *When we think about diagnosis of MS, I think this first case really gives us some important things to think about. In this case, the patient that was presented had a progressive neurological decline that occurred over an extended period of time, I think over 6 years, and that's quite a common instance when we run into patients that are sent for neurologic evaluation. One of the most important factors to remember when diagnosing anybody with multiple sclerosis is that it remains a clinical diagnosis. This requires a history of a focal neurologic symptom that occurs over a period of time. In the case of this primary*

progressive patient, this occurred over at least a year and, in many cases, you'll see that this occurs over a longer period of time. In the case of relapse and remitting MS, we're looking for focal neurologic deficits that are typical of inflammatory demyelination such as optic neuritis or transverse myelitis or brain stem signs. And so it remains essential that we use the comprehensive history in collecting the data from the person who is being analyzed or assessed.

Secondly, we require that there is a change on the physical examination or a finding on the physical examination that points to and is in keeping with the clinical history. And in the correct clinical scenario, that's when we can order our testing to help us understand if this is MS v. not MS and to help us rule out some of the common mimickers that we can sometimes see in patients who do not have MS but may have features that are similar.

So, we use McDonald's criteria. The most recently revised is in 2017 and currently, for primary progressive MS, this requires that we have at least 1 year of progressive disability clinically and then you must have at least 2 of 3 of the following paraclinical data and that includes either 1 or more T2-hyperintense lesions in the same areas that we see in dissemination in space, that's periventricular white matter, the cortical or juxtacortical space, infratentorial brain regions and then 2 or more hyperintense lesions in the spinal cord or the presence of CSF-specific oligoclonal banding. It's important, you need only 2 of these, plus the 1 year of disability progression that's been described by the patient in their history in order to make the diagnosis of primary progressive multiple sclerosis.

It's important that we also have to think about other diseases. There are many mimickers of MS, both inflammatory-mediated diseases as well as non-inflammatory-mediated diseases such as metabolic diseases. Even vascular diseases can sometimes give you a similar both MRI and clinical picture of MS, and so it's important that we utilize all of the tools that we have in our arsenal in order to make an accurate diagnosis.

Some of the important clinical features you may want to ask about is the timing of the clinical symptom. Was this something that's been a slow decline over time or was the symptom that occurred rather acutely and then there's been a more steady but new baseline compared to their presymptomatic state? That can help you in the case of inflammatory-mediated disease. It should have a slower progression and less of a stepwise progression you may see in other vascular diseases. Some other abnormal features that you may see include atypical presentation. So, purely cognitive or purely headache as the primary symptom is not a typical presentation for multiple sclerosis and so it's important in these situations, in these sorts of settings, that you think carefully about other diseases. When we think about some of the other inflammatory diseases that can mimic MS, you include sarcoidosis, other rheumatologic illnesses like lupus or Sjogren's, and in these cases, it's important that we use both laboratory testing and imaging to help guide us in being able to create an accurate diagnosis.

Case Scenario 2: A patient presents with an aggressive presentation of MS

Case content: A 46-year-old African American woman, Marla, is evaluated for increasing difficulty reading and recent episodes of tripping while climbing stairs. She has noted increasing spasticity in the legs and early fatigue of her gait with mild foot drop, particularly when overheated. The patient has a 10-year history of cigarette smoking (total 20-pack-years). She also has diet-controlled type 2 diabetes mellitus.

The results of standard laboratory tests are within normal limits. An MRI scan of the brain shows multifocal white matter disease, specifically areas of T2 hyperintensities in both hemispheres. Analysis of CSF shows 6 oligoclonal bands.

Marla is diagnosed with primary progressive MS (PPMS).

1. All the following characteristics of this case are risk factors for a highly aggressive disease course of MS, *except*:
    a. Smoking
    b. Visual symptoms**
    c. Progression from onset
    d. T2 lesion burden

Faculty Commentary

Edward J. Fox, MD, PhD: *The case of Marla is an excellent example of the diagnosis of primary progressive multiple sclerosis. The McDonald's 2017 criteria indicates that 2 of 3 criteria must be met: a positive MRI of the brain, positive MRI of the spinal cord and oligoclonal bands seen on spinal fluid. Marla has 2 of those 3, as you can see. The MRI of the brain shows lesions that are consistent with demyelination and oligoclonal bands were found on CSF.*

The diagnosis of primary progressive MS also requires the clinical components which is worsening over a period of 12 months, either prospective or retrospective, that is not caused by a relapse. In her case, she had worsening of symptoms over time without a very clear start date or a period of time in which you could say an active relapse has occurred. The presence of multiple symptoms would highly suggest that the MRI was going to show multifocal lesions consistent with demyelination. She'd had visual problems. She had had gait problems that were indicative of likely spinal cord problems as well as other CNS disease states.

She has this history of smoking in the past 10 years and diet-controlled diabetes which are comorbidities which may have an effect on her outcome, but it does not affect whether she has primary progressive MS as a diagnosis. Put together, the clinical and radiographic findings, as

well as the CSF findings, are highly supportive of a diagnosis of primary progressive multiple sclerosis.

Rationale

Multiple risk factors have been identified that suggest a patient may be at an increased risk of an aggressive disease course of MS or a poor prognosis (**Table 4**). Unfavorable neurologic manifestations, such as pyramidal, cerebellar, sphincter, and cognitive symptoms, are considered risk factors for a poor prognosis, but visual symptoms are not.[7]

Table 4: Examples of Potential Risk Factors for Aggressive Multiple Sclerosis or Cases with a Poor Prognosis[7-9]

Male sex
Older age
Nonwhite race
• African American
Smoking
Low vitamin D levels
Frequent relapses
Shorter inter-attack time
Incomplete recovery between attacks
Cerebellar, pyramidal, or sphincter involvement
Multisymptom presentation
Higher disability at clinical diagnosis onset
Progression from onset
High T2 lesion burden
Increased number of gadolinium-enhancing lesions
Whole brain atrophy
Significant grey matter atrophy
High infratentorial lesion burden
High spinal cord lesion burden
Presence of oligoclonal bands
High levels of neurofilament light chains

Faculty Commentary

Edward J. Fox, MD, PhD: *After a diagnosis of primary progressive multiple sclerosis is made, there are several other questions that somebody is going to have about their case. One is what the prognosis would be, what the outlook is for the future. And also, whether there are specific treatments that can be given for this disease state and how would we know whether that treatment would be effective. When looking at the prognosis of a patient, there are a number of factors that need to be taken into account. And Marla's case exhibits a number of risk factors which would have to be used in explaining to her what the risks are, over time, of worsening disability.*

Gender and age are 2 aspects of MS that are easily looked at over a long period of time to determine whether risk factors are greater for one person than another. In Marla's case, being female is not considered a higher risk factor for early disability because males with primary progressive MS often have a greater degree of disability earlier in their case. However, non-White race, African American, for Marla, is a notable risk factor for her which has to be taken into account as to the outlook for her future diagnosis with regards to worsening of gait over time and increasing levels of disability.

Other aspects, smoking, which she has as a risk factor, and very likely a low vitamin D level which is seen commonly in patients with primary progressive MS, would be considered risk factors as well. Her having gait disorder is actually a particular risk factor. The presence of urinary problems would only compound the difficulty that she would likely have with her activities of daily living. These are considered highly aggressive risk factors for people with multiple sclerosis, whether they have relapsing or progressive onsets to their disease.

In her case, the degree of problems found on the MRI may lend an additional factor as to whether she is at high risk or not. If there is notable brain atrophy or spinal cord atrophy, either focal or generally, that would be considered a significant risk factor for early worsening of disability. There are other biomarkers that we're looking at now which may lead to a lot more information, over time, for people like Marla to be able to accurately predict what the future might bring for her. But, as it stands right now, Marla has a number of risk factors that could lead to worsening of the disease on a yearly basis and an early development of critical disability.

Rationale (continued)

Identifying patients who have aggressive MS is important toward clinical decision-making, as these patients may be candidates for higher efficacy treatments, including natalizumab, alemtuzumab, fingolimod, siponimod, ocrelizumab, and cladribine. Natalizumab is a humanized monoclonal antibody which binds to $\alpha_4\beta_1$-integrin; alemtuzumab is a humanized monoclonal antibody that binds CD52; fingolimod and siponimod are sphingosine-1-phosphate receptor binding medications; ocrelizumab is a humanized monoclonal antibody binding CD20; and cladribine is a purine analogue. Note that ocrelizumab is the only agent approved by the United States Food and Drug Administration (FDA) for treatment of PPMS.[7]

Case content: Marla is prescribed therapy with the monoclonal antibody ocrelizumab. However, she is concerned that she may have a reaction to the infusion.

Which 1 of the following statements about infusion-related reactions to ocrelizumab is most appropriate in response to her concern?

e. Infusion-related reactions are rare with ocrelizumab.

f. Infusion-related reactions are rare with ocrelizumab, but those that do occur have been mild.
g. Infusion-related reactions are common with ocrelizumab, but only mild events have been reported.
h. Infusion-related reactions are common with ocrelizumab, but prophylactic measures can be taken**

Rationale

Infusion-related reactions (IRRs) are 1 of the most common side effects of monoclonal antibody therapy, including with ocrelizumab, occurring most commonly with the first dose and becoming less common with later doses. In the ORATORIO, OPERA I, and OPERA II phase 3 clinical trials of ocrelizumab, most IRRs were mild or moderate. However, 1.2% and 2.4% were rated as severe in the ORATORIO and OPERA studies, respectively.[10]

Multiple approaches may be used to manage IRRs. Study protocols have required pretreatment with intravenous methylprednisolone, alongside optional administration of an analgesic/antipyretic and an intravenous/oral antihistamine. In addition, antihypertensive medications may be withheld before the infusion. These measures may reduce or eliminate symptoms. However, infusion-rate adjustments and symptomatic treatment may be applied in the cases that IRRs do occur.[10]

Case Scenario 3: A patient presents with relapsing MS

Case content: A 28-year-old woman, Leslie, is evaluated for a vision disorder. Approximately 1 month ago, she noted a dull, aching pain behind her right eye that worsened with eye movement. It then progressed to worsening vision, and now she no longer can read the computer screen at work and notes that colors appear “washed out.” She reports a history of depression, for which she takes fluoxetine, 40 mg once daily. She is also slightly overweight. She is currently married and planning to have children in the foreseeable future.

On physical examination, visual acuity is determined to be 20/20 on the left side, and 20/30 on the right side. In addition, colors are desaturated in the right eye. The results of standard laboratory tests are within normal limits. An MRI scan reveals gadolinium-enhancement in the right optic nerve, as well as 1 periventricular and 1 infratentorial lesion. Analysis of CSF shows 7 oligoclonal bands.

Faculty Commentary

Matthew Schindler, MD, PhD: *Here we have in our third case a patient who was recently diagnosed with relapse-remitting multiple sclerosis. There are many features about her presentation that are very typical for people that present with relapse-remitting multiple*

sclerosis. She had developed an optic neuritis which is 1 of the typical presentations that the 2017 McDonald's criteria for the diagnosis of MS requires. And in this situation, she had a clear neurologic exam finding in the case of the decreased vision in the right side, the red denaturation. She underwent the MRI, revealing a scan that had both an enhancing as well as nonenhancing lesions, and then lesions which are disseminated in space, including a periventricular infratentorial, as well as CSF analysis having 7 oligoclonal bands. So, she meets the 2017 criteria for DIS and DIT and has a typical presentation, all meeting the requirements for an MS diagnosis.

Case content: Leslie is diagnosed with relapsing MS (RMS).

1. Leslie is concerned over her diagnosis of RMS, insisting that her physician select a treatment option that is highly effective, in lieu of concerns about side effects.

   Which 1 of the following statements about disease-modifying therapy (DMT) selection in this patient is most appropriate?

   a. Platform therapy is the best choice for initial DMT.
   b. High-efficacy therapy is the best choice for initial DMT.
   c. Symptomatic therapy only is the best choice for initial treatment.
   d. There is debate whether platform or high-efficacy therapy is the best choice for initial DMT.**

Rationale

There are 2 different approaches for administering DMTs. DMTs that can be initiated and continued on a long-term basis are referred to as platform therapies. Some patients may start treatment on a platform therapy, followed by close monitoring for disease progression. If the DMT is inadequate in managing the disease, the patient should be switched to a higher-efficacy medication. Other patients are now beginning treatment with a higher efficacy medication instead. This approach may be more intensive and aggressive, but can be a good option for certain patients with MS.[11,12] There is debate over which of the 2 treatment strategies is superior.[12] Some experts suggest high-efficacy agents in patients with high levels of disease activity.[8] However, emerging data may support initial administration with a high-efficacy DMT in other patients as well.[12]

Faculty Commentary

Matthew Schindler, MD, PhD: *When somebody is diagnosed with MS, we are currently at a state where we have many different options, up to … I think we're at 23 approved disease-modifying therapies, and there are still ongoing debates about what is the most appropriate drug to initiate treatment on. In the past, when we had fewer options, the usual clinical response was to choose 1 of the platform therapies, whether it's glatiramer acetate or one of*

the interferons, before, to initiate therapy and wait and see whether or not that therapy was effective at stopping disease. And there were different methods to rate whether or not something was effective. And that included clinical relapses and, with the use of MRI, whether or not there were new T2-hyperintense lesions that had formed. And if somebody had either of those, they may move on to either another platform therapy or to a higher-efficacy therapy.

There is a lot of debate going on now about if that is the appropriate sequencing of drugs or should we start with higher-efficacy drugs right away, even though they may expose patients to higher risks for adverse events, with the idea that we can control disease early and that the earlier we can control disease in the most number of people, then we can potentially avoid or limit some of the long-term progressive neurologic decline that many of our patients suffer.

Like I said, these are ongoing debates. In fact, there are 2 clinical trials that are ongoing now including DELIVER-MS and TREAT-MS. DELIVER-MS is the determining the effectiveness of early intensive vs escalation approaches for the treatment of relapse-remitting multiple sclerosis. The TREAT-MS is traditional vs early aggressive therapy for MS. Both of these are really, I think, well-designed trials where they are studying either starting with platform therapy and then increasing to higher-efficacy treatment only if there is evidence of disease activity, whether clinically or radiologically, as well as vs sort of the opposite approach which is starting with the higher-efficacy medications first and then seeing how the clinical outcomes occur over time. So, both of these are longitudinal studies.

In the real world, as clinicians, we're asking these questions of our patients and of ourselves. And it still is an ongoing discussion between you and your patient about what is the most appropriate therapy for that person. And it involves looking at what are the risks of these medications, what are the adverse events, what are those rates, what are your expectations in the next year, the next 5 years. Do you want to do family planning now? And these things are important questions that you have to determine when you're going to help your patient choose the right medication for them. It's also important to remember that you can always make a change. Some are easier than others and some come with more risks than others, but you can make changes over time. But with these sorts of 2 clinical trials, I think they're really going to teach us a lot about what is the best and safest route to treat our newly-diagnosed patient population.

Case content:

2. Leslie and her neurologist determine that an agent that coincides with her family planning goals would be the best choice for initial DMT for her.

   Which 1 of the following DMTs would be most appropriate for Leslie who is planning on having children?

   a. Glatiramer acetate**

b. Fingolimod
c. Teriflunomide
d. Cladribine

Rationale

Not all DMTs are appropriate for women who wish to become pregnant in the foreseeable future. Certain DMTs are known to be teratogenic. Therefore, counseling is recommended for such patients.[13]

Injectables such as glatiramer acetate and interferon-betas have been determined to be safe for these women, with glatiramer acetate being a particularly viable option for patients such as Leslie. The other agents listed may be problematic. For example, there is an increased risk for congenital malformation in patients taking fingolimod; teriflunomide has been determined to be teratogenic in animal studies, as has cladribine.[13]

Case content:

3. Leslie is started on a regimen that includes glatiramer acetate. You develop a follow-up plan that provides for monitoring her treatment response.

All the following findings are considered a suboptimal treatment response that warrants switching medication *except:*

a. ≥1 relapse in 1 year
b. ≥2 enhancing lesions in 1 year**
c. ≥2 T2 lesions in 1 year
d. Progressive disability

Rationale

Both the American Academy of Neurology (AAN) and the Consortium of Multiple Sclerosis Centers (CMSC) recommend monitoring patients with MS as early as disease onset.[14,15] This follow-up should consist of both MRI and clinical assessment. Clinicians should monitor for suboptimal treatment response, which is defined by CMSC as the presence of at least 1 of the following: (1) ≥1 relapse in 1 year, (2) ≥1 enhancing lesion or ≥2 T2 lesions in 1 year; (3) severe relapse with minimal recovery; or (4) continued and progressive disability. If a patient has a suboptimal response to therapy, switching to another medication should be considered.[16]

References

1. Faissner S, Plemel JR, Gold R, Yong VW. Progressive multiple sclerosis: from pathophysiology to therapeutic strategies. *Nat Rev Drug Discov*. 2019;18(12):905-922. doi:10.1038/s41573-019-0035-2

2. Newsome SD, Aliotta PJ, Bainbridge J, et al. CME/CNE Article: A framework of care in multiple sclerosis, Part 1: Updated disease classification and disease-modifying therapy use in specific circumstances. *Int J MS Care*. 2016;18(6):314-323. doi:10.7224/1537-2073.2016-051
3. Olek MJ. Multiple sclerosis. *Ann Intern Med*. 2021;174(6):Itc81-itc96. doi:10.7326/aitc202106150
4. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173. doi:10.1016/s1474-4422(17)30470-2
5. Miller DH, Weinshenker BG, Filippi M, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. *Mult Scler*. 2008;14(9):1157-1174. doi:10.1177/1352458508096878
6. Aharony SM, Lam O, Corcos J. Evaluation of lower urinary tract symptoms in multiple sclerosis patients: Review of the literature and current guidelines. *Can Urol Assoc J*. 2017;11(1-2):61-64. doi:10.5489/cuaj.4058
7. Bowen JD. Highly Aggressive Multiple Sclerosis. *Continuum (Minneap Minn)*. 2019;25(3):689-714. doi:10.1212/con.0000000000000731
8. Rotstein D, Montalban X. Reaching an evidence-based prognosis for personalized treatment of multiple sclerosis. *Nat Rev Neurol*. 2019;15(5):287-300. doi:10.1038/s41582-019-0170-8
9. Oh J, Vidal-Jordana A, Montalban X. Multiple sclerosis: clinical aspects. *Curr Opin Neurol*. 2018;31(6):752-759. doi:10.1097/wco.0000000000000622
10. Mayer L, Kappos L, Racke MK, et al. Ocrelizumab infusion experience in patients with relapsing and primary progressive multiple sclerosis: Results from the phase 3 randomized OPERA I, OPERA II, and ORATORIO studies. *Mult Scler Relat Disord*. 2019;30:236-243. doi:10.1016/j.msard.2019.01.044
11. Comi G, Radaelli M, Soelberg Sørensen P. Evolving concepts in the treatment of relapsing multiple sclerosis. *Lancet*. 2017;389(10076):1347-1356. doi:10.1016/s0140-6736(16)32388-1
12. Ontaneda D, Tallantyre E, Kalincik T, Planchon SM, Evangelou N. Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis. *Lancet Neurol*. 2019;18(10):973-980. doi:10.1016/s1474-4422(19)30151-6
13. Krysko KM, Bove R, Dobson R, Jokubaitis V, Hellwig K. Treatment of women with multiple sclerosis planning pregnancy. *Curr Treat Options Neurol*. 2021;23(4):11. doi:10.1007/s11940-021-00666-4
14. Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90(17):789-800. doi:10.1212/wnl.0000000000005345
15. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90(17):777-788. doi:10.1212/wnl.0000000000005347
16. Ford CC, Morrow SA. CMSC Practical Guidelines for the Selection of Disease-Modifying Therapies in Multiple Sclerosis. Published February 28, 2019. Accessed August 4, 2022. https://mscare.sharefile.com/share/view/s79d1bfdca884318b