Overview of New Medications for Multiple Sclerosis

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Assessment Question
1. Which classification of MS responds to currently available disease modifying therapies which prevent new attacks and stabilize EDSS score?
   a. RRMS – Relapsing-Remitting MS
   b. SPMS – Secondarily Progressive MS
   c. PPMS – Primary Progressive MS
   d. PRMS – Progressive Relapsing MS

Assessment Question
2. Which of the following parameters must be closely monitored during the first 6 hours after initiation of Gilenya?
   a. Blood Pressure
   b. Heart Rate
   c. Hepatic Function
   d. Vision

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3. Which of the following should be monitored for efficacy of Ampyra?
   a. Expanded Disability Status Scale
   b. Brain MRI
   c. Timed 25-foot Walk
   d. Clinical report of relapse

Objectives
• Describe the etiology of multiple sclerosis (MS)
• Recognize new treatment options for MS

Conflict of Interest Declaration
• I or my spouse have no actual or potential conflict of interest in relation to this activity.
Pathophysiology of MS

- An autoimmune disorder with both environmental and genetic predispositions
- Possible viral or bacterial infection link
- Dual nature
  - Inflammatory
  - Neurodegenerative
    - Demyelination leads to slower nerve conduction
    - Axonal injury is associated with permanent neurologic dysfunction
- Neurologic disability is correlated with atrophy in the spinal cord, cerebellum and cerebral cortex in patients with MS
  - Both gray and white matter brain atrophy are found in patients with MS


MS Symptom Presentation

- VISION CHANGES
  - Optic Neuritis
- PARESTHESIS
- Gait changes
- Ataxia
- Pain
- Spasticity
- Weakness
- Speech difficulty
- Psych changes
- Recurrent UTI
- Bowel/bladder dysfunction
- Sexual dysfunction
- Pressure Sores
- Muscle contractures
- Respiratory infections
- Poor nutrition
- Depression
- Cognitive changes
- Fatigue

Classifications of MS

- Relapsing-remitting MS (RRMS)
  - clearly defined relapses with full recovery
  - or with sequelae and residual deficit upon recovery
  - There is no disease progression between
- Secondary-progressive MS (SPMS)
  - initial RR disease course
  - followed by progression with or without occasional relapses, minor remissions, and plateaus.

Classifications of MS

- Primary-progressive MS (PPMS)
  - disease progression from onset with occasional plateaus
  - temporary minor improvements allowed
- Progressive-relapsing MS (PRMS)
  - characterized by progressive disease from onset
  - clear acute relapses with or without full recovery
  - progression continues during the periods between disease relapses

Disease progression

Disease type and natural history

<table>
<thead>
<tr>
<th>Disease type at diagnosis</th>
<th>Disease type 11-15 years after diagnosis among patients with RRMS at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>15% PPMS</td>
<td>42% RRMS 58% SPMS</td>
</tr>
</tbody>
</table>

PPMS = primary progressive multiple sclerosis.
RRMS = relapsing-remitting multiple sclerosis.
SPMS = secondary progressive multiple sclerosis.


The EDSS (Expanded Disability Status Scale): assessing the course of disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal neurologic exam</td>
</tr>
<tr>
<td>1.0-1.5</td>
<td>No impairment</td>
</tr>
<tr>
<td>2.0-2.5</td>
<td>Impairment is minimal</td>
</tr>
<tr>
<td>3.0-3.5</td>
<td>Impairment is mild to moderate</td>
</tr>
<tr>
<td>4.0-4.5</td>
<td>Impairment is relatively severe</td>
</tr>
<tr>
<td>5.0-5.5</td>
<td>Walking limitation in ability to walk</td>
</tr>
<tr>
<td>6.0-6.5</td>
<td>Confined to wheelchair</td>
</tr>
<tr>
<td>7.0-7.5</td>
<td>Confined to wheelchair, self-care with help</td>
</tr>
<tr>
<td>8.0-8.5</td>
<td>Confined to bed/chair; self-care with help</td>
</tr>
<tr>
<td>9.0-9.5</td>
<td>Completely dependent</td>
</tr>
<tr>
<td>10.0</td>
<td>Death due to MS</td>
</tr>
</tbody>
</table>

The EDSS Scale: 0-10 rating scale. 0 = Normal neurologic exam; 10 = Death due to MS.


FDA-approved RRMS therapies

<table>
<thead>
<tr>
<th>Agents</th>
<th>Administration</th>
<th>Cost/Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-β1b (Betaseron®)</td>
<td>SC 250 mcg/q other day 1/2</td>
<td>$2519</td>
</tr>
<tr>
<td>Low-dose IFN-β1a (Avonex®)</td>
<td>IM 30 mcg/wk 1/2</td>
<td>$1034</td>
</tr>
<tr>
<td>High-dose IFN-β1a (Rebif®)</td>
<td>SC 22 mcg or 44 mcg tiweek 1/2</td>
<td>$1699</td>
</tr>
<tr>
<td>Glatiramer acetate injection (Copaxone®)</td>
<td>SC 20 mg qday 1/2</td>
<td>$3400</td>
</tr>
<tr>
<td>Natalizumab (Tysabri®)</td>
<td>IV 300 mg q4wk</td>
<td>$2200 - vial</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone®)</td>
<td>IV 12 mg/m² over 5-15 min q3mo 2/3</td>
<td>$3000 annually</td>
</tr>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>PO 0.5mg qday</td>
<td>$4000</td>
</tr>
</tbody>
</table>

6. Copaxone® prescribing information. Teva Neuroscience, Inc.
11. Novantrone® prescribing information. EMD Serono, Inc.

Fingolimod (Gilenya)

- FDA approved September 2010
- Indication:
  - RRMS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability
- Mechanism of Action:
  - Unknown
  - Sphingosine 1-phosphate receptor modulator
    - Blocks capacity of lymphocytes to move from lymph nodes, reducing the number of lymphocytes in peripheral blood
    - Reduce lymphocyte migration into CNS


Gilenya – Clinical Evidence

- Phase III Trials
  - FREEDOMS 13
  - TRANSFORMS 14
- Reduce attack rate in RRMS
- Produces benefit on MRI, slows sustained disability progression based on EDSS
- Possible benefit over INFβ-1a IM (Avenox)
Before starting Gilenya

- Pregnancy
- Heart Rate – possible EKG
  - Bradycardia
  - AV conduction delay
  - Generally resolves within 24 hrs
- Eye exam
- CBC
- Hepatic function

Gilenya – Dosing

- 0.5mg qday
- Take with or without food
- 6 hour monitoring with 1st dose

Gilenya – Drug interactions

- 1a or Class III Antiarrhythmic drugs
- Ketoconazole (inhibitor)
- Antineoplastic, immunosuppressives, immunomodulating therapy
- HR lowering drugs
- Avoid live attenuated vaccines during & 2mo after

Gilenya - Monitoring

- Observed for 6 hrs after first dose
  - Bradycardia
- Eye exam – 3-4mo after initiation
- CBC – q 3-6 months
- BP/HR – q 3-6 months
- PFT as indicated
- LFT as indicated (3-4mo after initiation)

Dalfampridine (Ampyra)\textsuperscript{15, 16}

- FDA approved January 2010
- Indication:
  - Improve walking in patients with MS, based on increased walking speed.
- Mechanism of Action:
  - Broad spectrum potassium channel blocker.
  - Increase conduction of action potentials in demyelinated axons through inhibition of potassium.
  - Demonstrated by an increase in walking speed.

Ampyra – Clinical Evidence

- Phase III trials
  - MS-F203\textsuperscript{17}
  - MS-F204\textsuperscript{18}
- 50% of MS patients responded to therapy
- 2-4 week trial
- Risk evaluation & mitigation strategy (REMS) program

\textsuperscript{15} Ampyra\textsuperscript{®} prescribing information. Acorda Therapeutics, Inc.
Before starting Ampyra

- Seizure history
- Renal function
- Pregnancy (C)/Nursing
- > 18 years old

Ampyra – Dosing

- 10mg BID
- Slow release formulation
- With or without food

Ampyra – Drug Interactions

- None identified

Ampyra - Monitoring

- Renal function
- Walking speed
  - Timed 25-foot Walk (T25W)

Future Therapies

- Mylinax (cladribine): August 2011
  - EMD Serono, an affiliate of Merck
  - 3/11: FDA has requested improved understanding of safety risks & overall benefit-risk profile via additional analyses or studies
  - CLARITY (CLAdRibine Tablets Treating MS Orally)\(^1\)
- Laquinimod – Teva Pharmaceutical
- BG-12 – Biogen Idec
- Teriflunomide – Sanofi-Aventis

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