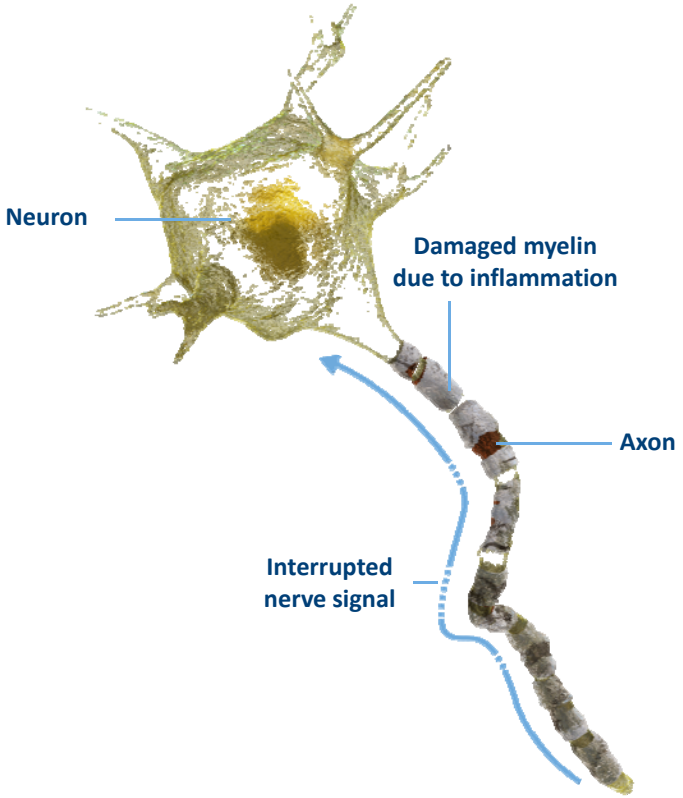
What is MS?[1]



- MS is a chronic immune-mediated disease that affects the central nervous system (CNS)
- Is a disease that affects both white and gray matter
- Target of the immune response is still unknown
- Symptoms of relapse are determined by which pathways are affected

Reference: 1. Definition of MS. NMSS website. www.nationalmssociety.org/What-is-MS/Definition-of-MS. Accessed May 5, 2015.

Common Symptoms of Relapse

- Gradual onset/build up of the following symptoms:
  - Optic Neuritis
  - Numbness or Tingling
  - Varying degrees of weakness
  - Coordination problems (including gait)
  - Diplopia
  - Vertigo
  - Bowel or bladder disturbances
  - Lhermitte's sign

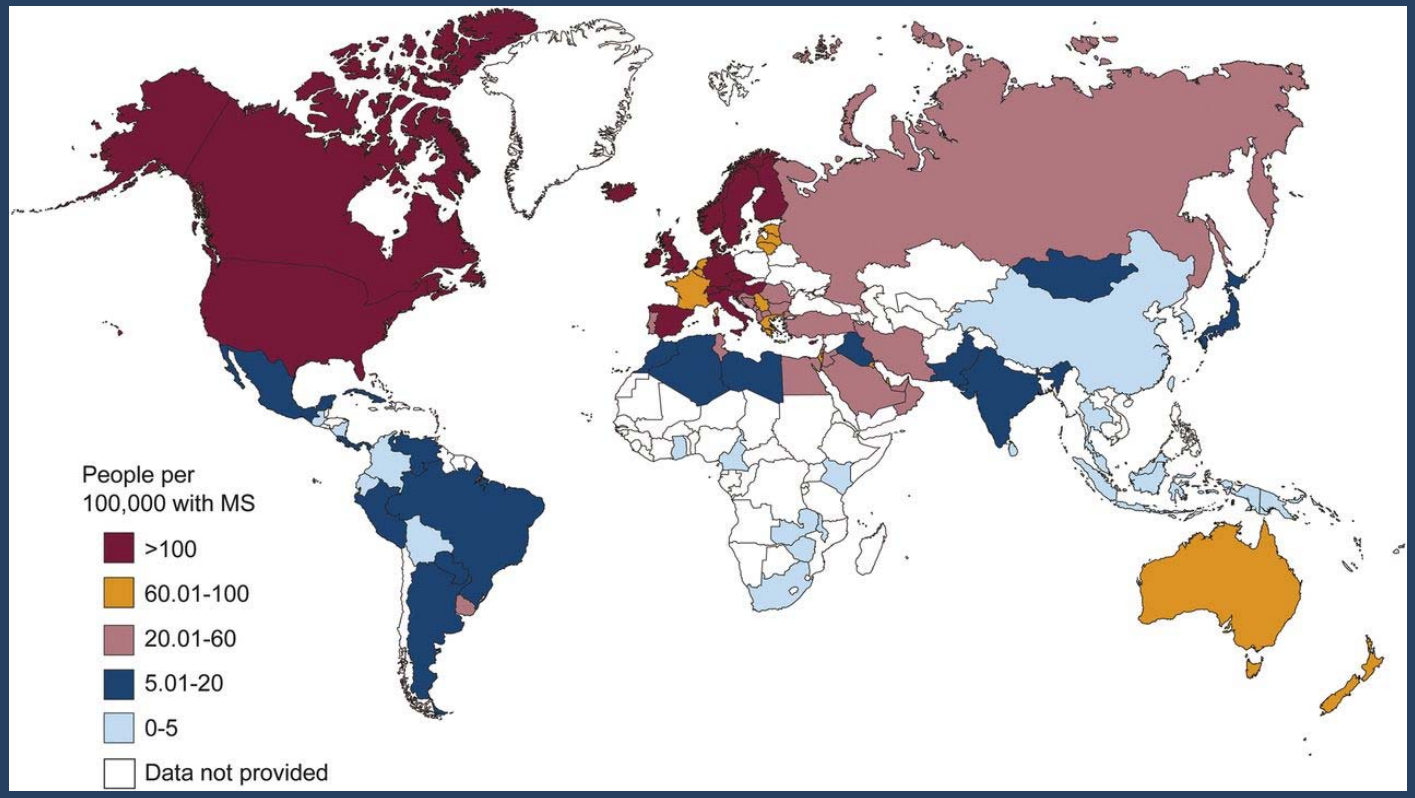
Uhthoff phenomenon

- Described in 1890 as a temporary worsening of vision with exercise in patients with history of ON
- Likely reflects poor nerve signal conduction in extremes of temperature (namely heat)
- Common cause of pseudoexacerbations in MS

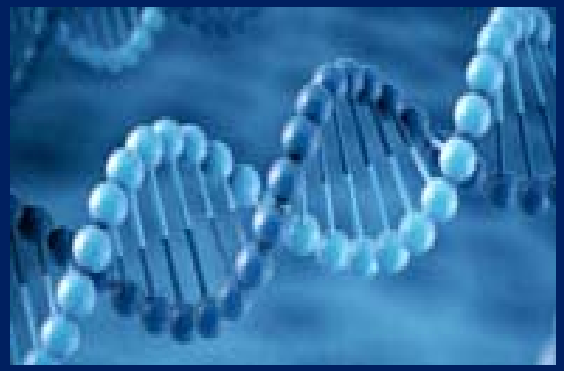
Who Does MS Affect?

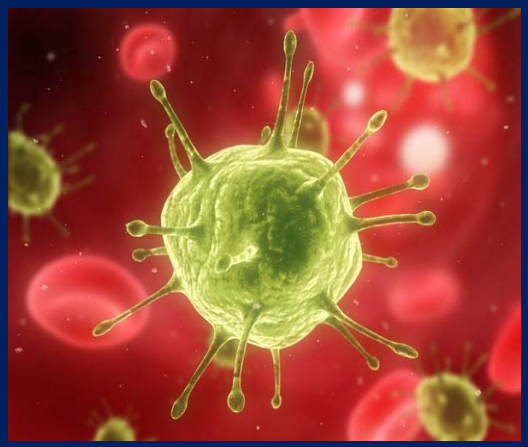
- MS affects approximately 400,000 people in the US and 2.5 million worldwide
- In the US, prevalence estimates are approximately **90 per 100,000 population**
- MS can affect any age group, but onset is usually between 20 and 50 years, with a mean of 32 years

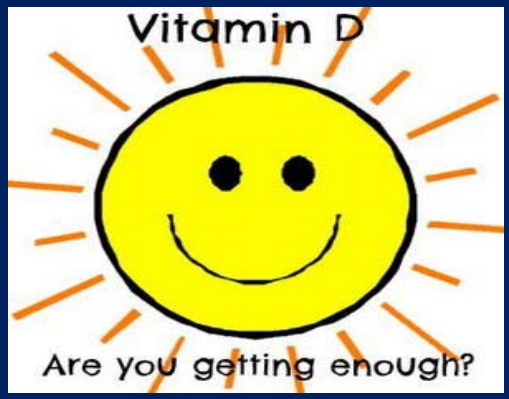
MS ATLAS 2013



Possible Risk factors for Developing MS





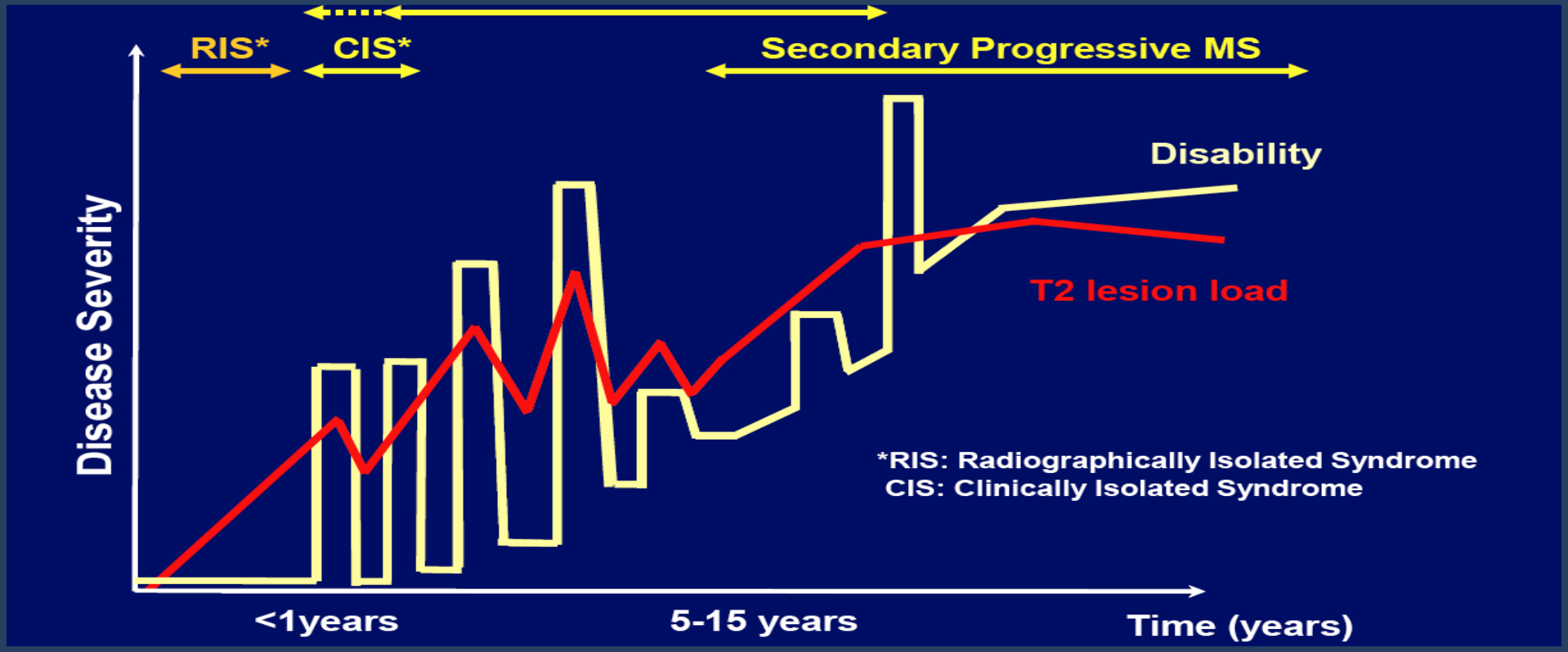


MS – Clinical Subtypes

Clinical Subtype	Description	Prevalence
Relapsing-remitting (RRMS)	Remissions followed by exacerbations or relapses with minimal disease progression 	80-85%
Secondary progressive (SPMS)	A decrease in relapses with an increase in disease progression 	
Primary progressive (PPMS)	A slow and steady decline in functionality from onset of disease 	10-20%
Progressive-relapsing (PRMS)	Steadily progresses from onset with acute exacerbations interspersed; no remissions 	Rarest form 5%

Lublin FD, Reingold SC. *Neurology.* 1996;46:907–911.

MS Disease Course



Proposed Natural History

Newer Concepts of Disease Classification

- ACTIVE/INFLAMMATORY/RELAPSING
  - New lesions seen on MR imaging (active versus T2)
  - Clinical relapse
- PROGRESSIVE DISEASE
  - Slow gradual worsening in absence of relapse and MRI changes

Our ability to diagnose MS has come a long way[1-4]

The "hot bath" test
Because increases in body temperature can cause a worsening of MS symptoms, a person was submerged in hot water to see if MS symptoms would appear or get worse!

For centuries, MS was not thought of as a distinct condition

Recognizing MS as a distinct disease opened the door for research and treatment discovery

The first modern criteria were followed by updates enabling earlier diagnosis

1868 Neurologist Jean-Martin Charcot defines MS and provides diagnostic criteria

Charcot's name for MS was "*Sclérose en plaques.*"

1965 Schumaker criteria

1983 Poser criteria

2001 McDonald criteria

2010 Revised McDonald criteria

References: 1. Murray TJ. *J Neurol Sci*. 2009;277(Suppl 1):S3-S8. **2.** Heat and temperature sensitivity. National Multiple Sclerosis Society website. http://www.nationalmssociety.org/Living-Well-With-MS/Health-Wellness/Heat-Temperature-Sensitivity. Accessed May 20, 2015. **3.** Poser CM, Brinar VV. *Clin Neurol Neurosurg*. 2004;106(3):147-158. **4.** Polman CH, et al. *Ann Neurol*. 2011;69(2):292-302.

McDonald Criteria – Past and Present

McDonald Criteria 2001	Revised McDonald 2005	Revised McDonald 2010
DIS: ≥ 3 required	**DIS: ≥ 3 required**	**DIS: ≥ 2 required**
➢ ≥ 9 T2 lesions or ≥ 1 gad lesion ➢ ≥ 3 periventricular ➢ ≥ 1 juxtacortical ➢ ≥ 1 posterior fossa **1 spinal cord lesion can be used to replace 1 brain lesion* **DIT:** ➢ ≥ 1 enhancing lesion > 3 months after CIS ➢ ≥ 1 new T2 lesion ≥ 3 months after CIS	➢ ≥ 9 T2 lesions or ≥ 1 gad lesion ➢ ≥ 3 periventricular ➢ ≥ 1 juxtacortical ➢ ≥ 1 posterior fossa ***Any number of cord lesions can be used to replace brain foci* **DIT:** ➢ ≥ 1 gad lesion > 3 months after CIS ➢ ≥ 1 new T2 lesion ≥ 30 days after CIS	➢ ≥ 1 periventricular ➢ ≥ 1 juxtacortical ➢ ≥ 1 posterior fossa ➢ ≥ 1 asymptomatic infratentorial **DIT:** ➢ ≥ 1 asymptomatic enhancing and non-enhancing lesions ➢ ≥ 1 new T2 focus

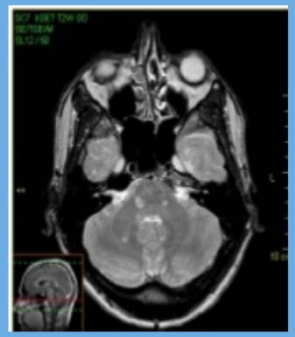
2010 McDonald Criteria

- **REQUIRE AT LEAST ONE CLINICAL EPISODE CONSISTENT WITH MS + FULFILLMENT OF MRI CRITERIA:**

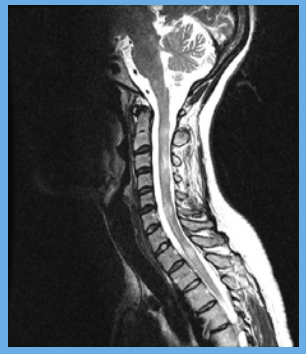
- **DIS: ≥ 2 required**
- ≥ 1 periventricular
- ≥ 1 juxtacortical
- ≥ 1 posterior fossa
- ≥ 1 asymptomatic infratentorial

- **DIT:**
- ≥ 1 asymptomatic enhancing and non-enhancing lesions
- ≥ 1 new T2 focus

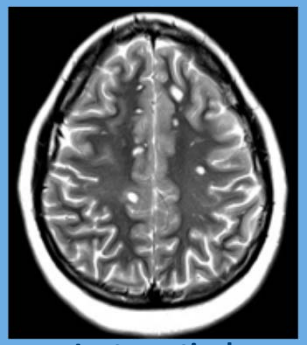
LESION LOCATION



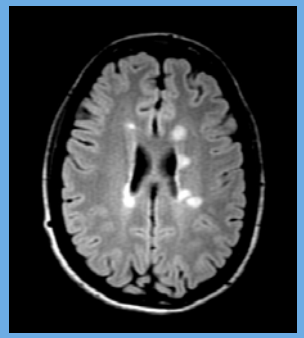
Posterior Fossa



Spinal cord

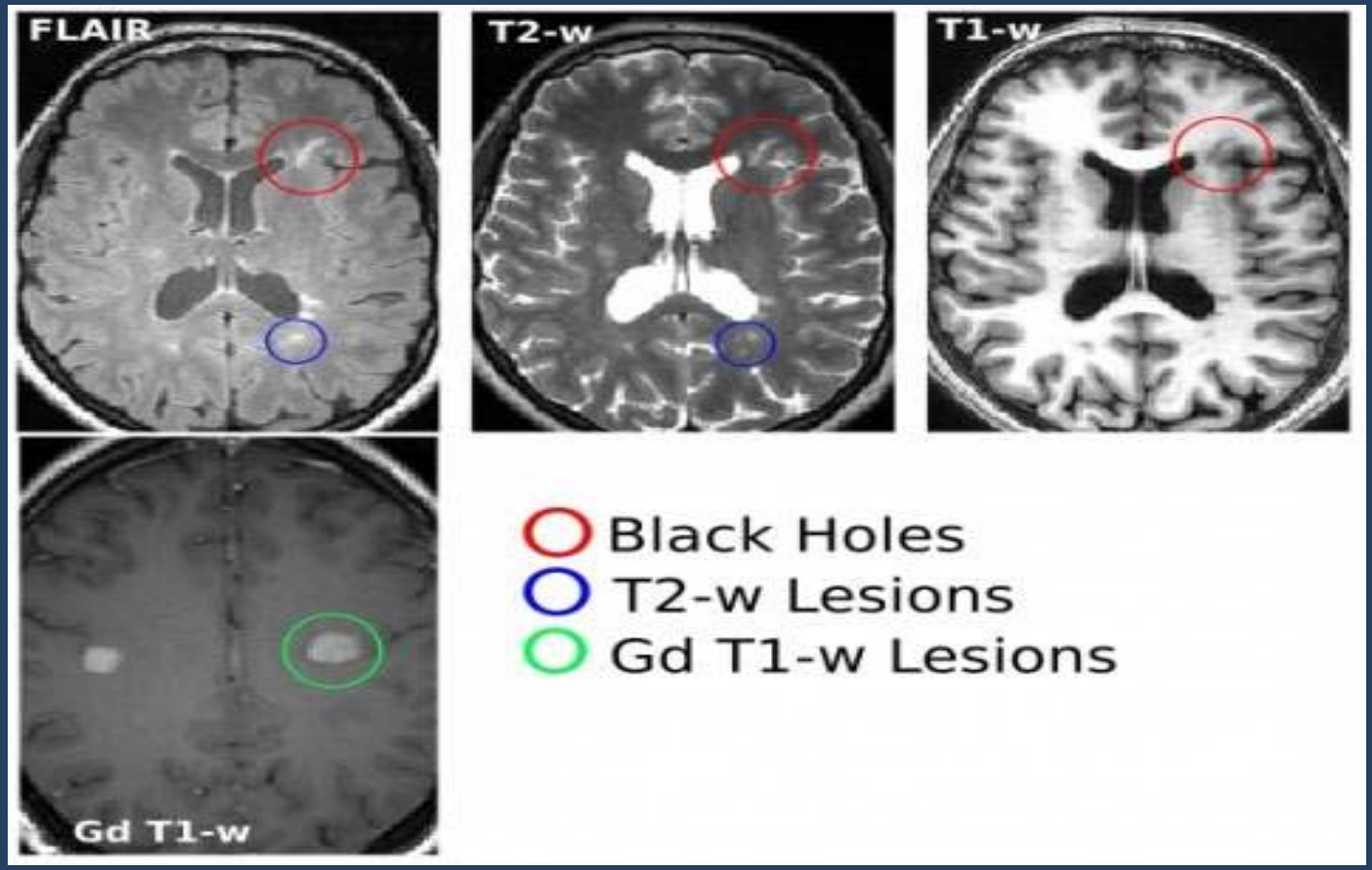


Juxtacortical



Periventricular

TYPES OF MS LESIONS



MRI IN MS

- Used for:
  - Confirming diagnosis
  - Routine monitoring of disease activity
  - To exclude other causes of new symptoms
    - Infection
    - Cervical stenosis

Treatment in MS

- TYPES:
  - Acute
  - Preventative
  - Symptomatic

The importance of early treatment

Axonal transection can occur early in the course of the disease, along with **demyelination**[1]

This disrupts the ability of the nerve to conduct electric impulses to and from the brain[1]

It is important to start treatment early to help decrease demyelination[1,2]

Damaged neuron

References: 1. Trapp BD, et al. *N Engl J Med.* 1998;338(5):278-285. **2**. Disease management consensus statement. National Multiple Sclerosis Society website. http://NationalMSSociety/media/MSNationalFiles/Brochures/ExpOp_Consensus.pdf. Accessed February 25, 2015.

- 2006 Treatment Guidelines issued by NMSS emphasize the following:
  - Importance of early, accurate diagnosis of initial MS sxn
  - Prompt, aggressive treatment with DMT as soon as MS is diagnosed
  - Continuation of DMT indefinitely with re-evaluation as needed (depending on tolerability, clinical and radiological efficacy, new emerging treatment options)

Acute Events

- The txn paradigm for acute relapses is IVSM in order to speed recovery
- Steroids are felt to preserve integrity of BBB, reduce inflammation, and reduce edema
- Txn of acute events with steroids has not been shown to improve long term outcomes, risk of further acute relapses, or progression of disability

Treatment of Acute relapse

- Use of steroids has been mainstay of txn since 1940's.
- No definitive study data available for IV versus PO steroids
- There is little evidence to support the use of IVIG in acute txn settings
- Plasma exchange can be beneficial for relapses that do not improve with steroids

Preventative Health

Current Available DMTs

- Interferon beta-1a (Avonex, Rebif, Plegridy)
- Interferon beta-1b (Betaseron, Extavia)
- Glatiramer acetate (Copaxone)
- Natalizumab (Tysabri)
- Fingolimod (Gilenya)
- Teriflunomide (Aubagio)
- Dimethyl fumarate (Tecfidera)
- Alemtuzumab (Lemtrada)
- Mitoxantrone (Novantrone)**

Fingolimod (Gilenya) – 1st oral disease modifying therapy in the treatment of multiple sclerosis

- Modulates sphingosine-1-phosphate receptor
- Prevents trafficking of lymphocytes outside of lymphatic tissue
- Indication – relapsing forms of MS
  (even 1st line treatment)
- Requires FDO, lab monitoring, and routine eye exams

Teriflunomide (Aubagio)

- Active metabolite of leflunomide
- Inhibits dihydro-orotate dehydrogenase and blocks pyrimidine synthesis
- Cytostatic effect on proliferating T and B cells
- Once daily dosing
- Pregnancy category X
- Monthly labs x 6 months

dimethyl fumarate (Tecfidera)

- An oral formulation of dimethyl fumarate
- Unknown mechanism of action
- Must be taken BID
- Requires routine lab monitoring
- Can cause lymphopenia (6%, 3%)

Kappos L, et al. *Lancet.* 2008;372:1463-1472
Gold R, et al. Presented at WCTRIMS, Montréal, Canada, September 17-20, 2008. [P50]
Gasperini C, et al. *Expert Opin Emerg Drugs.* 2008;13:465-477.

Natalizumab (Tysabri)

- Monoclonal Ab directed against alpha-4, beta-1 integrin found on T cells
- Is an infusion given q28 days that is indicated for RRMS
- Introduced to market in 2004, pulled in 2/2005 because 2 cases of PML and then reintroduced with guidelines in 2006
- Requires routine labs, MRI, monitoring of JCV status Q6 months if negative

Progressive Multifocal Leukoencephalopathy (PML)

- Clinical features:
  - Weakness, disturbances in speech or vision, personality changes, cognitive difficulties
- MRI features:
  - Larger than MS lesions
  - Have less clearly defined borders
  - May have a ‘microcystic’ appearance (on T2W)
  - Most are associated with T1 hypointensities
  - Associated with different enhancement pattern

Natalizumab (Tysabri) is associated with risk for progressive multifocal leukoencephalopathy (PML)

Anti-JCV Antibody Negative	TYSABRI Exposure†	Anti-JCV Antibody Positive	
		No Prior Immunosuppressant Use	Prior Immunosuppressant Use
<1/1,000	1-24 months	<1/1,000	1/1,000
	25-48 months	3/1,000	12/1,000
	49-72 months	6/1,000	13/1,000

Other considerations:

1. Natural history of seroconversion: 2-3% annually.
2. Anti-JCV Ab false negative rate of the assay is 3%.

Most important factors:

1. JC Virus Ab positivity
2. Prior exposure to chemotherapeutics
3. Duration of treatment with natalizumab

Biogen IDEC: http://www.tysabrihcp.com/

Mitoxantrone (Novantrone) is the only medication FDA approved for secondary-progressive MS

- Principally used in secondary progressive MS

  (FDA Approved 2000; Relapse rate reduction 67%)

- Associated with cardiac toxicity
- Associated with a lifetime risk of leukemia (1 in 120)
- Lifetime maximum dose: 140mg/m^2
- A medication that should not be used given other "better" treatment options

Alemtuzumab (Lemtrada)

- Monoclonal Ab targeting CD52 on mature circulating lymphocytes
- Given as an IV infusion daily for 5 days (year 1), 3 days (year 2)
- Requires monthly lab monitoring for 60 months from first infusion

MS Treatment – Non-FDA Approved

Non-FDA Approved Medications*:

Azathioprine (Imuran)
Methotrexate (Trexall, Rheumatrex)
Cyclophosphamide (Cytoxan)
Rituximab (Rituxan)
IVIg (intravenous immunoglobulin)
Mycophenolate mofetil (CellCept)

SYMPTOM MANAGEMENT

- Dalfampridime (Ampyra): walking pill
  - Taken Q12 hours
  - Can help improve balance, walking endurance/speed

- Treatments to address:
  - Spasticity/muscular pain
  - Bowel urgency/irregularity
  - Urinary urgency
  - Neuropathic pain
  - Fatigue

THANK YOU

- QUESTIONS?

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