KEEPING UP WITH ADVANCES IN MS:
CASES IN DIAGNOSIS AND TREATMENT, A CASE-BASED ROADMAP FOR IMPROVED PATIENT OUTCOMES IN MULTIPLE SCLEROSIS

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 are fundamental to optimizing management of patients with MS. Here, we present a series of online learning modules that cover key principles in all phases of management, with a focus on up-to-date and evidence-based principles of providing high-quality care.

CONTENT AREAS

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

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TARGET AUDIENCE

This activity is intended for neurologists, physician assistants, nurse practitioners, and allied healthcare professionals who diagnose and treat patients with multiple sclerosis.

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

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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
- Select a treatment based on its demonstrated clinical efficacy and a patient's MS presentation
- Recognize adverse event prevention, monitoring, and/or mitigation strategies
- Apply the latest clinical data on approved DMTs in order to optimize treatment based on consensus recommendations

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The estimated time to complete the activity is 1.0 hour.

This activity was released on August 25, 2022 and is eligible for credit through August 25, 2023.

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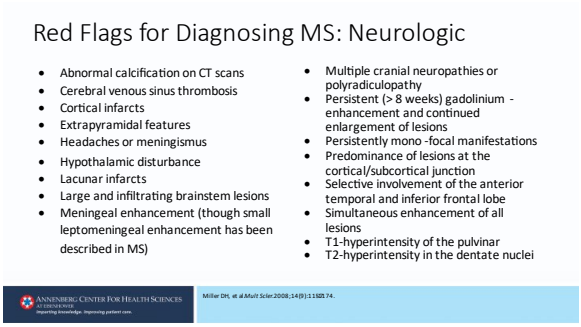
Editor's Note: This is a transcript of a presentation on July 5, 2022. It has been edited and condensed for clarity.

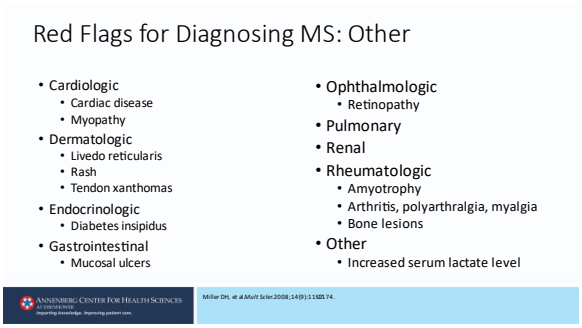
Diagnosis Basics

One issue we have had for many years with multiple sclerosis (MS) is making the correct diagnosis at the onset, as misdiagnoses can occur.

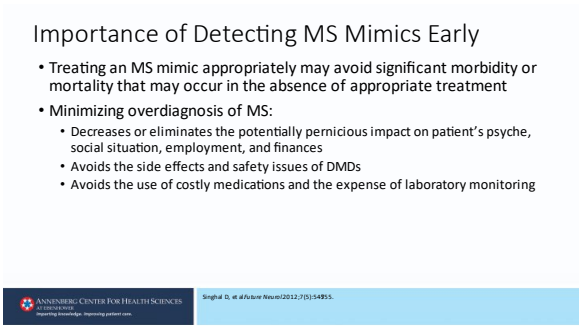


When looking at a patient with presumed MS, we should be on the lookout for red flags, that is, things that would be seen neurologically or on the general examination that would not fit with the standard definition of MS. Examples include abnormal calcifications, venous problems, and other circulatory problems. In addition, there are other reasons that we know of for white matter lesions that can be seen on a magnetic resonance image (MRI), including migraine headaches and microvascular disease. Also, you may see clinical involvement of areas that you would not expect necessarily to see in MS, but would be much more apt to see in patients who have had a cerebrovascular accident or other medical complication leading to neurologic symptoms.

We also find that there are other systems besides the neurologic system that could be involved that are red flags that we are not looking at MS.



There are findings that could be seen on fundoscopic examination, indicating retinal disease that might lead to vascular problems within the central nervous system (CNS) without being related to MS. With involvement of the heart, lungs, skin, and other organs, we must look at the differential diagnosis to find out whether there are other conditions that could better explain the neurologic symptoms that might have been associated with MS.



The reason for making the correct diagnosis is that the treatment options vary depending on the underlying diagnosis. We want to minimize the overdiagnosis of MS. In addition to MRI findings, the history, physical examination, comorbidities and other factors will determine whether we have a definitive diagnosis of MS.

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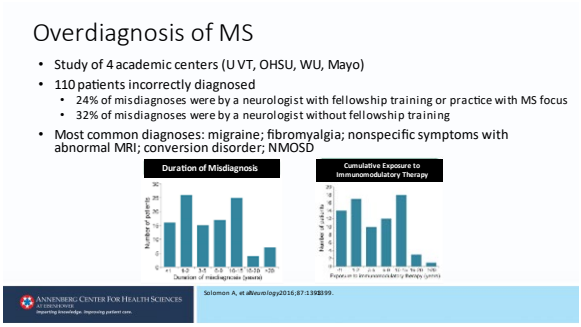
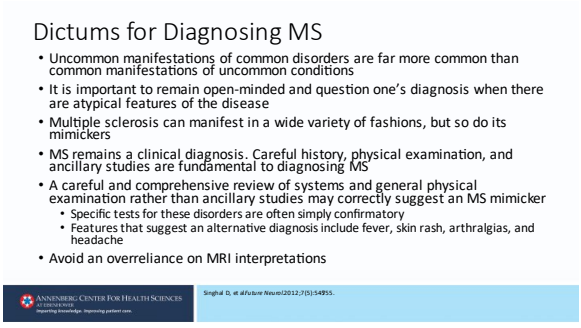


The incidence of overdiagnosis of MS is not small. A study of multiple centers that would be considered major centers of referral for people with MS found 110 patients that had been misdiagnosed in this small group. Twenty-four percent of the misdiagnoses were by a neurologist with fellowship training or practice with MS focus. But sometimes other factors have been overlooked, for example, those not seen in the past medical history and when these come to light, it leads to an alternative diagnosis.

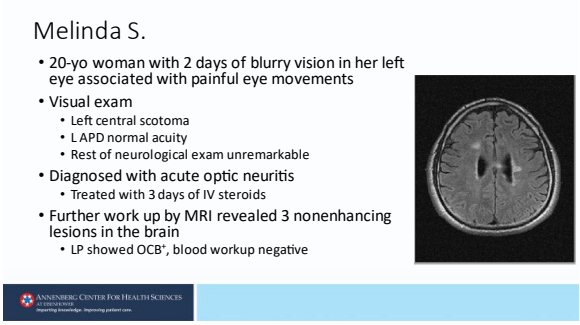
The most common diagnoses that are mistaken for MS are because of the MRI findings. Migraines can cause white spots that are seen in the subcortical regions on an MRI which can be mistaken if they have the right morphology for MS lesions. In addition, there are other conditions, like fibromyalgia, conversion disorders, and most importantly, neuromyelitis optica, that can cause brain lesions or spinal cord lesions that could be mistaken for MS.



One rule of what we should be looking for in determining whether somebody has MS is whether they have uncommon manifestations of common disorders, like migraine headaches. Also, it is important to remain open-minded during treatment, especially if inadequate control of the disease is maintained by multiple sclerosis therapeutics. In addition, the physical examination should be in keeping with upper motor neuron and CNS findings rather than peripheral nervous system findings. By going through family history and review of systems, keeping an open mind will lead to a much lower incidence of misdiagnosis of MS.

Relapsing MS Presentation

Here, we present Melinda S. who is a 20-year-old woman with 2 days of blurred vision in her left eye associated with painful eye movements. On visual examination, she had a central scotoma on the left eye, as well as an afferent pupillary defect with normal acuity.

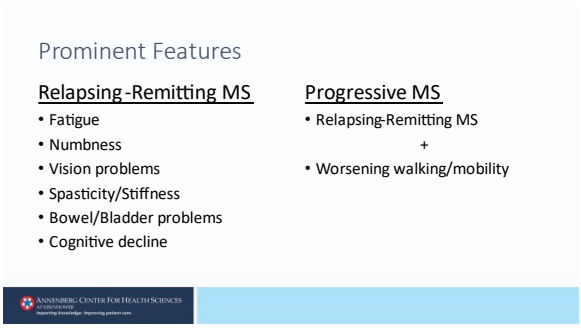


The rest of the neurologic examination was unremarkable. She was appropriately diagnosed with acute optic neuritis and treated with 3 days of IV steroids. Further workup included an MRI of the brain, which showed nonenhancing lesions in the brain. A lumbar puncture showed oligoclonal bands, and the blood workup was negative.

How does this patient meet the criteria for relapsing-remitting MS? Note that the diagnosis includes dissemination in space and time. Here, we find a clinically isolated syndrome. Then, we

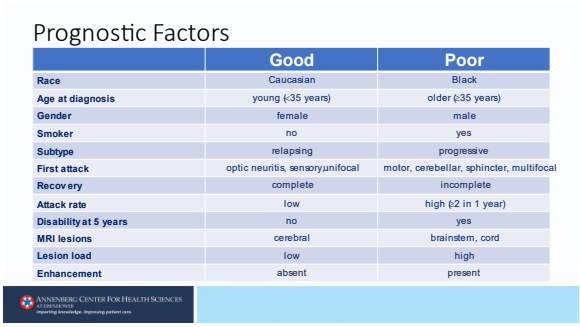
look at the MRI findings to assist us in making this diagnosis. The dissemination in time criteria is met by the positive oligoclonal bands, as were seen in the spinal tap.

What would suggest a poor vs favorable diagnosis? This is key in determining how we should best treat patients over time. We will discuss these prognostic categories to better understand what we should expect for Melinda in the future, untreated or treated.



The prominent features of relapsing-remitting MS can be fatigue, numbness, vision problems, spasticity or stiffness, bowel and bladder problems and cognitive decline. As you can see, these symptoms may stem from various areas of the CNS, for example, gray matter, white matter, brain and spinal cord, and optic nerves. Within the progressive MS category, what we see is that in secondary progressive MS, patients start with a relapsing form of MS, but have gone on to have worsening walking or mobility and other signs of spinal cord or brain dysfunction that have worsened in the absence of an active relapse.

Prognostic factors can help us in determining who is going to have early, aggressive disease, as opposed to those who have a milder form of the disease where there may not be early accumulation of disability.



	Good	Poor
Race	Caucasian	Black
Age at diagnosis	young (<35 years)	older (≥35 years)
Gender	female	male
Smoker	no	yes
Subtype	relapsing	progressive
First attack	optic neuritis, sensory,unifocal	motor, cerebellar, sphincter, multifocal
Recovery	complete	incomplete
Attack rate	low	high (≥2 in 1 year)
Disability at 5 years	no	yes
MRI lesions	cerebral	brainstem, cord
Lesion load	low	high
Enhancement	absent	present

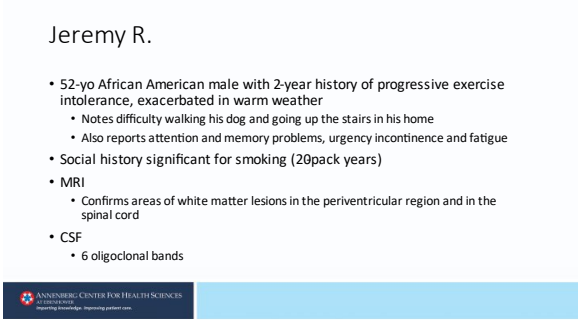
Some of these factors are listed, such as race. Caucasians tend to have a better prognosis than those patients who are Black or another minority group. The age at diagnosis is also important in that the younger you are diagnosed with MS, typically the less damage that has occurred that is irreversible and so a poorer prognosis can occur with older patients that have had a delayed diagnosis.

Females, overall, have a better prognosis than males. Likely, the reason for this is the higher degree of involvement of the spinal cord in men with multiple sclerosis. In addition, smoking is an independent risk factor. Also, starting with progressive symptoms at onset is a bad prognostic factor as well. When spinal cord damage has occurred, such as bowel and bladder dysfunction, this is a much worse prognostic factor than just having problems with the subcortex.

The complete recovery of the first or any relapses is a good sign. Incomplete resolution of symptoms, that is, persistent accumulation of disability, is a bad prognostic sign. Regarding MRI, if you have lesions in the brainstem or spinal cord, you are more likely to have persistent irreversible symptoms. Also, a high lesion load, especially with black holes or T1 hypointensities, are considered a significant prognostic indication of early, active, worsening disease.

Progressive MS Presentation

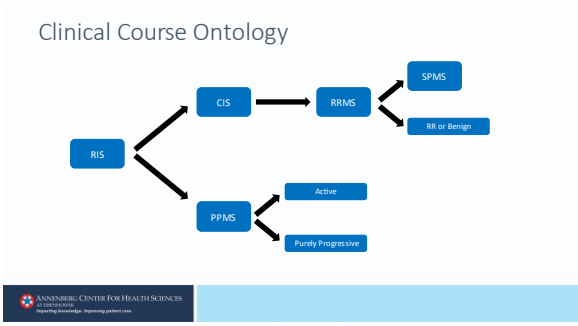
Progressive MS is defined by a patient who has worsened over a period of a year or more with a steady increase in objective findings on examination, or subjective symptoms, as well as a decrease in quality of life and activities of daily living, because of their neurologic disability. On the MRI, we cannot determine who has progressive disease, although we can certainly say that those patients who have more advanced atrophy are much more likely to have a progressive course.



Here, we present a case study of Jeremy R. who is a 52-year-old African American male with a 2-year history of progressive exercise intolerance, worsened by warm weather. He notes difficulty walking his dog, going up the stairs in his home, attention and memory problems, urgency and incontinence of urination, and fatigue. He has a 20-pack-year history of smoking. MRI confirms areas of white matter lesions in the periventricular region and spinal cord. His cerebrospinal fluid (CSF) is also positive for 6 oligoclonal bands.

Regarding Jeremy's prognosis, we can see that there are numerous factors that bode poorly for him. One is being male. Another is his race of being Black. Other examples include his smoking history, progressive symptoms from onset, and long track symptoms including bladder problems. There are many different prognostic factors here which are much worse than we had seen in the previous case.

Note also that Jeremy meets the criteria for primary progressive MS because he has had progression over a period that is objectively seen. You can see it on examination. It affects activities of daily living and cannot be explained by a diagnosis of a relapsing form of MS.

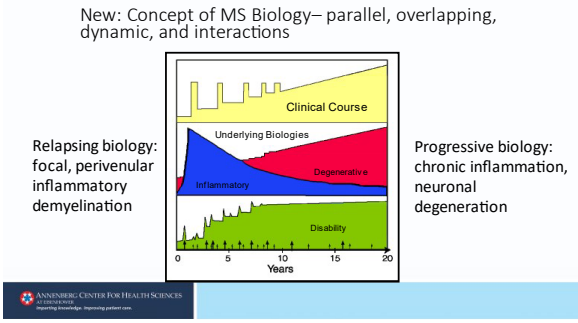


When looking at the different types of MS, we know that if somebody has MRI findings without clinical findings, they have radiographic isolated syndrome. Quite often, this is the case when an MRI was done for other reasons and multiple sclerosis-appearing lesions were seen without a clinical history or evidence of clear demyelinating disease on physical examination. But at some point, the patient will then express themselves as either having primary progressive MS or having had that first clinically isolated syndrome, at which point we can make the determination as to whether a patient has relapsing multiple sclerosis or purely primary progressive MS.

In each of those categories, we can talk about the disease as being active or inactive over a period, such as a year. Unfortunately, many patients with relapsing-remitting MS go on to have secondary progression, even though the number of relapses that occur over time may diminish dramatically. A patient may also have a benign course where they have had relapses in

the past, but no accumulation of disability and no secondary progression during their lifetime.

We understand that we have different types of MS and underlying pathology for each of these. We need to better understand, on an individual basis, whether a patient is having active disease or not.



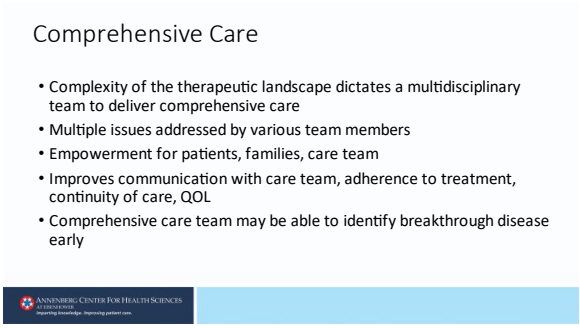
The early stage of MS is known to be much more inflammatory than later stages, but then the disease goes on to a degenerative phase where there is more of an issue with atrophy, axonal loss, and loss of tissue deep within the brain, as well as in the cortex and spinal cord. At that point, you see the disability level start to rise, independent of relapse. That is what we refer to as the secondary progressive phase of MS.

Treatment Planning

Looking at the different symptoms that may occur in the relapsing and progressive forms of MS, you can see that motor, sensory and other components of multiple sclerosis may be present simultaneously or that there may be a much greater amount of disability from 1 of these factors.

This may have to do with the geography of the lesions, for example, where the lesions are most destructive or where they are most congregated. We must understand also that other factors may come into play, such as underlying fatigue or depression, which may affect activities of daily living, reduce exercise tolerance, and cause symptom progression over time.

Multiple factors determine quality of life for a patient. We must be mindful that not all patients with MS have similar outcomes.



Comprehensive care for people with multiple sclerosis requires a multidisciplinary team. There may be multiple symptoms outside of the typical neurologic symptoms, requiring physical therapy, occupational therapy, speech therapy, and so on. Each team member has a unique role to play at the various stages of a patient's disease.

We need to empower patients to understand what is necessary for maintenance of optimal

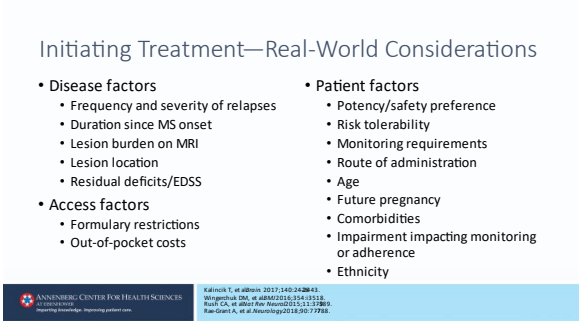
health. We also need to work with families and care teams to coordinate this level of care. This communication is necessary to have adherence to a treatment plan and continuity of care. The comprehensive care team can identify breakthrough disease early, not just by MRI but by ascertaining whether there are symptoms that should be addressed at an earlier stage.

There are multiple diagnostic and therapeutic issues that may arise. At the onset of disease, we may have somebody who is minimally affected and not aware of the risks that they have with long-term accumulation of disability.

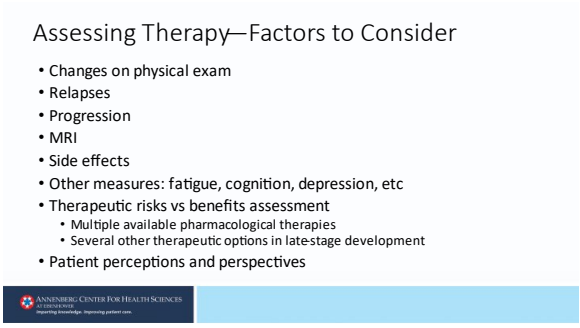
We need to educate patients on the risks of the disease itself and make certain that there is no denial of what has already transpired. We need to deal with anxiety, depression, and the unpredictability of the disease early on so that patients feel like they have a firm grasp of what our overall treatment goals are and how they can participate in reaching those goals.

Patients need to adjust by also understanding what therapeutic interventions are possible with medications, and understanding some of what risk factors are modifiable that they would be able to change, so that they may improve their quality of life. We need to address any symptoms that are limiting their activities of daily living, such as pain, tingling, fatigue or depression, appropriately treating those over time, pharmacologically or nonpharmacologically.

Each disease-modifying therapy (DMT) is unique and needs to be discussed with patients so that they understand the nature of their treatment.



We need to understand the risks that each patient has of breakthrough disease, as well as understand their goals in being able to maintain normal quality of life, despite the need for medication. We must discuss any issues patients may have either with administration or access to medicine itself, address these concerns directly so that we can ensure that we have the maximum capability of involving ourselves in the initiation of this therapy.

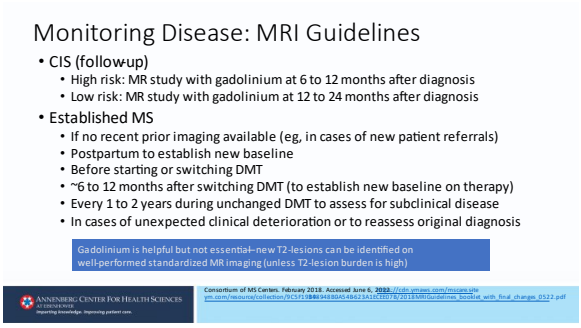


We consider various factors when initiating therapy. There may be breakthrough disease that we note on physical examination or by documentation of relapses. We may also see that MRIs change over time, indicating breakthrough activity as well. We must assess the tolerability of a medicine, as well as its safety. For example, is it causing any debilitating side effects or is it leading to any increased risk of morbidity or mortality over time? Also, we need to be able to assess patients in

consideration of the changing landscape of the therapeutic field. The longer a patient has been on medicine, the more we may have learned about what their risk factors are for side effects or safety issues that we may need to address.

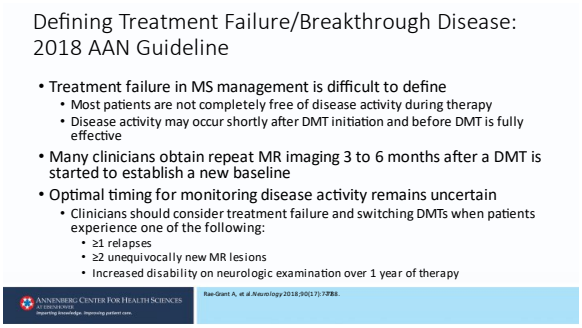
We need to review patient perceptions of medication, as well as whether it is overall benefitting them or whether they have increasing level of stress based on their concerns about their medications.

By monitoring MRIs, we often see a positive impact for patients who are on adequate treatment of their multiple sclerosis, showing that they have stability, that they are not developing new or enlarging lesions, that there are not enhancing lesions and that they are not developing new T1 hypointense black holes or generalized atrophy.



MRIs may help us predict whether we might see relapses or progression. For example, patients with clinically isolated syndrome are at much higher risk if they have gadolinium-enhancing lesions during the early stages of their disease.

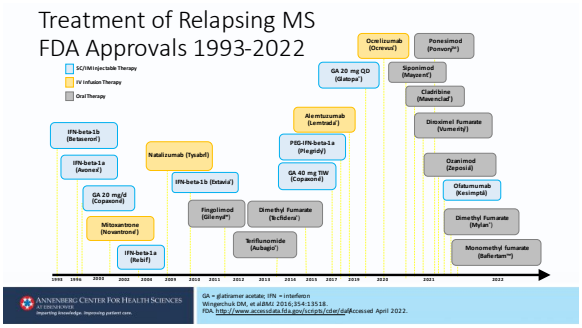
For patients with established MS, we can assess whether a medication is fully effective, whether we have no evidence of disease activity or whether there is radiographic breakthrough that would indicate an incomplete response to the medication that they are on. Accordingly, it is generally recommended that, after initiating or switching medications, we get a new baseline of an MRI 6 to 12 months later and that there should be monitoring on an ongoing basis using MRIs to ensure the maintenance of control of disease.



The 2018 American Academy of Neurology (AAN) guidelines indicate that although it is hard for us to define what true treatment failure is, it is not that hard to determine whether a patient has a stable or unstable MRI. Although we do not have guidance on exact timing because it depends on what treatment patients are on and what degree of activity of MS they have had before, there are guidelines that allow us to periodically order MRIs and assess patients for ongoing stability.

Relapsing MS Treatment

The treatment of relapsing MS has changed dramatically over the years with the development of many new products, the initial one coming out in 1993 and now new products being FDA-approved on a nearly yearly basis.



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By having 20 or more therapeutic options for MS now, we can individualize therapy based on our perceptions of risk to the patient of their disease and risk of side effects or safety issues.

Summary of MS Therapies by Mechanism of Action

Immunomodulation	Cell Migration Inhibition / Lymphocyte-Sequestering	Lymphocyte-Depleting	Remyelination
Fumarates	Natalizumab	Alemtuzumab	Multiple investigational products in clinical development
Glatiramer acetate	Sphingosine 1-phosphate agonists*	Cladribine	
Interferonβ		Ocrelizumab	
Teriflunomide		Ofatumumab	

*Examples include fingolimod, siponimod, ozanimod, ponesimod

Gohil KPT. 2015;40:185.

Here is a summary of multiple sclerosis therapies by mechanism of action. We have immunomodulation, which is a change in the immune system that boosts its anti-inflammatory nature. We can help patients understand the idea of immunomodulation as opposed to other techniques by talking to them about how we have white blood cells that are mistaking myelin for something that is foreign and attacking. By using a proper anti-inflammatory type drug, we can modulate or change the immune system to lessen chances of relapses or MRI findings. Within this category, we have the fumarates, glatiramer acetate, the beta interferons and teriflunomide.

In addition, we can modify the immune system by interfering with the migration of cells, either out of the lymphoid organs, such as the lymph nodes, or from crossing the blood-brain barrier and getting into the brain and the spinal cord. Natalizumab and the sphingosine 1-phosphate (S-1-P) agonists fall into this category.

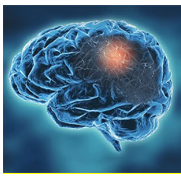
We also have products which can deplete lymphocytes. This may include lymphocytes of many different types or may be specific to a certain type of lymphocyte. Within this category, we have alemtuzumab and cladribine, which can deplete different cell types, including T and B lymphocytes. We also have B-cell specific monoclonal antibodies, including ocrelizumab and ofatumumab.

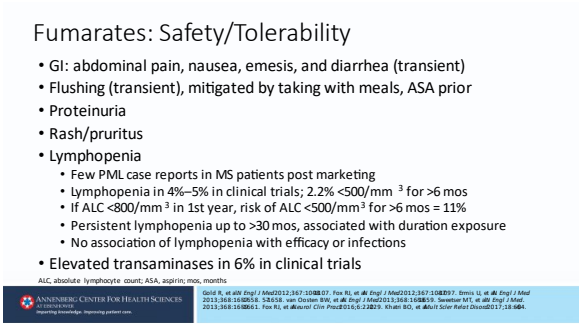
Finally, we have a number of products that are being studied to see if they can assist in remyelination. At this point, we have nothing approved yet within this category, but there are hopes that with future research, we will find products that can help stimulate regrowth of myelin.

Fumarates (Dimethyl fumarate, Diroximel fumarate, Monomethyl fumarate)

- Pros
  - Moderate to high effectiveness
  - Strong safety record
  - Oral medication
- Cons
  - Twice daily dosing
  - Tolerability issues
    - GI symptoms (lower with diroximel fumarate)
    - Flushing
  - Safety
    - 7 PML cases with DMF, as of December 2021

Fumarates are within the immunomodulatory category of medications. There are now several options within the fumarate category. These agents have moderate to high effectiveness with a strong safety record because of the number of people that have used them over many years. Also, they are oral medications. The downside to these agents is that the oral medicines must be taken every day and, in fact, twice a day to have full efficacy. In addition, tolerability issues can occur with both gastrointestinal upset and flushing. Regarding safety, one thing that we look at with all the multiple sclerosis medicines is the incidence of opportunistic infections. There have been a small number of cases of progressive multifocal leukoencephalopathy (PML) that have occurred in patients who have been on this treatment.

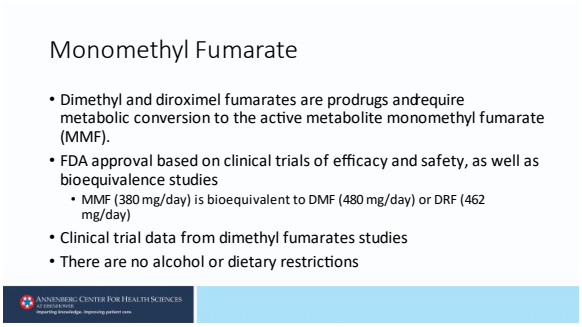




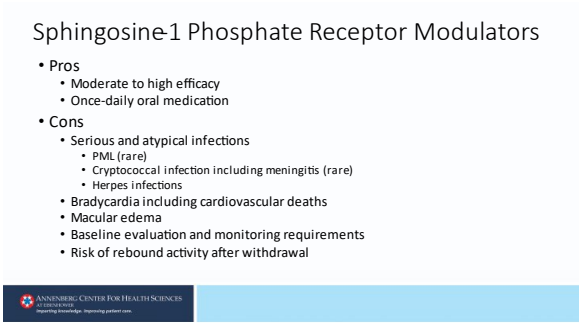
The gastrointestinal upset can be upper or lower gastrointestinal upset. It can cause indigestion or nausea, and it can cause diarrhea or bloating. The flushing that may occur is transient, and it is time-related, after taking a dosage, based on the absorption rate of the medication. It can be limited by eating foods that are better able to spread out the absorption of the medicine and by taking aspirin, which decreases the amount of flushing that occurs due to this category of medication.

There are other side effects that may occur within this category of medication, but the one that we are monitoring actively is lymphopenia. The idea of immunomodulatory drugs is not to lead to immunosuppression. When we looked at PML cases, we saw that those patients were more apt to have had significant lymphopenia, so that is measured on an ongoing basis to ensure an adequate lymphocyte count.

We see, in a small percentage of patients, elevated transaminases, liver function test elevation, but the incidence of patients who are having to discontinue the medicine outright because of liver function abnormalities is relatively small.



Regarding the types of agents in the fumarate categories, note that all of them have the active component of monomethyl fumarate. Because dimethyl and diroximel fumarates will change into monomethyl fumarate within the circulation, we think of those as prodrugs where the active drug is monomethyl fumarate. The FDA approved monomethyl fumarate at 380 mg a day, which was found to be a bioequivalent to dimethyl or diroximel fumarate as well, so we have clinical data from all 3 of these agents. With monomethyl fumarate, we do not have to worry about the absorption of the medicine in quite the same way because, at that point, it is no longer a prodrug. Rather, it is the active drug.



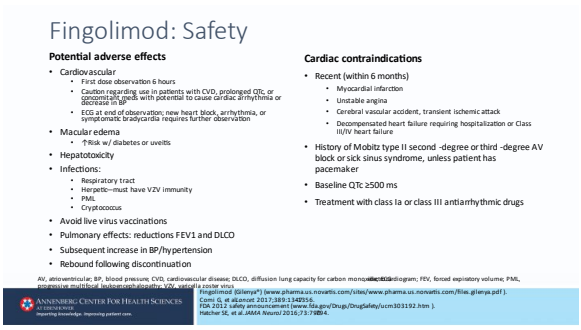
Regarding the sphingosine-1-phosphate (S-1-P) receptor modulators, there are several in this category that are moderate to high efficacy, once daily oral medications. Being able to take it once a day is considered to be a plus for this medication, but we do need to understand that any discontinuation of this medicine for a period requires reinitiating the medication. It is based on each one of the medicines in this category as

to how the reinitiation occurs, but gaps in treatment should not be allowed, if possible.

We have seen opportunistic infections in small numbers, as well PML, cryptococcal infections and disseminated herpes. Bradycardia can occur with this class of medications, which lends to a first-dose observation to make certain that a patient is not developing any degree of abnormalities on the ECG. This may be considered concerning, but also can be mitigated by an increasing dosage with some of these products where the up-titration of the dosage prevents us from needing a first-dose observation.

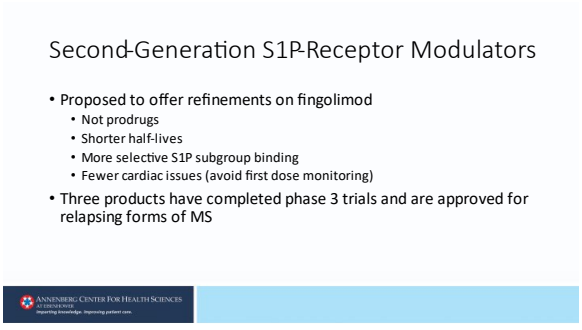
Patients also need to be monitored for visual changes because there can be a low incidence of macular edema brought on by the drug, which may be totally reversible by discontinuation of the drug as soon as it is identified. We also have ECG monitoring that is done beforehand to make sure that there is not either a type 2 second degree heart block or worse that could lead to further difficulties with initiation of this medication.

We also must be mindful that discontinuation of the medicine over a long period of time, such as for pregnancy attempts, may lead to an increased risk of significant relapses off the medication. We need to make our patients aware of the potential risks of discontinuing the medication.



Here, we discuss specifics within this category. The initial medicine that was approved was fingolimod. Fingolimod requires a first-dose observation because the dosage of 0.5 mg a day is the initial dosage and maintained throughout all treatment. If patients have underlying cardiac, cardiovascular or cerebrovascular disease within the past 6 months, that might be a contraindication. Thus, within the last 6 months, if there have been clinical events, either cardiac, cardiovascular, or cerebrovascular, this would not be an appropriate medication. Similarly, there are abnormalities on the ECG which would preclude use of this medication.

Also, what we know about this class of medications is (as with many for MS) that we should avoid live or live-attenuated vaccinations during that time. It is good news that we have few of these vaccines left now and that almost all vaccines that our patients are being recommended to receive are either nonviral or totally killed virus vaccinations.



The second-generation options, that is, the ones that came after fingolimod, are not prodrugs and they have shorter half-lives. There are 5 different receptors for S-1-P. These agents are more selective in the type of receptors within the S-1-P group. By targeting receptors that are more specific to the lymphocytes and have less cross-reactivity with other organ tissues, we have seen fewer cardiac issues and we have been able to avoid first-dose monitoring.

S1P-Receptor Modulators

	Fingolimod	Siponimod	Ozanimod	Ponesimod
Dose	0.5 mg	2 mg	1 mg	20 mg
$t_{½}$	6-9 days	30 (26-37) hours	20-22 hours; metabolites 10 days	32 hours
Washout	1-2 months	7 days	Metabolites ~50 days	~6 days
Receptor targets	1,3,4,5	1,5	1,5	1
Pro Drug	Yes	No	No	No
		+SPMS phase 3 (EXPAND)	+RRMS phase 3 trials vs IM IFNβ-1a (SUNBEAM, RADIANCE)	+RR phase 3 (OPTIMUM) vs teriflunomide

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Now, we have approval of multiple drugs within this category. Let's look at the different ones that are on this list. You can see that the dosages, half-lives, and washouts are different. We also have had different clinical trials that have been done, as well, where different types of patients have been looked at. Because of that, we now feel like we can tailor the medication better to the patient because we have an ability to select 1 based on the criteria just discussed.

Comparison of S1P Receptor Modulators

- Prior to initiation of therapy
  - Genetic testing only for siponimod
  - Ophthalmological evaluations only recommended for patients with history of diabetes mellitus or uveitis in patients starting ozanimod; for all with others
- Initiation of therapy
  - First dose observation with fingolimod; seldom for all others
  - Titration: 5 days for siponimod; 7 days for ozanimod; 14 days for ponesimod
- Return of normal lymphocyte counts
  - Longer for fingolimod and ozanimod
  - Shorter for siponimod and ponesimod

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When comparing these agents, we look at the testing that needs to be done prior to initiation of the drug. For siponimod, we need genetic testing to make certain that it can be metabolized properly. We also get ophthalmological evaluations for patients with diabetes or uveitis in patients starting ozanimod because they are at higher risk of developing macular edema. With the other agents, the ophthalmological evaluations are for all patients, not just those that are of higher risk.

The initiation of therapy includes first-dose observation for fingolimod only. Rarely do we need first-dose observation for the other medications. Also, these medications have different titration periods, where they start at a lower dosage and increase over time. The amount of time it takes for this to be reversible, where you no longer have lymphopenia as seen on blood testing, is longer for the fingolimod and ozanimod and shorter for siponimod and ponesimod, having to do with their half-lives.

Teriflunomide

- MOA: immunomodulation
- Pros
  - Moderate effectiveness
  - Once a day oral medication
  - Only drug with statistically significant reduction in disability progression in 2 trials
  - Extensive good safety record of leflunomide
- Cons
  - Moderate effectiveness
  - Need for liver monitoring monthly x6
  - Mild hair loss
  - Pregnancy Category X
  - Need for accelerated elimination protocol

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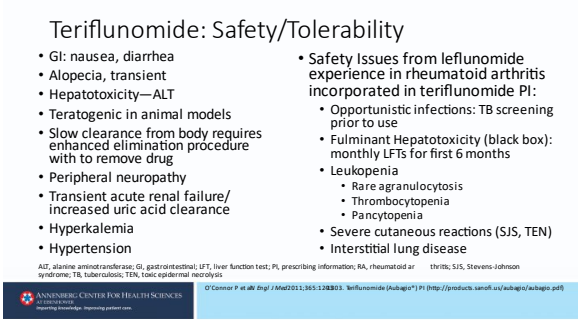
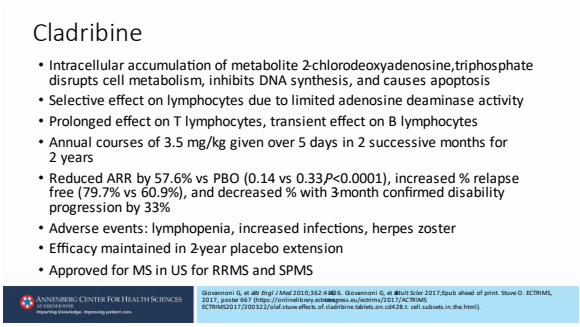
Here, we discuss a different category, teriflunomide, which was also mentioned in the list of medications that are immunomodulatory. The plus for this medication includes that it is, again, a once-a-day oral medication. It is considered to be of moderate effectiveness, and it is the only drug that had multiple trials that showed a reduction in the risk of disability progression. It also has a very good track record of safety because of the previous use of leflunomide, which is a related drug that has been used in rheumatoid arthritis and other conditions. The cons include that we need to monitor liver function tests monthly for 6 months because there have been incidences of significant liver function abnormalities with leflunomide, as seen in the past, whether used as a single agent or in combination with other potentially hepatotoxic drugs.

Also, it can lead to mild hair loss, not complete alopecia, but thinning of hair. In addition, it is a pregnancy category X agent, although the categories are not generally used. Rather we discuss it as being considered high risk and

absolutely contraindicated to be used in patients who have risk of becoming pregnant or being pregnant. We also have an accelerated elimination protocol for this agent, which is very helpful. If a patient needs to be taken off it, we can do so in a much less than 1-month period of time by using medications that'll help absorb the medicine out and remove it from the body.

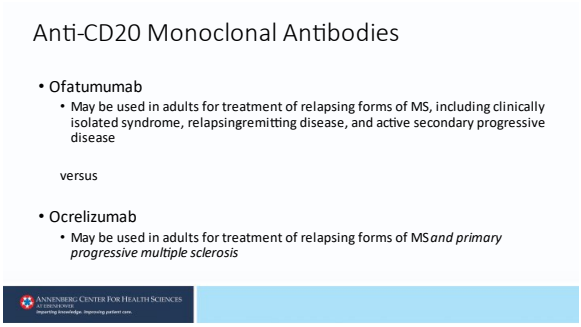


Here, we review the safety and tolerability of teriflunomide. The kind of side effects that we are going to be mentioning to patients include gastrointestinal upset, hair thinning, the need for liver function testing and the absolute contraindication for pregnancy on this medication. It does have very slow clearance from the body if you do not use the rapid elimination protocol and so that is always a choice that we have. We have seen some unusual side effects on this agent in terms of rarity, like peripheral neuropathy. Therefore, unexplained numbness or tingling of the extremities on this medicine could lead to a workup for peripheral neuropathy and cessation of the medicine, if peripheral neuropathy is confirmed. There would also be monitoring for opportunistic infections as well, but the incidence of that has been quite low over time.

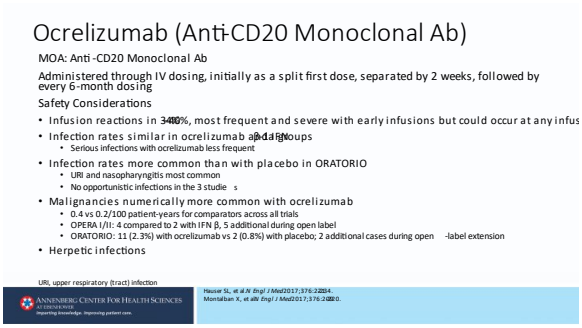


Here, we discuss cladribine. Cladribine is 1 of the immunosuppressant medicines in that it does cause a transient lymphopenia by inhibiting DNA synthesis and causing apoptosis of the fully developed, matured lymphocytes. It does not have the same effect on bone marrow cells, including stem cells. It has a selective depletion of lymphocytes because of limited adenosine deaminase activity. There is a bypass pathway that is available to other cells that is not available to lymphocytes, so it will cause cell death of lymphocytes with preservation of other cell types in the body.

This medicine is given in a short course over a period of 2 years. There is a maximum total of 20 days of oral treatment when using cladribine. The clinical findings on cladribine include a reduction in annualized relapse rate and a decrease in confirmed disability progression. Lymphopenia is an effect of this medication that can be seen on repeated CBC testing. Infection rates, including herpes zoster, have been monitored and found to be modestly elevated. In extension trials, we have seen that the benefits of this extend beyond the treatment period of 2 years without further medication. This agent has been approved in the United States for relapsing and secondary progressive forms of MS.



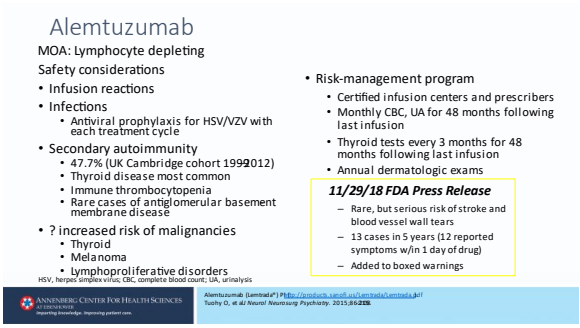
Here, we discuss the cell-depleting types of medication that target B-cells, that is, the anti-CD20 monoclonal antibodies, including ofatumumab and ocrelizumab. Both medications have been approved for relapsing forms of MS, but in clinical trials, ocrelizumab was also found to be potentially beneficial for primary progressive MS patients and therefore received indication for that disease as well.



Ocrelizumab is given in intravenous (IV) dosing, starting with a split first dose, separated by 2 weeks, followed by every 6-month dosing after the completion of the first course. Infusion reactions are common with this agent, most frequently seen with early infusions. Further, the incidence of infusion reactions decreases over time.

The infection rates are similar in ocrelizumab and beta-interferon groups, but serious infections have been seen with ocrelizumab at times. Infection rates are higher in patients who have primary progressive MS. In the ORATORIO trial, urinary tract infections and nasopharyngitis were the most common, and increased in frequency in patients who were on ocrelizumab. However, there were no opportunistic infections found in all 3 studies that were done with this product. The malignancies were numerically more common with ocrelizumab as seen in the OPERA and the ORATORIO trial with special attention to breast cancer. Thus, the recommendation is that the routine monitoring for cancer prevention be administered in every patient who is receiving ocrelizumab to diminish the risk of undiagnosed cancer in continued MS treatment.

Herpetic infections, including zoster, were seen in a somewhat increased amount in patients on ocrelizumab. Vaccination would be appropriate for those patients before initiation of treatment.

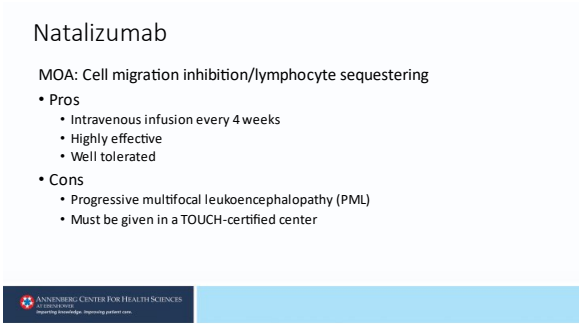


Here, we discuss alemtuzumab, which is also lymphocyte-depleting and in the immunosuppressive category. Infusion reactions are common in this medication. It is given 5 days in a row in the first year, and 3 days in a row at the beginning of the second year. Antiviral prophylaxis is indicated for each person on this agent because of the increased risk of herpes and herpes zoster infections.

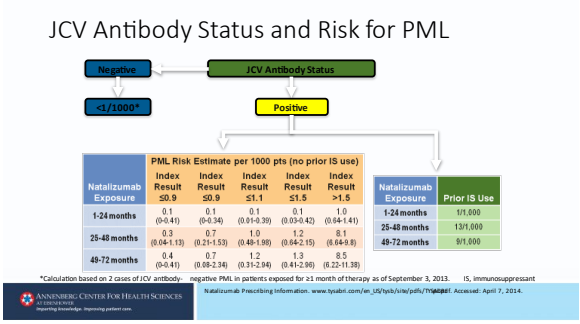
Secondary autoimmunity is a feature of this medication. In other words, there is an increased risk of other autoimmune conditions, such as thyroiditis, immune thrombocytopenic purpura (ITP), rare autoimmune cases, or basement membrane disease of the kidney. It is unknown

whether there is an increased risk for cancer in patients who have received alemtuzumab, but monitoring is necessary for the assurance of early diagnosis of cancer. There is a risk management program for patients on this medication, and it must be given at a certified center with professionals who understand the potential risks of the infusion reactions, as well as what monitoring is necessary afterwards, including having blood work and a urinalysis done 48 months after the last dosage to ensure the diagnoses of ITP, thyroid disease and other problems are made in a timely manner. In addition, an annual dermatologic examination is also recommended.

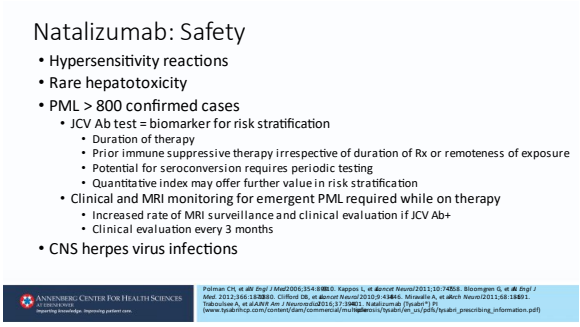
In 2018, there were additional risks that were added to this list. Potential cerebrovascular or cardiovascular diseases that could be seen at an increased risk with the use of this medication was added to the boxed warnings.



Natalizumab is an IV medication that is typically given every 4 weeks. It is considered highly effective, and it is well tolerated. The con is that, for patients in which the presence of antibodies to JC virus are detected, these patients are at notably higher risk of developing PML over time, particularly the longer they are on the medicine. There is also an increased risk for patients who have been on immunosuppressive therapy in the past. Because of this, a risk management program also exists where patients are given this medication in a TOUCH-certified center. In the TOUCH program, a patient is asked questions to be able to determine the risk level of the patient to capture all data available about the incidence of PML.

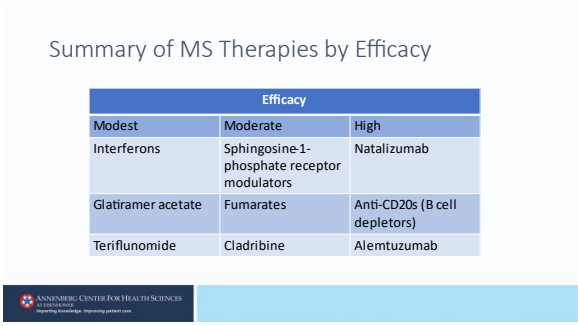


Looking at JCV antibody status and the risk of PML, we see that for those patients who are negative for JCV antibodies, the risk remains low, no matter the duration of treatment. However, for those patients who are JCV antibody-positive, we see that over the years the incidence of PML is increased. Further, it is increased more for those patients who have had exposure to immunosuppressive medications as well. Therefore, we can see that there is an incidence of PML that may have risk factors that we can use to determine whether the patient is at highest risk of development of PML or much lower risk.

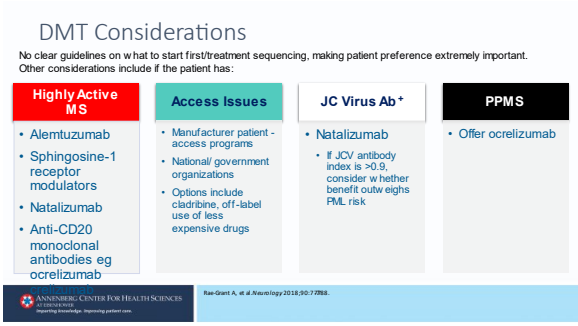


In addition to safety concerns surrounding PML, we have also seen rare instances of hypersensitivity reactions and hepatotoxicity. There have been more than 800 cases of PML. Patients who are on natalizumab should be routinely monitored for their JCV antibody status

so that we understand what their risks may be. We also need ongoing clinical and MRI monitoring to limit the chance of undiagnosed PML, as it could become much more severe prior to the diagnosis. We also need to be aware that CNS herpes virus infections have occurred, and we should be on alert for any patient who is showing signs of neurologic dysfunction not easily explained by an MS relapse.



In summary of the MS therapies by efficacy, we can say that there are ones that are considered modestly effective for MS compared to either placebo or as seen in many open-label extension trials. We have interferons, glatiramer acetate and teriflunomide in this category. We have a moderately effective group as well, which includes S-1-P agonists, fumarates and cladribine. Then, the high efficacy medications include natalizumab, the anti-CD20 B-cell depletors and alemtuzumab.



In making the decision about which disease-modifying therapy to use for an individual, we must consider how these medicines were tested, for what categories of multiple sclerosis, and whether we have ample evidence that it could be effective for patients. For patients with highly active MS, we have studied the use of alemtuzumab, the S-1-P agonists, natalizumab and B-cell depleting medications as DMT and found clinical evidence of stability to a higher degree than patients on other medications.

Regarding access issues, there are formularies that may exist for these medicines. National and government organizations may prefer a first-line therapy before going to highly effective medications. There has been off-label use of other medicines as well, but this is becoming less necessary now that we have so many choices in front of us.

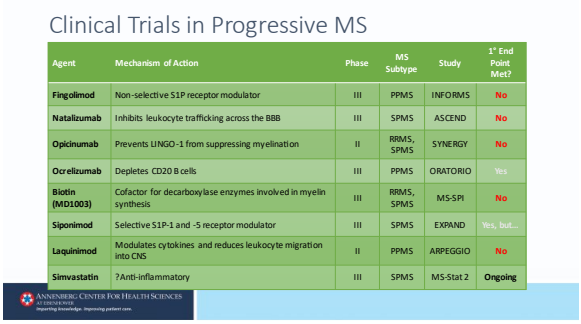
The JC virus antibodies will help determine whether natalizumab would be at a higher or lower risk for causing PML. We know now that index matters and that we can look at it over time to ensure that patients remain at the lowest possible risk.

If patients have primary progressive multiple sclerosis, we still, at this moment in time, only have 1 medicine that has been approved for use in this condition, that is, ocrelizumab.

Progressive MS Treatment

Regarding clinical trials in progressive MS, there have been many trials that have been done, both on primary and secondary progressive MS. Ocrelizumab was approved for primary progressive MS because of positive clinical data. We have also seen data from siponimod in a clinical trial where secondary progressive MS patients were included and, accordingly, it was approved for that indication as well as for relapsing forms of MS, including clinically isolated syndrome. For patients who have secondary progressive MS, the caveat is that it should be active secondary progressive MS,

where there have been changes over the past year, either clinically related to a relapse or a worsening of MRI function.



We have ongoing studies as well, but what we see overall is that we do have many medications that have now been approved for relapsing forms of MS, giving us ample choices to be able to look at the individualized cases and determine the best options for that patient.

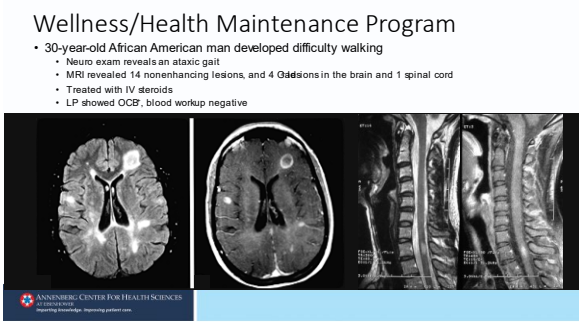
In review, we need to look at each patient individually and screen for comorbid symptoms which might give us an indication as to whether 1 class of medication would be more apt to have complications. We choose medications that have the better safety profile based on their comorbidities. We also should be looking at cognitive dysfunction for a couple of reasons. One is we might consider that to be an indication of more severe disease if cognitive dysfunction is occurring. We also need to be able to monitor those patients for likelihood of adherence to their treatment protocol if they are having significant memory issues.

We have practical advice for preventing and treating serious adverse events. We need to let patients know what their role is in getting ongoing monitoring, whether it be blood work or MRI or return visits. But also, patients should be mindful of side effects to look out for and know that they should be contacting their healthcare provider should they have unexplained symptoms.

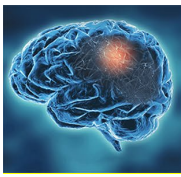
Lastly, we should be aware that rebound relapses can occur after rapid discontinuation of multiple sclerosis therapeutics. Patients should understand the need for ongoing therapy, that there should not be unplanned gaps and, should there be any difficulty with access to medication or tolerability, that the healthcare provider should be notified immediately so we can take steps to limit the risk of severe debilitating relapses over time.

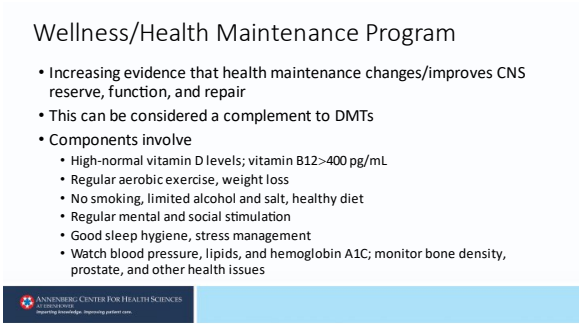
Ongoing Monitoring

We need to maintain wellness and a health maintenance program for patients, which includes exercise, a proper diet, rest, and all those factors which we would certainly wish for any of our patients with multiple sclerosis.



Here, we have a 30-year-old African American man with difficulty walking. You can see that his neuro examination shows difficulty with ataxia, given that he had a significant spinal cord lesion. We also know that he could have many other neurologic symptoms based on the number of lesions that were seen in the confluent basis within the periventricular regions.





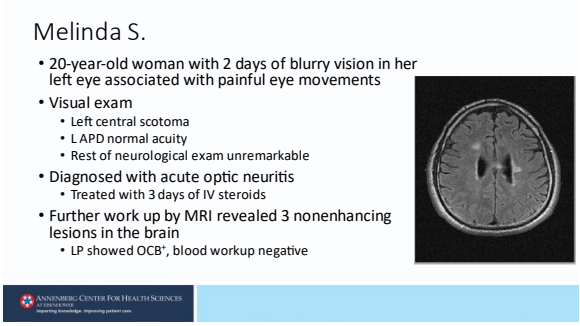
He was treated with IV steroids because of this large rim-enhancing lesion. We would hope that a patient who gets IV steroids would have a rapid benefit in terms of improvement of the clinical signs and symptoms, but at that point it would be imperative to get on a DMT to limit the risk of further problems.

We do want to improve CNS reserve function and repair, and 1 way to do that is by quitting smoking, having a better exercise regimen, getting an adequate amount of sleep at night, making certain that patients do not have sleep apnea or some other condition which would cause further problems, and watching for comorbidities, such as high blood pressure, hyperlipidemia, diabetes, making certain that there is not development, either because of the medicines, inactivity, early bone density loss, or other health issues.

Again, there are many different factors that can be modified here to lessen the risk of worsening disability. Unfortunately, some of the risk factors cannot be modified, in which case, we must be aware that this patient is at high risk and treat this condition accordingly.

Cases

Let us come back to the case of Melinda, who had the relapsing form of MS, as well as issues with optic neuritis findings on neurologic examination and modest changes on the MRI. Here, we also have a patient that would benefit using treatment with IV steroids to allow for a faster return of normal vision. The case, too, is clear that we can use disease-modifying therapies to reduce the risk of developing more lesions on MRI, relapses and worsening of disability over time.

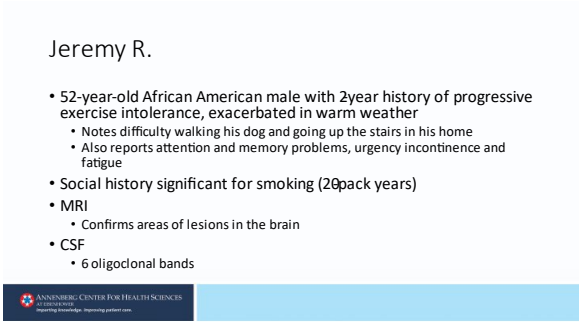


We have multiple treatment options that would be viable for this patient because we have a number of medicines that have been used in clinical trials in people exactly like Melinda S. where we have seen excellent clinical outcomes.

Regarding factors that would be used to determine which of these medicines is best, we would consider things like quality-of-life measures, ease of use of the medicine, access to the medicine, and what monitoring would be necessary for a patient with that medicine. The question about whether a patient could be on platform therapy vs high-efficacy therapy at its onset is an ongoing question. This is somewhat answered by head-to-head trials which show that high efficacy treatments had benefits for patients, such as Melinda S. But we also now have further studies that are ongoing which hopefully will be able to address the question about whether most patients should be initiated with high-efficacy therapy or whether there are some factors that we could use to determine that a moderate-efficacy medication or lower-efficacy medicine might be sufficient.

How do we monitor this patient if 1 of these medicines is being used? Well, certainly the

safety monitoring needs to be done, but what about efficacy monitoring? That requires repeat neurologic examination, taking a history from the patient to determine whether new symptoms were occurring and, lastly, periodic MRIs to ensure that there is not breakthrough radiographic disease that could indicate a worse prognosis.



Lastly, let us talk again about Jeremy R., the 52-year-old African American male with a 2-year history of progressive exercise intolerance and gait disorder. As mentioned, he has many risk factors that are considered very significant, as well as the diagnosis of primary progressive MS. The treatment options are limited for him, but the factor that should be considered in selecting a therapy is not only the clinical trials that have been done, but how those patients in those clinical trials were evaluated. For instance, walking speed, endurance, disability level, as well as MRIs. Monitoring for this patient is more clinical than anything else, but the MRIs, again, can be very helpful to determine whether somebody does have active disease.

Conclusion

In conclusion, MS remains a clinical diagnosis. The MRI can be supportive. The history and physical examination, however, should point to a demyelinating central nervous system disorder. We use the ancillary testing, such as MRIs and lumbar punctures, to confirm our clinical diagnosis of demyelinating disease. It is extremely important to differentiate it from its mimics, as overdiagnosis of MS can lead to unnecessary morbidity and even mortality by over-diagnosing a situation, by giving a patient who does not need immunotherapy a medication that can increase their risks, or by not treating the underlying condition which needed treatment, which might be vascular disease or another conditions.

We use a multidisciplinary team to best get the patient to understand their role in ongoing wellness so that they can initiate proper health choices for themselves, whether it be the obvious ones like stopping smoking or the ones that are more difficult like diet, exercise and sleep maintenance. We need to discuss with these patients their treatment options which change over time. They need to understand why they are on the medication, what our goals are for treatment and medication, and what they need to do to monitor for ongoing safety and tolerability and maintenance of good quality of life and activities of daily living.