AN UPDATE IN MULTIPLE SCLEROSIS

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Session Objectives:

At the conclusion of this session, participants should be able to:
1. Describe the commonly known epidemiology and natural disease history of Multiple Sclerosis.
2. List the diagnostic criteria for Multiple Sclerosis and indicators for poor prognosis.
3. Identify the mechanisms of action of the currently available and FDA-approved treatments for Multiple Sclerosis along with their risks, benefits and alternatives.
4. Evaluate the lifestyle impact that these treatment options may have to determine the best treatment, medically and personally, for the individual needs of a patient.

Multiple Sclerosis (MS) is a degenerative disease affecting the central nervous system which can have an unpredictable course, varying from patient to patient and even in the same patient over the course of a lifetime. There is an estimated 2-3 million people diagnosed with MS world-wide, effecting females two to three times that of males. Most MS patients are diagnosed between the ages of 20 and 40, during the most productive years of their lives personally and professionally. While there is no cure for MS, there are currently thirteen FDA-approved medications for the treatment of relapsing forms of MS with more on the immediate horizon. Most have differing mechanisms of action which portends to the complex, and not fully understood, pathophysiology of this disease. While these medications all have the goals of preserving physical and cognitive function as well as maintaining quality of life, they vary in mechanisms of action, adverse event profiles, and routes of delivery. Therefore, it is important to understand the differences for patient safety and adherence. Both the diagnosis and treatment of MS can affect the patient and their family physically, emotionally, and financially.

In establishing the diagnosis of MS, the McDonald criteria is often used. This criteria, revised in 2010, uses patient history, clinical observations, radiographic and or laboratory data in combination. Once an alternative diagnosis has been excluded, dissemination of central nervous system lesions in space and time must be proven. In order to fulfill dissemination in space, one or more T2 lesions must be observed on MRI in at least 2 out of 4 stereotypical areas such as: periventricular, juxtacortical, infratentorial or spinal cord. To fulfill dissemination in time, an asymptomatic abnormally enhancing lesion plus non-enhancing lesions in different anatomical regions of the Central Nervous System must be observed or a new T2 and or enhancing lesion is seen on a follow up MRI. With the revised criteria, the diagnosis of MS can be made by careful history taking and use of MRI. However, when questions remain, Cerebrospinal Fluid (CSF) evaluation may be needed. The presence of greater than 5 oligoclonal bands in the CSF which are not present in the serum may be indicative of MS.

While phenotypically different, most cases of MS will progress over time if left untreated. This progression leads to increased physical and cognitive disability. Most commonly, the Expanded Disability Status Scale (EDSS) is used to measure and track disability over time in a given patient. This is typically used in clinical trials but not necessarily in clinical practice. One reason is that it is a measure of physical status and neglects the often seen and equally disabling cognitive changes that occur in patients over time.

Predictors of physical disability progression include both clinical and radiographic factors. An increased number and frequency of clinical relapses as well as high T2 lesion burden, gadolinium enhancing lesions and atrophy seen on MRI are all indicators of future disability accumulation.

Predictors of poor prognosis include: a devastating relapse at onset, early high relapse rate, high lesion activity and or lesion load on brain MRI at first attack, rapid onset of disability (cognitive, physical, activities of daily living), and high-risk populations with histories of more malignant forms of MS.

While the exact pathophysiology of MS continues to evolve, it is thought to be a complex autoimmune disorder creating chronic inflammation which attacks the central nervous system, targeting myelin and other neuronal membrane systems. This chronic inflammation sets the stage for apoptosis which, if left untreated, can lead to atrophy with subsequent physical and cognitive decline and functional impairment in these domains.

As of February 2017, there are 13 different FDA-approved disease modifying therapies (DMTs) for relapsing forms of MS with several different mechanisms of action and different routes of delivery (Table 1). Unfortunately, we are not at a point with personalized medicine in MS where we can predict which mechanism of action is best suited for a given patient. All DMTs have the therapeutic goals of reducing disease progression and preventing additional disability accumulation but how they exactly do that varies. While there are no set guidelines as to selection of a DMT for a given patient, it is generally thought that initiating therapy should occur as soon as possible once the definitive diagnosis of MS has been made. In 2014, the Consortium of MS Centers convened a consensus conference to create best practices for not only selecting an initial DMT but on when to consider switching a DMT.

Many factors are included in initiating or switching a DMT and include: a medication's safety profile, potential for adverse events, insurance formulary access and cost, routes of administration, and a patient's risk tolerance. A patient's comorbidities (cardiac or hepatic disease) and antibody status to certain viruses should be taken into consideration when deciding which DMT may or may not be contraindicated.

Patients should be engaged in shared decision making strategies to improve adherence. Other strategies include: patient and family/caregiver education, managing patient expectations, managing adverse events, and addressing patient concerns. MS is a chronic disease spanning a patient's lifetime. Partnering with a patient regarding all of their needs and coordinating with other providers is as important as DMT selection.

Table 1

Agent	US FDA Approval	Dose	Route	Schedule
Interferon (IFN) β-1b (Betaseron®)	1993	250 mcg	SC	QOD
IFNβ-1a (Avonex®)	1996	30 mcg	IM	QW
Glatiramer acetate (Copaxone®)	1996 2014	20 mg 40 mg	SC SC	QD TIW
Mitoxantrone (Novantrone®)	2000	12 mg/m^2	IV	Q3M
IFNβ-1a (Rebif®)	2002	22 mcg or 44 mcg	SC	TIW
Natalizumab (Tysabri®)	2004	300 mg	IV	Q4W
IFNβ-1b (Extavia®)	2009	250 mcg	SC	QOD
Fingolimod (Gilenya®)	2010	0.5 mg	PO	QD
Teriflunomide (Aubagio®)	2012	7 mg or 14 mg	PO	QD
Dimethyl fumarate (Tecfidera®)	2013	240 mg	PO	BID
PeglFNβ-1a (Plegridy®)	2014	125 mcg	SC	Q14D
Alemtuzumab (Lemtrada®)	2014	12 mg	IV	x5D/x3D in 1 Yr
Daclizumab (Zinbryta®)	2016	150 mg	SC	Q4W

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