Multiple Sclerosis: An Overview & Treatment options

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March 19th, 2016

Disclosures

* Teva
* Biogen
* Novartis
**Multiple Sclerosis**

Diagnosis generally occurs between 20 and 50 years of age\(^1\)

MS is 2-3x more common in women

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**Potential Triggers for Multiple Sclerosis**


**MS: A Chronic Autoimmune Disease (at least partly)**

* MS is characterized by inflammation, demyelination, and axonal loss
* All current disease modifying treatments are thought to work via influencing the immune system
Proposed Pathophysiology of MS

VCAM = vascular cell adhesion molecule.

Proposed Immunopathogenesis of MS: Cell Activation and Proliferation

Degeneration May Result From Chronic Demyelination


A B C

Axonal Loss
Frequent Inflammation, Demyelination, Axonal Transection, Plasticity, and Remyelination

Continuing Inflammation, Persistent Demyelination

Infrequent Inflammation, Chronic Axonal Degeneration, Gliosis

Clinical Disability
Inflammation
Axonal Loss
Brain Volume

Relapsing-Remitting
Secondary Progression

Clinical Threshold

MS Presentation

- Focal Neurologic symptom
- Paresthesia
- Weakness
- Diplopia
- Mono-ocular vision loss
- Imbalance

Evaluation

- History
- Examination
Further Evaluation

- MRI brain/spinal cord
- Bloodwork:
  - ANA, ESR, RF, SS-A, SS-B
  - Lyme, RPR
  - NMO antibody (aquaporin-4)
- Lumbar puncture - often, not always
- Evoked response testing - rarely

Imaging
**MS Treatment**

- Exercise
- No tobacco
- Diet
- Adequate rest
- Stress Management
- Medications

**MS Medication Treatments Fall Into Three Categories**

- Medications to treat specific symptoms
- Corticosteroids/ACTH to treat relapses
- Disease-modifying agents to treat underlying disease
  - Injectables
  - Orals
  - Infusables
Neurology Care Coordination, Nov. 16, 2013

Prognostic factors

- Age
- Gender
- Race
- Presentation-Motor vs Sensory
- Spinal cord involvement
- T2 lesion burden
- Frequency of flares

The Injectables
Interferon Beta Therapies

* Avonex, Rebif, Betaseron, Extavia, Plegidy
* Multiple potential MOA:
  * Preventing T-cells from being activated
  * Preventing T-cells from multiplying
  * Preventing T-cells from migrating into the brain
  * Reducing Inflammation in Central Nervous System

Interferon Beta  Risks

* Flu-like symptoms
* Depression
* Anemia
* Liver damage
* Injection site reactions
**Copaxone (glatiramer acetate)**

- Daily or three times a week sub-q injections
- Pregnancy category B
- Multiple potential MOA:
  - Prevents T-cells from being activated
  - Prevents T-cells from multiplying
  - May make immune cells become anti-inflammatory by mimicking myelin

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**Copaxone Risks**

- Injection site reactions
- Rare dramatic injection reactions
- Lipoatrophy
The Orals

Fingolimod

Works by sequestering lymphocytes in the lymph nodes

Fingolimod: Mechanism of Action (MOA)

- Activation
- Proliferation and differentiation
- Afferent lymphatic vessel
- S1P
- Lymphatic sinus
- Sinus-lining endothelium
- Efferent lymphatic vessel
- Naïve T cell
- Lymph node
- S1P1 receptor
- Activated T cells
- Sinus-lining endothelial cell
- Barrier enhancement
- Reduced T cell egress

Fingolimod: Mechanism of Action (MOA)

- First dose effect (bradycardia)
- Macular edema (1%)
- GI upset
- Infection
  - Small increased risk serious infections
  - several cases PML
S1P Receptor Is Located in Other Organ Systems

- Airways hyperactivity (S1P1–3)
- Vasoconstriction, blood pressure increase (S1P1–3)
- Swelling (S1P2)
- Heart-rate reduction and regulation (S1P1, 3)
- Angiogenesis (S1P1–3)
- Vasodilation (S1P1, 3)
- Barrier decrease (S1P2–3)
- Barrier enhancement (S1P1)

Tecfidera (Dimethyl fumarate)

- Activates the Nrf-2 pathway to reduce the activity inflammatory cells on the CNS. May decrease inflammation and oxidative stress in the central nervous system.
- Oral medicine
- Twice daily

**Tecfidera Risks**

- GI upset
- Flushing
- Decrease lymphocytes
- Infection, several cases of PML

**Aubagio (Teriflunomide)**

- Inhibit dihydro-orotate dehydrogenase (DHODH), an enzyme involved in formation of white blood cells.
- Anti-inflammatory effects and decreases the production of WBCs
- Oral medication, once daily
Aubagio Risks

* Pregnancy category X
* Hair loss
* Liver damage
* Infection (?)
* Malignancy (?)

The Infusables
**Tysabri (Natalizumab)**

- TYSABRI prevents white blood cells (WBCs) from binding to the wall of blood vessels
- This prevents WBCs from entering the central nervous system

Proposed Mechanism of Action

1. **Leukocyte migration from blood to tissue**
   - Blood-Brain Barrier
   - Endothelial Cells
   - VCAM-1
   - α4-integrin

2. **Leukocyte priming and activation**
   - Extracellular Matrix (ECM)
   - TYSABRI
   - Paracrine Cell

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2. TYSABRI® (natalizumab) US Prescribing Information, 2004;
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

* Hemianopsia common, diplopia can occur
* Hemiparesis, ataxia, personality changes
* Progressive over weeks
* TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML)
* Risk of PML in patients treated with Tysabri is determined by:
  * Exposure to the JC virus (can test for antibodies, 50% population)
  * Duration of treatment (>2 years)
  * History of prior treatment with immunosuppressant drugs

Please see full Prescribing Information, including Boxed Warning, for Important Safety Information

LEMTRADA (ALEMTUZUMAB)

* Targets CD52 antigen, lysis multiple types of WBCs
* Daily infusion for 5 days first year
* Daily Infusion for 3 days second year
* Highly effective
Lemtrada Risks

- Infusion reactions
- Other autoimmune diseases
  - Thyroid 30%
  - Hemolytic anemia 1%
  - Other-kidney, lungs
- Bloodwork-month for 5 years

Ocralizumab

- anti-CD20 monoclonal antibody
- Deplete B cells
- Infusion every six months
- Data for Relapsing and Progressive MS
Thank you!

Questions?